

## Observations Made in Exploring a Pyridinium Salt Photochemical Approach to the Synthesis of (+)-Lactacystin

Jiwen Zhou, Maozhen Gong, Patrick S. Mariano,\* and Ung Chan Yoon†\*

Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131, USA

\*E-mail: mariano@unm.edu

†Department of Chemistry, College of Natural Sciences, Pusan National University, Busan 609-735, Korea

E-mail: ucyeon@pusan.ac.kr

Received September 27, 2007

The key step in a strategy for the synthesis of (+)-lactacystin involving photocyclization reaction of a cyclopenta-fused pyridinium salt has been probed by using a model substrate. Observations made in this effort led to the discovery of a highly unusual cascade process that leads to stereoselective formation of an interesting tricyclic carbamate. The results of this study are presented and discussed in the context of a (+)-lactacystin synthetic approach.

**Key Words :** (+)-Lactacystin, Cyclopenta-fused pyridinium salt, Photochemistry

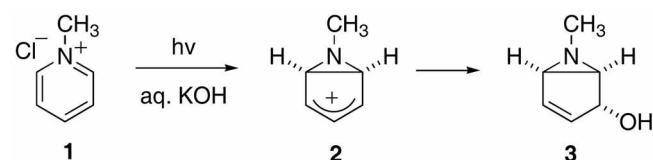
### Introduction

Studies in our laboratory during the past two decades<sup>1-3</sup> have led to the development and synthetic applications of a novel photochemical reaction of pyridinium salts, discovered by Wilzbach, Kaplan and Pavlik in the early 1970s.<sup>4</sup> In the early investigation by Wilzbach and his coworkers, it was observed that irradiation of a basic aqueous solution of *N*-methylpyridinium chloride **1** results in stereocontrolled formation of the bicyclic allylic alcohol **3** (Scheme 1). The authors proposed that this process takes place by excited state electrocyclicization (a photo-Nazarov cyclization) to produce the intermediate bicyclic allylic cation **2**, which then undergoes addition of hydroxide to the least sterically hindered exo-face. Later in a study of pyridinium salt electron transfer photochemistry we observed that irradiation of *N*-allyl- or *N*-methyl-pyridinium perchlorate **4** in methanol leads to efficient formation of the trans,trans-3,5-dimethoxyaminocyclopentenes **6** (Scheme 2).<sup>5</sup> Further investigation of this process demonstrated that the cyclopentene products arise by stereoselective ring opening of the initially formed

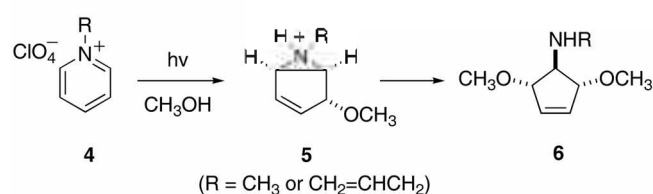
bicyclic ammonium cations **5**.

In the intervening years, we probed several features of pyridinium salt photoreactions as part of a program aimed at demonstrating its applications to syntheses of amino-cyclitols,<sup>6-9</sup> amino sugars,<sup>10</sup> and polyhydroxylated indolizidines.<sup>11,12</sup> In a more recent effort we showed that irradiation of a basic aqueous solution of the cyclopenta-fused pyridinium perchlorate **7** results in regioselective and stereoselective generation of the tricyclic allylic alcohol **8** (Scheme 3).<sup>13</sup> Furthermore, we observed that **8** can be transformed to spirocyclic amino diol derivatives related to **9**.

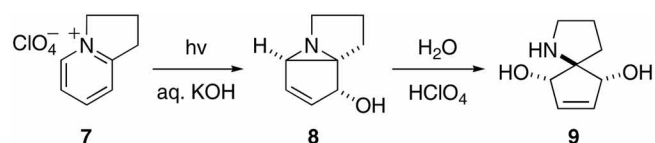
An interesting feature of the sequence shown in Scheme 3 is that it produces an  $\alpha,\alpha$ -disubstituted pyrrolidine ring system that would be difficult to generate by other routes. We believed that this unique characteristic might make the photochemical based methodology applicable to synthetic



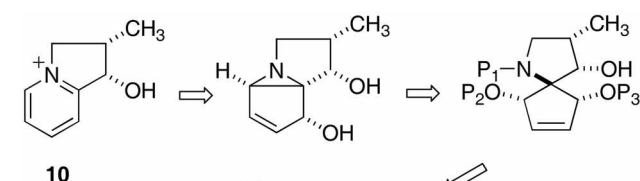
Scheme 1



Scheme 2



Scheme 3



11 (+)-lactacystin

Scheme 4

routes targeted at biomedically interesting natural products. In order to explore this proposal, we designed a new strategy for the synthesis of the biologically interesting proteasome inhibitor<sup>14-17</sup> (+)-lactacystin **11**, which has been the target of several earlier synthetic studies.<sup>18-26</sup> The plan relies on photocyclization reaction of the cyclopenta-fused pyridinium salt **10** (Scheme 4) and it incorporates a cyclopentene ring cleavage protocol that is patterned after methodology we developed earlier as part of routes for the synthesis of 3-aminoaldo pentenoses.<sup>10</sup>

In an investigation aimed at probing key steps in this lactacystin synthesis, we explored the preparation and photochemical behavior of the model pyridinium salt **17** (Scheme 5). Below we describe observations made in this preliminary effort which led to the discovery of a highly unusual cascade process that leads to a model of a potentially important intermediate in the preparation of the target.

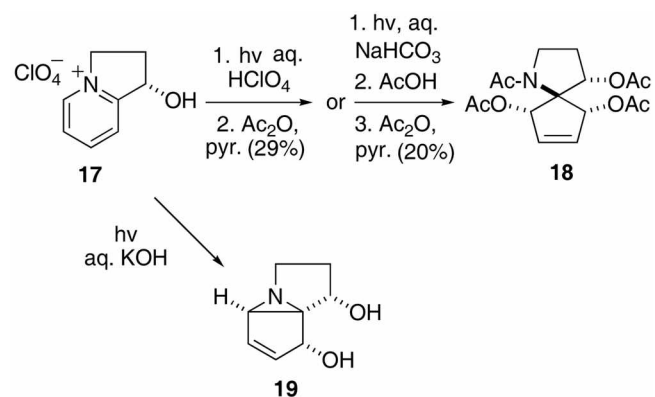
## Results and Discussion

Prior to embarking on the lactacystin synthesis following the route outlined in Scheme 4, we felt that it would be instructive to explore the preparation and photochemistry of the model cyclopenta-fused pyridinium salt **17**. This salt was produced by using the short route shown in Scheme 5 that begins with aldol reaction of pyridine 2-carboxaldehyde with the enolate of ethyl acetate. TIPS protection of the alcohol in the product of this process **12** followed by reduction of the ester moiety in **13** gives the selectively protected 2-pyridyldiol **14**. Corey-Kim type cyclization<sup>27</sup> of **14** forms the pyridinium chloride **16**, which is transformed to the target **17** by TIPS-deprotection and ion exchange.

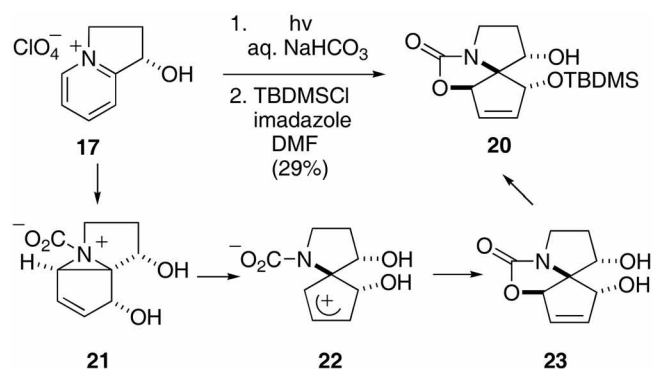
The photochemistry of **17**, unlike that of its non-hydroxyl counterpart **7**,<sup>13</sup> proved to be interesting and unusual. For example, irradiation ( $\lambda = 254$  nm) of a solution of **17** in aqueous perchloric acid, followed by treatment of the crude photolysate with acetic anhydride and pyridine and chromatographic separation led to isolation of the tetracetylated spirocyclic product **18** in a 29% yield (Scheme 6). Our earlier findings suggest that formation of **18** is likely due to *in situ* acid promoted ring opening of the initially formed *N*-protonated form of the tricyclic allylic alcohol **19** (Scheme 3). As expected, photoreaction of **17** in aqueous NaHCO<sub>3</sub> immediately followed by sequential treatment with acetic

acid and acetic anhydride/pyridine generates **18** in a 20% isolated yield. This process likely proceeds by way of initial formation of the tricyclic diol **19** which then undergoes acetic acid promoted aziridine ring opening and then triacetylation. In addition, the tricyclic diol **19** is produced in a only *ca.* 5% yield by irradiation of **17** in aqueous KOH (Scheme 6). Contributing to the low yield of **19** isolated in this process is its exceptionally high polarity, which makes extraction from aqueous solutions and chromatographic separation difficult. Moreover, although not proven the relative stereochemistry assigned to **19** is consistent with observations made in studies described below.

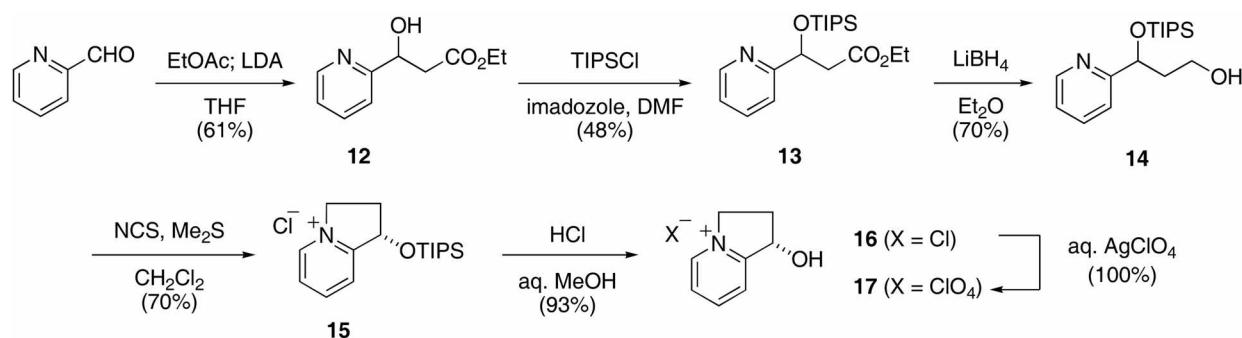
Quite unusually, when irradiation of an aqueous NaHCO<sub>3</sub> solution of **17** is followed by treatment of the concentrated photolysate with *t*-butyldimethylsilyl chloride and chromato-



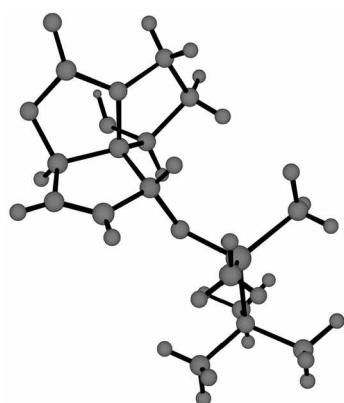
Scheme 6



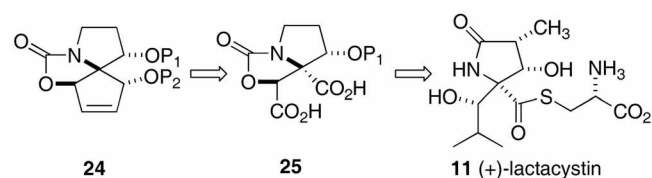
Scheme 7



Scheme 5



**Figure 1.** Chem-3D plot of the X-ray crystallographically derived coordinates of **20**.



**Scheme 8**

graphic separation, the tricyclic carbamate **20** is isolated in a 27% yield (Scheme 7). Owing to its unique structure and complex stereochemistry, **20** was characterized by using X-ray crystallographic analysis (Figure 1).

The complicated process producing diol **23**, the precursor of **20**, proceeds with a remarkable degree of stereochemical control. Specifically, the single chiral center in the starting pyridinium salt **17** directs installation of the other three stereocenters in **23**. A possible mechanistic scenario for the production of **23** begins with photochemical formation of the tricyclic diol **19** (Scheme 6). Liberation of CO<sub>2</sub> when the crude photolysate containing NaHCO<sub>3</sub> is treated with excess TBDMSCl, likely promotes reversible formation of the ammonium carboxylate **21**. Ring opening of **21** followed by carboxylate addition to the allylic cation moiety in **22** would then give **23**.

It is interesting that, despite its low yield, the reaction that transforms **17** to the tricyclic carbamate **20** is potentially compatible with the general strategy we have designed for the synthesis of (+)-lactacystin. Accordingly, an analogous process operating in the photochemistry of enantiomerically pure pyridinium salt **10** would produce the cyclic carbamate **24** (Scheme 8). Cyclopentene ring opening, hydroxyl inversion and selective side chain manipulation would furnish diacid **25** which contains all of the stereocenters with the same relative and absolute stereochemistry as in (+)-lactacystin. Despite this optimistic appraisal, work on this synthetic pathway will not be continued.

## Experimental Section

**General Procedures.** Commercial reagents were used as received, unless otherwise stated. Dynamic Absorbents silica

gel was used for chromatography, and Analtech silica gel plates with fluorescence F<sub>254</sub> were used for thin-layer chromatography (TLC) analysis. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker Advance 500, and chloroform-d was used as a solvent, unless otherwise stated. Chemical shifts are recorded in ppm with reference to solvent peaks at 7.26 ppm for CDCl<sub>3</sub> and at 4.80 ppm for D<sub>2</sub>O. Data for <sup>1</sup>H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Mass Spectra were obtained from University of New Mexico mass spectral facility.

**Compound 12.** To a solution of LDA, made from diisopropylamine (28.0 g, 0.28 mol) in THF (150 mL) and *n*-butyllithium (112 mL, 0.28 mol, 2.5 M in hexane), at -78 °C was added a solution of ethyl acetate (24.0 g, 0.27 mol) in THF (50 mL). After stirring at -78 °C for 1 h, a solution of 2-pyridinecarboxaldehyde (20.0 g, 0.19 mol) in THF (50 mL) was added. The resulting mixture was stirred overnight at room temperature, diluted with satd. aq. ammonium chloride and separated. The organic layer was dried and concentrated *in vacuo* to give the residue which was subjected to chromatography on silica gel (1:4 to 1:1 ethyl acetate-hexane) to provide 22.0 g (61%) of **12**. <sup>1</sup>H NMR 1.12 (m, 3H), 2.64 (q, *J* = 8.5 Hz, 1H), 2.80 (q, *J* = 4 Hz, 1H), 4.04 (q, *J* = 7 Hz, 2H), 5.09 (q, *J* = 4.5 Hz, 1H), 7.09 (q, *J* = 6 Hz, 1H), 7.34 (d, *J* = 8 Hz, 1H), 7.59 (m, 1H), 8.41 (t, *J* = 4 Hz, 1H); <sup>13</sup>C NMR 13.9, 42.3, 60.4, 69.9, 120.1, 122.3, 136.7, 148.3, 160.9, 171.7. HRMS (ES) *m/z* 196.0974, calcd for C<sub>10</sub>H<sub>14</sub>NO<sub>3</sub> 196.0977.

**Compound 13.** A solution of **12** (30.0 g, 0.15 mol), imidazole (16.0 g, 0.24 mol) and triisopropylsilyl chloride (40 mL, 0.19 mol) in DMF (50 mL) was stirred overnight at room temperature, diluted with satd. aq. sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with aq. sodium chloride, dried and concentrated *in vacuo* to give a residue which was subjected to column chromatography on silica gel (hexane to 1:4 ethyl acetate-hexane) to afford 26.0 g (48%) of **13**. <sup>1</sup>H NMR 0.96 (m, 21H), 1.15 (m, 3H), 2.77 (m, 2H), 4.04 (m, 2H), 5.34 (d, *J* = 5.5 Hz, 1H), 7.11 (d, *J* = 5 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.65 (d, *J* = 6 Hz, 1H), 8.46 (s, 1H); <sup>13</sup>C NMR 12.3, 14.0, 17.9, 44.6, 60.3, 73.3, 120.5, 122.2, 136.4, 148.4, 163.3, 170.6; HRMS (ES) *m/z* 352.2308, calcd for C<sub>19</sub>H<sub>34</sub>NO<sub>3</sub> Si 352.2303.

**Compound 14.** To a solution of **13** (5.0 g, 14 mmol) in ethyl ether (150 mL), was added a solution of lithium borohydride (15 mL, 30 mmol, 2 M in THF) at 0 °C. The resulting solution was stirred for 24 h at room temperature, diluted with satd. aq. sodium bicarbonate, and the organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo* to give a residue which was subjected to column chromatography on silica gel (1:4 to 1:1 ethyl acetate-hexane) to afford 3.1 g (70%) of **14**. <sup>1</sup>H NMR 1.01 (d, *J* = 22.5 Hz, 18H), 1.13 (m, 3H), 2.03 (q, *J* = 6.9 Hz, 1H), 2.20 (q, *J* = 5.5 Hz, 1H), 3.54 (t, *J* = 5.5 Hz, 1H), 3.68 (t, *J* = 5.5 Hz, 1H), 3.81 (s, 1H), 5.19 (d, *J* = 5.1 Hz, 1H), 7.17 (t, *J* = 5.7 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.4 Hz,

1H), 8.48 (s, 1H);  $^{13}\text{C}$  NMR 12.1, 17.9, 40.9, 59.1, 74.8, 120.4, 122.1, 136.8, 148.0, 163.9; HRMS (ES)  $m/z$  310.2202, calcd for  $\text{C}_{17}\text{H}_{32}\text{NO}_2\text{Si}$  310.2202.

**Compound 15.** To a solution of *N*-chlorosuccinimide (4.7 g, 35 mmol) in methylene chloride (150 mL) was added dimethylsulfide (2.8 mL, 38 mmol) at 0 °C. To the resulting mixture at -30 °C was added a solution of **14** (9.0 g, 29 mmol) in methylene chloride (20 mL). The resulting solution was stirred for 4 h at 0 °C, poured into satd. aq. Sodium chloride at 0 °C, and extracted with methylene chloride. The organic layers were dried and concentrated *in vacuo* to give a residue which triturated with acetonitrile and ethyl acetate to afford 8.6 g (90%) of **15**.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ) 0.97 (d,  $J = 4$  Hz, 18H), 1.12 (m, 3H), 2.28 (m, 1H), 2.86 (m, 1H), 4.57 (m, 1H), 4.78 (t,  $J = 9.5$  Hz, 1H), 5.73 (t,  $J = 7.5$  Hz, 1H), 7.82 (t,  $J = 7$  Hz, 1H), 7.98 (d,  $J = 8$  Hz, 1H), 8.36 (t,  $J = 7.5$  Hz, 1H), 8.64 (d,  $J = 6$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ) 13.3, 35.0, 58.0, 76.1, 126.0, 128.9, 142.8, 147.9; HRMS (ES)  $m/z$  292.2097, calcd for  $\text{C}_{17}\text{H}_{30}\text{NOSi}$  292.2102.

**Compound 16.** A solution of **15** (10.4 g, 32 mmol) in a mixture of distilled water (50 mL), conc. HCl (36%, 50 mL) and methanol (100 mL) was stirred overnight at room temperature, concentrated *in vacuo* to give a residue which triturated with acetonitrile and ethyl acetate to afford 5.0 g (93%) of the **16**.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ) 2.21 (m, 1H), 2.74 (m, 1H), 4.58 (m, 1H), 4.77 (m, 1H), 5.50 (t,  $J = 7.5$  Hz, 1H), 7.80 (d,  $J = 6.5$  Hz, 1H), 7.94 (d,  $J = 8.0$  Hz, 1H), 8.36 (t,  $J = 8.0$  Hz, 1H), 8.63 (d,  $J = 6.0$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ) 33.0, 58.1, 74.1, 125.9, 128.8, 142.6, 147.8, 159.5; HRMS (ES)  $m/z$  136.0689, calcd for  $\text{C}_8\text{H}_{10}\text{NO}$  136.0762.

**Compound 17.** A solution of **16** (1.0 g, 6 mmol) and silver perchlorate hydrate (1.1 g, 5.3 mmol) in distilled water (220 mL) was stirred for 4 h at room temperature and filtered. The filtrate was concentrated *in vacuo* to afford 0.65 g of **17**.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ) 2.19 (m, 1H), 2.74 (m, 1H), 4.58 (m, 1H), 4.77 (m, 1H), 5.49 (t,  $J = 7.5$  Hz, 1H), 7.79 (m, 1H), 7.93 (d,  $J = 8$  Hz, 1H), 8.36 (t,  $J = 8$  Hz, 1H), 8.62 (d,  $J = 6$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ) 32.8, 57.9, 74.0, 125.8, 128.7, 142.5, 147.6, 159.4; HRMS (ES)  $m/z$  136.0689, calcd for  $\text{C}_8\text{H}_{10}\text{NO}$  136.0762.

**Photoreaction of 17 in Aqueous Sodium Bicarbonate Followed by Sequential Treatment with Acetic Acid and Acetic Anhydride Producing 18.** A solution of **17** (0.65 g, 2.8 mmol) and sodium bicarbonate (0.6 g, 7.1 mmol) in water (600 mL) was irradiated for 11 h at room temperature (70% conversion), concentrated *in vacuo* to afford a residue, which was dissolved in anhydrous DMF (20 mL) and glacial acetic acid (2 mL). The resulting solution was stirred overnight at room temperature and then mixed with pyridine (2 mL) and acetic anhydride (2.5 mL), stirred overnight at room temperature, diluted with satd. aq. sodium bicarbonate and extracted with ethyl acetate (2 × 100 mL). The extracts were dried and concentrated *in vacuo* to give a residue which was subjected to column chromatography on silica gel (1:4 acetone-hexane) to afford 0.13 g (yield 20%) of **18**.  $^1\text{H}$  NMR 2.01 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.08 (s, 3H), 3.43 (m, 1H), 3.58 (m, 1H), 5.44 (q,  $J = 5.5$  Hz, 1H),

5.88 (m, 1H), 6.10 (m, 1H), 6.12 (s, 1H), 6.35 (s, 1H);  $^{13}\text{C}$  NMR 20.9, 21.0, 21.1, 23.5, 28.3, 45.4, 73.2, 75.9, 78.8, 79.0, 130.4, 134.6, 169.7, 169.9, 170.2; HRMS (ES)  $m/z$  340.1395 (M+1), calcd for  $\text{C}_{16}\text{H}_{22}\text{NO}_7$  340.1396.

**Photoreaction of 17 in Aqueous Perchloric Acid Followed by Treatment with Acetic Anhydride Producing 18.** A solution of **17** (0.6 g, 2.6 mmol) in water (600 mL) containing perchloric acid (2.5 mL, 70%) was irradiated for 14 h at room temperature (40% conversion), concentrated *in vacuo* to afford a residue, which was mixed with DMF (20 mL), pyridine (2 mL) and acetic anhydride (2.5 mL). The resulting mixture was stirred overnight at room temperature, diluted with satd. aq. sodium bicarbonate (20 mL), and extracted with ethyl acetate. The extracts were dried and concentrated *in vacuo* to give a residue, which was subjected to column chromatography on silica gel (1:4 acetone:hexane) to afford 0.10 g (29%) of **18**.

**Photoreaction of 17 in Aqueous Potassium Hydroxide Producing 19.** A solution of **17** (235 mg, 1 mmol, UV:  $\lambda_{\text{max}}$  266 nm) in  $\text{H}_2\text{O}$  (500 mL) containing KOH (112 mg, 2 mmol) was irradiated (RPR-2537 Å reactor lamps, Rayonet company) for 12 h (70% conversion). Concentration *in vacuo* was followed by extraction with  $\text{CHCl}_3$ . The extracts were filtered and concentrated *in vacuo*, giving a residue that was subjected to column chromatography (silica gel, 1:1 ethyl acetate/MeOH) to yield compound **19** (5%) as red oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 3.02 (m, 1H), 3.31 (m, 1H), 4.81 (s, 1H), 4.94 (s, 1H), 5.93 (d, 1H), 6.21 (d, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 29.7, 32.4, 48.1, 51.7, 70.4, 74.0, 135.4, 137.3; HRMS (ES)  $m/z$  154.0871 (M + 1), calcd for  $\text{C}_8\text{H}_{12}\text{NO}_2$  154.0868.

**Photoreaction of 17 in Aqueous Sodium Bicarbonate Followed by Treatment with *t*-Butyldimethylsilyl Chloride Producing 20.** A solution of **17** (0.6 g, 2.6 mmol) and sodium bicarbonate (0.6 g, 7.1 mmol) in water (600 mL) was irradiated for 10 h at room temperature (70% conversion) and concentrated *in vacuo* giving a residue, which was mixed with DMF (20 mL), imidazole (1.0 g, 15 mmol) and *tert*-butyldimethylsilyl chloride (1.0 g, 6.6 mmol). The resulting mixture was stirred overnight at room temperature, diluted with satd. aq. sodium bicarbonate and extracted with ethyl acetate. The extracts were dried and concentrated *in vacuo* to give a residue which was subjected to column chromatography on silica gel (1:4 acetone-hexane) to afford 0.13 g (yield 27%) of **20** as a crystalline solid, mp 152.1-152.9 °C (20:1 ethyl acetate-hexane)  $^1\text{H}$  NMR 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 2.15 (m, 2H), 3.22 (m, 1H), 3.73 (m, 1H), 4.42 (s, 1H), 4.56 (s, 1H), 5.55 (s, 1H), 5.97 (q,  $J = 1.5$  Hz, 1H), 6.06 (q,  $J = 1.5$  Hz, 1H);  $^{13}\text{C}$  NMR -5.1, -4.0, 17.9, 25.6, 34.6, 43.3, 70.1, 79.6, 81.4, 83.1, 132.1, 136.9, 161.1; HRMS (ES)  $m/z$  312.1638, calcd for  $\text{C}_{14}\text{H}_{26}\text{NO}_4\text{Si}$  312.1631.

**Acknowledgements.** PSM expresses his appreciation to the National Science Foundation for providing financial support (CHE-0506758) for this study. UCY acknowledges the Ministry of Information and Communication, Korea.

under the ITRC support program supervised by the Institute of Information Technology Assessment (IITA).

### References

1. Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.
  2. Mariano, P. S. *A New Look at Pyridinium Salt Photochemistry in Handbook of Organic Photochemistry and Photobiology*; Horspool, W., Ed.; CRC Press: 2003.
  3. Yoon, U. C.; Mariano, P. S. *Bull. Korean Chem. Soc.* **2006**, *27*, 1099.
  4. Kaplan, L.; Pavlik, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1972**, *94*, 3283.
  5. Yoon, U. C.; Quillen, S. L.; Mariano, P. S.; Swanson, R.; Stavinoha, J. L.; Bay, E. *J. Am. Chem. Soc.* **1983**, *105*, 1204.
  6. Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072.
  7. Cho, S. J.; Ling, R.; Kim, A.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 1574.
  8. Lu, H.; Mariano, P. S.; Lam, Y.-F. *Tetrahedron Lett.* **2001**, *42*, 4755.
  9. Feng, X.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2005**, *70*, 5618.
  10. Lu, H.; Su, Z.; Song, L.; Mariano, P. S. *J. Org. Chem.* **2002**, *67*, 3525.
  11. Song, L.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2004**, *69*, 7284.
  12. Zhao, Z.; Song, L.; Mariano, P. S. *Tetrahedron* **2005**, *61*, 8888.
  13. Zhao, Z.; Duesler, E.; Wang, C.; Guo, H.; Mariano, P. S. *J. Org. Chem.* **2005**, *70*, 8508.
  14. Omura, S.; Fujimoto, T.; Otogura, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113.
  15. Omura, S.; Fujimoto, T.; Otogura, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 117.
  16. Dick, L. R.; Cruikshank, A. A.; Grenier, L.; Melandri, F. D.; Nunes, S. L.; Stein, R. L. *J. Biol. Chem.* **1996**, *271*, 7273.
  17. Adams, J.; Stein, R. *Ann. Rep. Med. Chem.* **1996**, *31*, 279.
  18. Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 2293.
  19. Brennan, C. J.; Pattenden, G.; Rescourio, G. *Tetrahedron Lett.* **2003**, *44*, 8757.
  20. Page, P. C.; Leach, D. C.; Hayman, C. M.; Hamzah, A. S.; Allin, S. M.; McKee, V. *Synlett* **2003**, 1025.
  21. Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609.
  22. Iwama, S.; Gao, W.-G.; Shinada, T.; Ohfuné, Y. *Synlett* **2000**, 1631.
  23. Panek, J. S.; Masse, C. E. *Angew. Chem. Int. Ed.* **1999**, *38*, 1093.
  24. Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677.
  25. Corey, E. J.; Reichard, G. A.; Kania, R. *Tetrahedron Lett.* **1993**, *44*, 6977.
  26. Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; Omura, S.; Smith, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 5302.
  27. Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339.
-