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

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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 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. In the early investigation by Wilzbach and his coworkers, it was observed that irradiation of a basic aqueous solution of N-methylpyridinium chloride results in stereocontrolled formation of the bicyclic allylic alcohol (Scheme 1). The authors proposed that this process takes place by excited state electrocyclization (a photo-Nazarov cyclization) to produce the intermediate bicyclic allylic cation, 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 in methanol leads to efficient formation of the trans,trans-3,5-dimethoxyaminocyclopentenes (Scheme 2). Further investigation of this process demonstrated that the cyclopentene products arise by stereoselective ring opening of the initially formed bicyclic ammonium cations.

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, amino sugars, and polyhydroxylated indolizidines. In a more recent effort we showed that irradiation of a basic aqueous solution of the cyclopenta-fused pyridinium perchlorate results in regioselective and stereoselective generation of the tricyclic allylic alcohol (Scheme 3). Furthermore, we observed that can be transformed to spirocyclic amino diol derivatives related to.

An interesting feature of the sequence shown in Scheme 3 is that it produces an α,α-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
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 \(^{14-17}\) (+)-lactacystin \(^{11}\), which has been the target of several earlier synthetic studies. \(^{18-26}\) 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. \(^{10}\)

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\(^{27}\) 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-hydroxy counterpart \(^{7,13}\) 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\(_3\) 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\(_3\) solution of \(^{17}\) is followed by treatment of the concentrated photolyaste with \(t\)-butyldimethylsilyl chloride and chromatographic separation, a highly unusual cascade process that leads to a model of a potentially important intermediate in the preparation of the target.
gel was used for chromatography, and Analtech silica gel plates with fluorescence F254 were used for thin-layer chromatography (TLC) analysis. \(^1\)H and \(^1\)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\(_3\) and at 4.80 ppm for D\(_2\)O. Data for \(^1\)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 \(-78^\circ\text{C}\) was added a solution of ethyl acetate (24.0 g, 0.27 mol) in THF (50 mL). After stirring at \(-78^\circ\text{C}\) 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.** \(^1\)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); \(^1\)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\(_{10}\)H\(_{14}\)NO\(_3\)Si 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 ethyl acetate) to afford 26.0 g (48%) of **13.** \(^1\)H NMR 0.96 (m, 2H), 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); \(^1\)C NMR 12.3, 14.0, 17.9, 44.6, 60.3, 73.3, 120.5, 122.2, 136.4, 148.3, 163.3, 170.6; HRMS (ES) m/z 352.2308, calcd for C\(_{10}\)H\(_{14}\)NO\(_3\)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 (hexane to ethyl acetate-hexane) to afford 3.1 g (70%) of **14.** \(^1\)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).
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 0.13 g (yield 20%) of 15. HRMS (ES) m/z 312.2202, calcd for C₁₇H₃₀NOSi 312.2102.

Compound 16. A solution of 15 (1.0 g, 32 mmol) in a mixture of distilled water (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 16. HRMS (D₂O) 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); ¹³C NMR (D₂O) 33.0, 58.1, 74.1, 125.9, 128.8, 142.6, 147.8, 159.5; HRMS (ES) m/z 292.2097, calcd for C₁₉H₂₈NO₇S 292.2102.

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. HRMS (D₂O) 2.19 (m, 1H), 2.74 (m, 1H), 4.58 (m, 1H), 4.77 (m, 1H), 5.50 (t, J = 7.5 Hz, 1H), 7.79 (m, 1H), 7.93 (d, J = 8.0 Hz, 1H), 8.36 (t, J = 8.0 Hz, 1H), 8.62 (d, J = 6 Hz, 1H); ¹³C NMR (D₂O) 32.8, 57.9, 74.0, 125.8, 128.7, 142.5, 147.6, 159.4; HRMS (ES) m/z 136.0689, calcd for C₇H₁₂NO 136.0762.

Photoreaction of 17 in Aqueous Potassium Hydroxide Producing 19. A solution of 17 (235 mg, 1 mmol, UV: λₘᵡₓ 266 nm) in H₂O (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 CHCl₃. 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. HRMS (CDCl₃) 3.02 (m, 1H), 3.31 (m, 1H), 4.81 (s, 1H), 4.94 (s, 1H), 5.93 (d, 1H), 6.21 (d, 1H); ¹³C NMR (CDCl₃) 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 C₇H₁₄NO 154.0868.

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