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The Swern Oxidation: Development of a High-Temperature Semicontinuous Process

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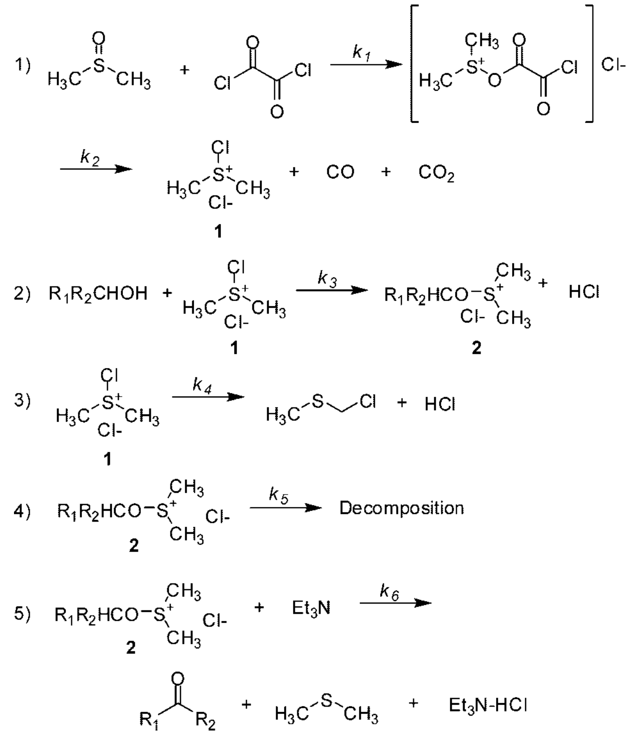
Abstract:

The Swern oxidation has been widely exploited for the oxidation of alcohols to their respective carbonyl compounds. The cryogenic operating conditions (<-60 °C) employed for the Swern oxidation, however, limit its utility for scale-up operations. Process development efforts on the Swern oxidation have demonstrated that an in-line reactor system can be used for the successful formation of the alkoxysulfonium salt precursor of the carbonyl compound. Two reagent streams, consisting of the alcohol/dimethylsulfoxide/methylene chloride and the oxalyl chloride, are loaded at ambient temperature to an in-line reactor, allowing the temperature to rise to 40 °C. The alkoxysulfonium chloride intermediate is discharged directly into triethylamine to complete the reaction. Residence times of 0.1−1.4 s in the in-line reactor were demonstrated to produce successful results in 750-gal pilot-plant equipment.

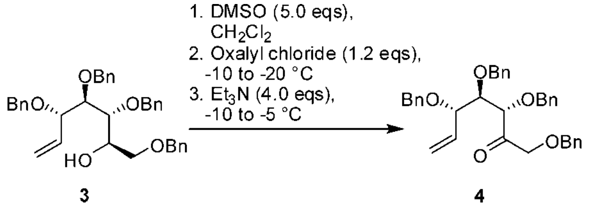
Introduction

The combination of dimethylsulfoxide (DMSO) with an electrophilic species to form "activated DMSO"[1–9] has been widely exploited for the oxidation of alcohols to their respective carbonyl compounds. Research by Daniel Swern demonstrated that oxalyl chloride was particularly suitable for use as the electrophilic partner.[10,11] The combination of oxalyl chloride and DMSO typically affords high conversion of the alcohol to the carbonyl compound and demonstrates good functional group selectivity. In the classical Swern oxidation, dimethylsulfoxide is added to a cold (<-50 °C) solution of oxalyl chloride in an inert solvent. This results in the rapid evolution of carbon dioxide and carbon monoxide and the formation of the "activated" DMSO intermediate **1** (Scheme 1, eq 1). The addition of the alcohol results in the formation of the alkoxysulfonium chloride intermediate **2** (Scheme 1, eq 2), which is subsequently converted to the desired carbonyl compound by the addition of a tertiary amine, commonly triethylamine (Scheme 1, eq 5).

Scheme 1. **Swern oxidation reaction steps**



Scheme 2. **Preparation of heptenulose 4**



The problem associated with the Swern oxidation from an industrial viewpoint is the formation of the "activated" DMSO intermediate **1** at low (−50 to −60 °C) temperatures. The intermediate **1** is unstable at or above about −20 °C,[12] decomposing to afford chloromethyl methyl sulfide. The Swern oxidation has been conducted at −10 °C, but a 100% excess of the oxidant was employed to compensate for its loss due to the formation of chloromethyl methyl sulfide.[11] A nonclassical approach to the Swern oxidation was developed to support the preparation of heptenulose **4** (Scheme 2). Previous preparations of **4** were carried out with *N,N′*-dicyclohexyl carbodiimide/DMSO,[13] pyridinium chlorochromate,[14] or trifluoroacetic anhydride/DMSO.[15] In the nonclassical approach to the Swern

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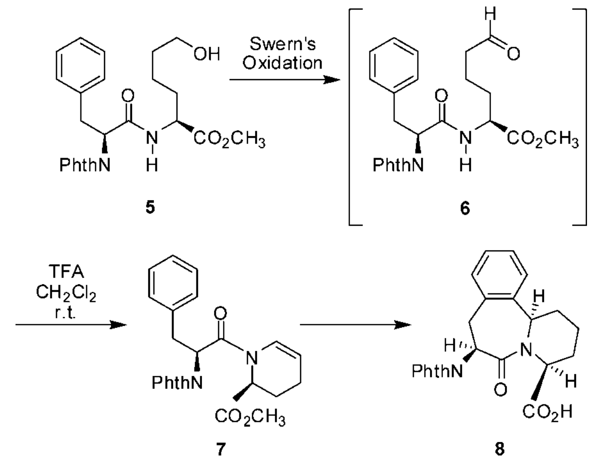
Scheme 3. **Preparation of the tricyclic acid 8**



oxidation, oxalyl chloride is added to a solution of the alcohol **3** and dimethylsulfoxide, while maintaining the temperature between −10 and −20 °C. Under these conditions the "activated" DMSO intermediate **1** is formed as a transient species which is rapidly consumed by the alcohol **3** to form the alkoxysulfonium chloride **2**. Addition of triethylamine afforded the ketone **4** in approximately 75% yield. This approach reduced the oxalyl chloride required for the conversion at higher temperatures and worked well at the 1-L reactor scale. At the 100-gal scale longer oxalyl chloride addition times were required to maintain the temperature at −10 to −20 °C. The extended oxalyl chloride addition time resulted in poor conversion (<10%) of **3** to **4** and the formation of numerous impurities. This behavior was attributed to the decomposition of intermediate **2** during the longer addition times required at the 100-gal scale. Consequently, the order of reagent addition was preserved, but cryogenic conditions (<−50 °C) were employed for the balance of the campaign, affording the ketone **4** in an average yield of 67%.[16] A subsequent request for the production of the tricyclic acid **8**[17] (Scheme 3) prompted a renewed investigation into the Swern oxidation.

Results and Discussion

The difficulties associated with the nonclassical approach to the Swern oxidation were attributed to the instability of the intermediate alkoxysulfonium salt **2**. Consequently, a reactor design which minimized the hold time of **2** prior to the reaction with triethylamine was evaluated. A conceptual drawing of the reactor design is shown in Figure 1. In this approach, a mixture of the alcohol **5**, dimethylsulfoxide, and methylene chloride is mixed with oxalyl chloride in a short "pipe" line under conditions of turbulent flow. The oxalyl chloride can be used neat or dissolved in methylene chloride.

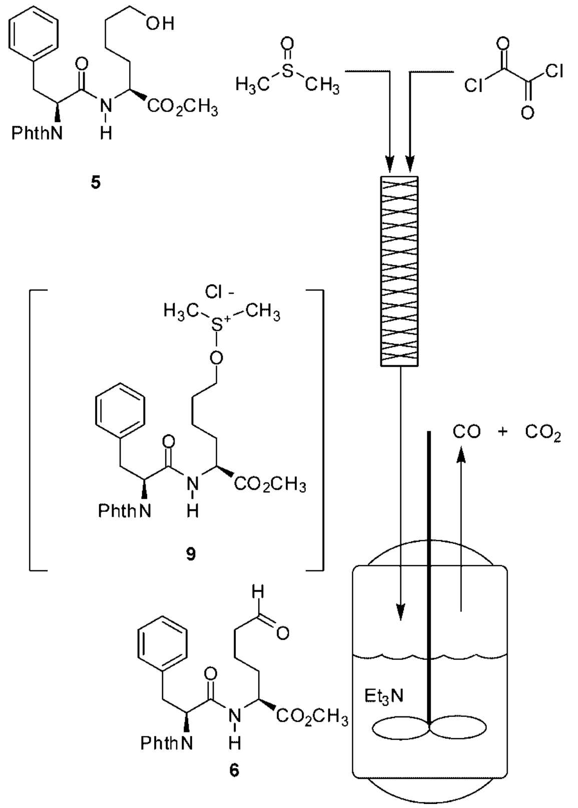


Figure 1. **Design of in-line reactor.**

Table 1. **Stoichiometry and residence times for the in-line Swern oxidation**

run	wt % 5	5 (g)	DMSO (equiv)	$(COCl)_2$ (equiv)	volumetric flow rate (mL/min)[a]	residence time (s)[b]	yield (%) 7[c]
1	13.5	13.50	10.72	2.62	378	0.56	74
2	13.5	13.55	5.31	1.28	162	1.30	79
3	13.5	13.55	7.97	1.97	241	0.87	81
4	7.2	7.16	7.81	1.91	127	1.65	72
5	13.5	13.51	7.99	1.96	479	0.44	80
6	13.5	13.08	7.99	1.96	468	0.45	76
7	13.5	69.89	10.81	1.99	1451	0.14	72
8	13.5	64.03	10.80	1.92	1078	0.19	81
9	13.5	60.07	10.88	1.31	715	0.29	74
10	13.5	60.26	10.98	1.76	937	0.22	84
11	13.5	60.34	11.01	1.30	615	0.86	75
12	13.5	54.27	10.81	1.57	728	0.73	79
13	8.9	45.79	10.83	1.84	553	0.95	79

[a] The volumetric flow rate is the combined flow rate of the liquid reagent streams to the in-line mixer plus the volume of gas generated at STP. [b] Residence times were determined by dividing the volume of the in-line mixer by the total volumetric flow rate (liquid plus gas flow). [c] Yield determinations were made by wt % assay of the acylenamine **7** solutions against an analytical standard.

The "activated" alcohol **9** forms rapidly under these conditions and is discharged directly into a methylene chloride solution of triethylamine with concomitant disengagement of the carbon dioxide and carbon monoxide.

The stoichiometry and residence times evaluated are summarized in Table 1. The alcohol **5** was available as a solution in methylene chloride from a previous pilot-plant campaign. In practice, the aldehyde **6** produced from the in-line Swern oxidation was not purified but converted directly to the acylenamine **7**, for which an analytical standard was available. Acid-catalyzed ring closure of aldehydes structurally similar

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(16) The 1-L and 100-gal nonclassical Swern oxidation results are unpublished data from work conducted at the Dow Chemical Company.

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Figure 2. **Photograph of laboratory in-line mixer.**

to **6** have been reported in the literature to proceed in high yield (>98%),[18,19] although lower yields (55−77%) have been described.[20–22] A purified sample of aldehyde **6** has been converted directly to the tricyclic acid **8** in a 51% yield.[23] The initial set of runs (1−13 of Table 1) was directed at establishing rough operating ranges for the chemistry. The oxalyl chloride/methylene chloride solution and the alcohol **5**/DMSO/methylene chloride solution were delivered to the in-line mixer (Figure 2) using a dual syringe pump. The load lines were submersed in a dry ice/acetone bath to chill the streams prior to mixing, and the in-line static mixer was jacketed at about −5 °C. The inlet temperature of the oxalyl chloride solution was −20 to −10 °C. The outlet temperature from the in-line mixer was not measured for runs 1−3. A thermocouple was installed, however, for runs 5−13 to allow for the determination of the solution outlet temperature. A 3−16 wt % solution of triethylamine in methylene chloride was charged to the quench reactor, which was jacketed at −5 °C. The quench temperature did not exceed 7 °C during this set of runs. The mole ratio of DMSO to oxalyl chloride was held fairly constant at 4/1, but the stoichiometry relative to **5** was varied, as was the residence time in the in-line mixer. Despite the range in reagent stoichiometry and residence times, the average solution yield of **7** (76.5%) for runs 1−13 was within about ±4% of the yield range. The methylene chloride solution of **7**, prepared from runs 3 and 4, was subsequently converted to the tricyclic acid **8** in a recrystallized yield of 47% and 40%, respectively. This was lower than the expected yield of 54% typically observed from the nonclassical batch Swern oxidation. Consequently, a nonclassical Swern oxidation was carried out with the alcohol feed used for the in-line procedure and afforded **8** in only 45% yield. The lower yields were attributed to the age of the alcohol solution which had been in cold storage for 4 years.

Two processing changes were evaluated for runs 5 and 6. The feeds to the in-liner mixer, as well as the mixer itself, were not chilled, and for entry 6 the oxalyl chloride was loaded neat to the in-line mixer. The reagent stoichiometry and residence times were kept constant between the two runs. The yield of **7** was 80% and 76%, respectively. Compound **7**, from run 5, was converted to **8** in 47% recrystallized yield, comparable to the nonclassical Swern oxidation result.

Runs 7−10 represent a greater than 4-fold scale-up over the previous runs. The DMSO loading was held at 10.8−11.0 equiv relative to the alcohol **5** and the oxalyl chloride loading varied (1.3−2.0 equiv). As in run 6, the oxalyl chloride was loaded neat, and no cooling was applied to the load lines or in-line mixer. A residence time of about 0.2 s was targeted for the reaction. In addition, the triethylamine for these runs was charged to the quench vessel without methylene chloride as a diluent. The quench vessel was jacketed at 15 °C during run 7. Consequently, a maximum quench temperature of about 35 °C was realized during the reaction. The triethylamine quench for runs 8−10 was carried out at a jacket temperature of −10 °C, affording a maximum in pot temperature of 25 °C. The lower yield obtained from run 7 (72%) was attributed to the higher quench temperature. Runs 8−10 afforded **7** in 74−84% yields. In subsequent runs the quench vessel was jacketed at −10 to −15 °C to moderate the temperature rise. Methylene chloride was also used as a diluent to provide additional mass as a heat sink.

Runs 11−13 were conducted in much the same way as runs 7−10. The major changes made were an increase in the residence time and methylene chloride was combined with the triethylamine in the quench vessel for all the runs. The average yield of compound **7** was 77%. Concurrent process development efforts on improving the recovery of the tricyclic acid **8** enabled the isolation of **8** in an average recrystallized yield of 53%. The temperature profile for run 12 is shown in Figure 3.

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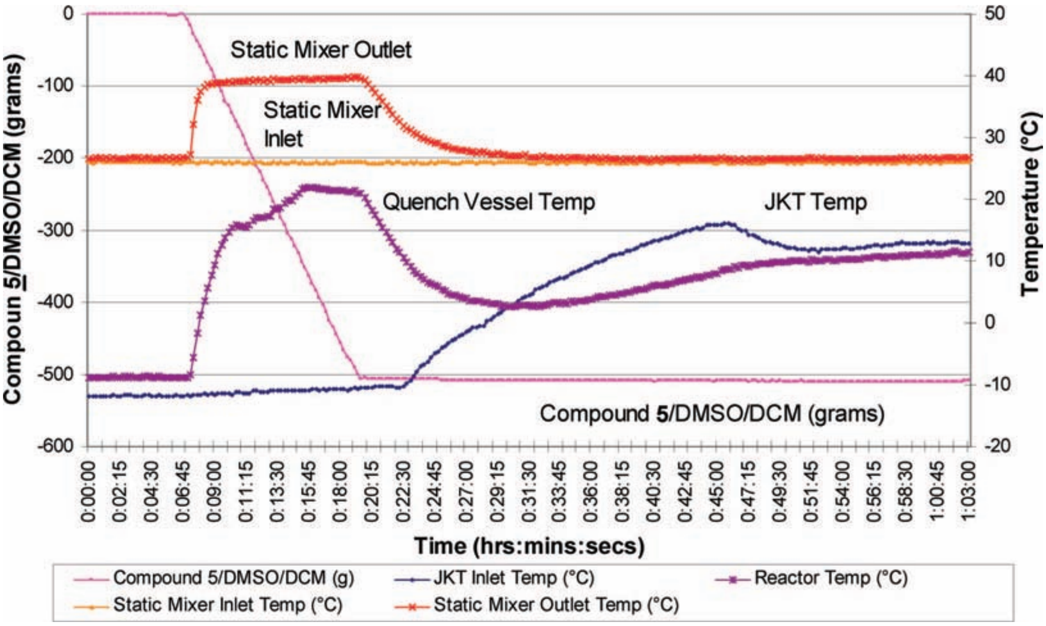

Figure 3. **Temperature profile for run 12.**

Figure 4. **Diagram of pilot-plant in-line reactor.**

The exothermic reaction to form the intermediate alkoxysulfonium salt **9** is clearly visible, occurring rapidly as the reagent streams are mixed and resulting in a temperature rise from ambient to the boiling point of the methylene chloride.

The laboratory investigation demonstrated that acceptable yields of compound **7** could be achieved using a range of residence times (0.14−1.7 s) and reagent stoichiometry. The chemistry was subsequently transferred to the pilot plant for scale-up. The stoichiometry targeted for pilot-plant scale-up was DMSO (10.8 equiv), triethylamine (5.8 equiv) and oxalyl chloride (1.5−1.6 equiv). The oxalyl chloride loading was adjusted, as needed, to compensate for the water content of the alcohol **5**/DMSO/methylene chloride solution in order to ensure 1.5−1.6 equiv for the oxidation. A diagram of the in-line reactor used for the scale-up is shown in Figure 4. The reagents streams were delivered into the in-line reactor at right angles, directed through two 90° elbows leading to a straight length of pipe and then discharged directly into the reactor headspace. The internal diameter was 2.1 in., and the in-line reactor had a total length of 31.5 in. The superficial velocity through the in-line reactor was about 8 m/s, affording a residence time of about 0.1 s. The alcohol **5**/DMSO/methylene chloride solution was loaded to the in-line reactor at a targeted rate of 15.3 lbs/min for all of the scale-up batches. The oxalyl chloride target flow rate ranged from 0.78 to 0.82 lbs/min, depending on the water content of the alcohol solution. The rapid evolution of 2 moles of gas per mole of oxalyl chloride within the in-line reactor can contribute to back mixing. In order to eliminate this concern, a one standard cubic feet per minute (SCFM) nitrogen sweep through the in-line reactor was conducted to ensure plug flow conditions and to provide for decreased residence times. The pressure build within the in-line reactor was less than 25 psig during operation. The quench vessel was a 750-gal, glass-lined steel reactor equipped with a retreat curve impeller agitator loaded with triethylamine. The reactor contents were chilled to less than −10 °C prior to the loading of the in-line reactor. The maximum quench temperature realized during the campaign was approximately 10 °C. The gas generated during the in-line Swern oxidation was directed to a 1000-gal, glass-lined steel reactor equipped with a retreat curve impeller agitator. Water was loaded to the 1000-gal reactor to provide some capture for adventitious hydrogen chloride from the process. The aldehyde **6** prepared from the in-line Swern oxidation was converted to compound **7** without isolation. The methylene chloride solution of compound **7** was subjected to solvent exchange into *n*-butyl acetate, followed by crystallization and drying to afford the desired product for the pilot-plant campaign. The pilot-plant scale-up proceeded well. Fourteen batches were executed, converting 6075 lbs of the alcohol **5** to 3525 lbs of compound **7**, for an overall crystallized yield of 61%.

Conclusions

Laboratory studies demonstrated that a "high" temperature semicontinuous in-line Swern oxidation could be successfully carried out. The process was successfully transferred to the pilot plant with the execution of 14 750-gal batches, affording an isolated yield of compound **7** in 61% from the alcohol **5**. The in-line process is scaleable to standard fine chemical manufacturing plants. Cryogenic operations, as required for the classical Swern oxidation, require specialized pipe, valve, pump, and vessel specifications. Since the rate of gas evolution from the in-line process is directly proportional to the feed rates, uniform gas evolution is realized during the oxidation providing an advantage for vent gas incineration systems.

Experimental Section

General. HPLC analyses were performed on a Zorbax SB-Phenyl (4.6 mm × 250 mm) column at 210 nm and an injection volume of 10 μL. Separation was carried out using a gradient at 2 mL/min. Eluent A: 35/65 (v/v) CH_3CN/water (pH 2.2−2.5 with H_3PO_4). Eluent B: CH_3CN. Gradient profile: 100% A (10 min) to 75% A (over 20 min) to 50% A (over 10 min) with a 5 min hold. Weight % assay determinations were made using analytical standards of compounds **5**, **7**, and **8**.

2-Pyridinecarboxylic Acid, 1-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-methyl Ester, Compound 7. A 13.5 wt % methylene chloride solution of (*S*)-*N*-[2-(1,3-dihydro-1,3-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-6-hydroxy-(*S*)-norleucine methyl ester **5** (412.4 g, 0.127 mol) and dimethylsulfoxide (107.2 g, 1.37 mol) were combined in a pump delivery bottle. Oxalyl chloride (33 mL) was loaded to a 50-mL gastight syringe and placed on a Harvard 33 syringe pump. Triethylamine (74.31 g, 0.734 mol) was loaded to a 1-L jacketed glass bottom drain reactor. The reactor jacket was set to full cooling (∼−10 °C), and the triethylamine cooled to about −6 °C with stirring.

The oxalyl chloride delivery rate was set at 1.351 mL/min, and the delivery rate for the alcohol **5**/DMSO/methylene chloride solution was set to approximately 33 mL/min using a model 187-000-010 pump by MicroPump, Inc. Simultaneous addition was started with a total addition time of 12.53 min. The mass of the **5**/DMSO/methylene chloride solution delivered to the system was 506.5 g, resulting in the delivery of oxalyl chloride (16.92 mL, 24.62 g, 0.194 mol, 1.56 equiv), compound **5** (54.3 g, 0.124 mol) and DMSO (104.5 g, 1.337 mol, 10.8 equiv) to the in-line mixer. The inlet temperature of the oxalyl chloride was about 26 °C, and the outlet temperature of the in-line mixer was about 40 °C. The maximum temperature observed in the quench reactor was 22 °C.

The reactor jacket set point was increased to 12 °C, the slurry stirred for 50 min and then was transferred to a 3-L jacketed glass bottom drain reactor jacketed at 12 °C. The quench vessel was rinsed with methylene chloride and the rinse added to the 3-L reactor. Water (419.3 g) was added to the stirred slurry, resulting in the dissolution of the solids and the formation of a two-phase mixture. Stirring was continued for 30 min, agitation stopped, and the phases were allowed to settle for 60 min. The phases were separated. The upper aqueous phase (557.4 g) was discarded, and the lower organic phase (458.1 g) was returned to the 3-L reactor.

A solution of Oxone (150.0 g) in water (942.6 g) was added to the stirred methylene chloride solution during 45 min, maintaining the temperature during the addition less than 30 °C, to allow for the oxidation of the odorous dimethyl sulfide. Stirring was continued for 45 min and then settled for 45 min. The phases were separated. The upper aqueous phase (1104.7 g) was discarded. The lower organic phase (363.1 g) was returned to the 3-L reactor. A solution of 37% hydrochloric acid (471.6 g) was added. The mixture stirred for 30 min, settled for 30 min, and the phases were separated. The upper aqueous phase (499.6 g) was discarded. The lower organic phase (307.9 g) was transferred to a sample bottle. The 3-L reactor was rinsed with methylene chloride (61.96 g) and the rinse transferred to the sample bottle.

A magnetic stir bar was placed in the sample bottle containing the crude aldehyde **6** solution. Anhydrous magnesium sulfate (48.58 g) was added to the solution. To the stirred slurry was added trifluoroacetic acid (4.2 mL). The sample bottle was capped and stirred at room temperature for 16 h 25 min. The reaction slurry was vacuum filtered, and the filter cake washed with methylene chloride (67.79 g). The combined filtrate (294.1 g) was transferred to a sample bottle. HPLC analysis gave 13.94 wt % of the acylenamine **7** for a conversion yield across the two steps of 79%.

[4*S*-(4α,7α,12b*β*)]-7-(1,3-Dihydro-1,3-dioxo-*2H*-isoindol-2-yl)-1,2,3,4,5,6,7,8,12b-octahydro-6-oxopyrido[2,1-*a*][2]-benzaepine-4-carboxylic Acid, Compound 8. Trifluoromethanesulfonic acid (55.7 g, 0.371 mol), trifluoroacetic anhydride (11.66 g, 0.0552 mol) and methylene chloride (26.5 g) were combined in a 500-mL round-bottom flask and chilled in an ice bath. To the stirred solution was added 97.5 g of the 13.94 wt % methylene chloride solution of the acylenamine **7** (13.59 g, 32.5 mmol) at such a rate that the temperature did not exceed 10 °C. The resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was added to 240 g of stirred ice in a 1-L flask. The phases were separated, and the lower organic phase washed with water (2 × 240 mL).

The organic phase (139.9 g) was concentrated on a rotary evaporator at room temperature, affording 22.85 g of residue. Acetonitrile (48 g) was added with stirring to afford a solution. On continued stirring at room temperature a slurry developed. The slurry was stirred overnight, chilled in an ice bath, and collected by vacuum filtration. The product filter cake was washed with cold (<10 °C) acetonitrile and vaccuum dried to a constant weight. A yield of 10.16 g (70%) of the acetonitrile solvate of compound **8** was produced. The overall yield from the starting alcohol **5** was 55%.

Pilot-Plant Preparation of the Acylenamine 7. Approximately 3627 lbs of city water was loaded to a 1000-gal reactor in preparation to receive the vent gases from the 750-gal reactor. The 750-gal reactor was dried under vacuum and loaded with about 1871 lbs of a methylene chloride solution of the alchohol **5** and 954 lbs of dimethylsulfoxide through a dip pipe. About 1217 lbs of additional methylene chloride was loaded to obtain a final solution that was approximately 12 wt % in the alcohol **5**. The reactor contents were mixed, and a sample was taken to measure water content. Water content for these batches was used to determine the oxalyl chloride charge rate. The solution was drained from the 750-gal reactor and filtered through a 0.2 μm filter to two 330-gal totes. Filtering was critical to maintain the reliability of the magnetic drive positive displacement pumps. Triethylamine (657 lbs) was then pump loaded to the 750-gal reactor through the designated dip pipe and chilled to −10 °C.

About 225 lbs of oxalyl chloride was pump loaded to a portable reactor in preparation for the Swern oxidation. The two 330-gal totes were set up in parallel with a transfer line to the in-line reactor and a Coriolis flow meter in line. The two streams were mixed at a controlled rate in the in-line reactor. The reaction zone was 31.5 in. long with a 2.1 in. inside diameter. The alcohol **5**/DMSO/methylene chloride solution was loaded at 15.3 lbs/min and the oxalyl chloride at 0.78 to 0.82 lbs/min, depending on the water content of the alcohol solution. A 1 SCFM nitrogen sweep was applied to the in-line reactor to ensure uniform flow.

The aldehyde **6** slurry was transferred from the 750-gal reactor to the headspace of the agitated contents of the 1000-gal reactor. The contents were settled for 90 min, and the lower organic phase was returned to the 750-gal reactor. About 1251 lbs of 10% sodium hypochlorite was loaded to the 1000-gal reactor and mixed for 10 min, and the aqueous phase drained to a tote for incineration. The 1000-gal reactor was dried under vacuum at a jacket temperature of 100 °C for 15 min and then cooled. Oxone (849 lbs) was loaded through the manway and dissolved in 4889 lbs of city water. The methylene chloride product solution was slowly transferred from the 750-gal reactor to the stirred contents of the 1000-gal reactor at such a rate that the temperature did not exceed 25 °C. The contents were settled for 60 min, and the lower organic phase was returned to the 750-gal reactor. The pH of the 1000-gal reactor contents was adjusted to about 7 by the addition of 50 wt % sodium hydroxide and then drained to a waste tote for incineration. Water (3913 lbs) and 32% aqueous hydrochloric acid (301 lbs) were loaded to the 1000-gal reactor. The methylene chloride product solution was transferred from the 750-gal reactor to the 1000-gal reactor through the headspace and mixed. The phases were settled for 120 min. The lower organic phase was returned to the 750-gal reactor. The pH of the 1000-gal reactor contents were adjusted to about 7 by the addition of 50 wt % sodium hydroxide and drained to a waste tote for incineration.

Trifluoroacetic acid (54.5 lbs) was vacuum loaded through the dip pipe port into the 750-gal reactor. The water formed during the ring closure to the acylenamine **7** was removed by azeotropic distillation. The jacket was set to ΔT control with an offset of 10 °C and a limit of 60 °C. Distillation times varied from 8 to 16 h. Additional methylene chloride (565 lbs) was loaded, and the azeotropic distillation continued. The jacket system was set to ΔT control with an offset of 5 °C and a limit of 60 °C. Distillation times varied from 4 to 16 h. The bulk of the methylene chloride was then removed by distillation.

About 1172 lbs of *n*-butyl acetate was loaded to the 750-gal reactor, and the distillation was continued under reduced pressure until the volume in the reactor was about 70 gallons. The acylenamine **7** was crystallized from *n*-butyl acetate. The jacket setpoint (SP) was set to 10 °C with a ramp rate (RR) of 0.1 °C. When the jacket temperature was less than 24 °C, the SP was changed to −5 °C and a RR of 0.15 °C. When the jacket temperature was less than 10 °C the RR was decreased to 0.083 °C/min. When the jacket reached 0 °C, the product slurry was held for about 2 h. The product slurry was collected on a centrifuge, washed with 40 lbs of cold *n*-butyl acetate and 150 lbs of city water. The wet cake (4−14% LOD) was tumble dried under vacuum at 50 °C with a slight nitrogen purge to afford the acylenamine **7** as a finely divided white powder. The overall yield for the 14-batch campaign was 61%.

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