A Practical and Efficient Preparation of the Releasable Naphthosultam Side Chain of a Novel Anti-MRSA Carbapenem

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A practical large-scale synthesis of the naphthosultam-based side chain of the anti-MRSA antibiotic **1** has been achieved in 29% overall yield over seven steps from 1-methylnaphthalene. The synthesis was completed without the use of protecting groups, featuring a novel naphthosultam annelation, a chemoselective acid-catalyzed triflation, and the use of a novel naphthosultam dianion to effect functionalization through benzylic metalation.

Introduction

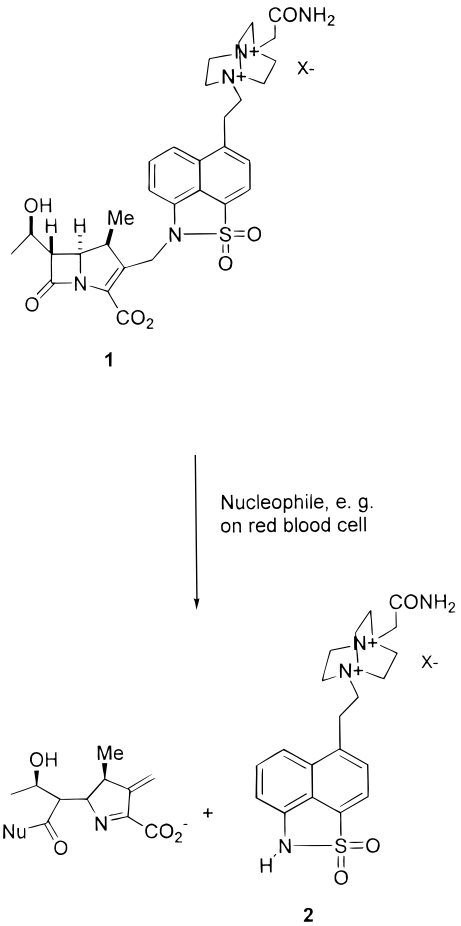
The Merck Research Laboratories have recently disclosed the novel β-lactam (**1**) as an anti-MRSA (Methicillin-resistant *Staphylococcus aureus*) antibiotic from a series of 1β-methyl-2-(naphthosultamyl)methyl cationic carbapenems.[1] The 1,8-naphthosultamyl side chain (**2**) was identified as a novel PBP2a-binding, anti-MRSA pharmacophore, designed to be released upon opening of the β-lactam ring (Scheme 1), in analogy to the cephalosporin and penem antibiotics.[2]

Our strategy for the synthesis of **1** relied on the highly convergent coupling of this naphthosultam side chain **2** with an appropriately substituted β-methyl carbapenem nucleus (Scheme 2).[3] The clinical needs of **1** as a potentially life-saving drug prompted us to develop a highly efficient and practical synthesis of **2**.

The initial synthesis of **1** was developed with the goal of defining structure−activity relationships which required divergence of intermediates and did not incorporate the entire naphthosultam fragment **2**.[1] Instead, the naphthosultam ethanol piece **3** (Scheme 3) was coupled and the diazabicyclooctane unit incorporated in an activation−displacement, two-step manner. Convergent retrosynthetic analyses that focus solely on the synthesis of **1** ideally incorporate the zwitterionic bis cation-(1,8-naphthosultam) DABCO-acetamide **2** as a complete unit and, herein, we report the attainment of the first convergent synthesis of this essential fragment.

Our retrosynthetic analysis (Scheme 3) highlights three important issues in the synthesis of compound **2**: (1) the availability and cost of the naphthalene starting material, (2) the method of installation of the sultam ring system, and (3) the method of incorporation of the cationic DABCO acetamide. Naphthylethanol **5** had been used previously as starting material in the initial synthesis (route A), but was extremely expensive compared to other naphthalene derivatives and not commercially available on large scale. Additionally, protection of the primary hydroxyl was needed in order to carry out the nitration and sulfonation. We envisioned 1-methylnaphthalene **4** as the starting material of choice as it would not require the use of a protecting group and was available from a wide variety of suppliers at low cost.[4]

Scheme 1



(1) Ratcliffe, R. W.; Wilkening, R. R.; Wildonger, K. J.; Waddell, S. T.; Santorelli, G. M.; Parker, D. L., Jr.; Morgan, J. D.; Blizzard, T. A.; Hammond, M. L.; Heck, J. V.; Huber, J.; Kohler, J.; Dorso, K. L.; St. Rose, E.; Sundelof, J. G.; May, W. J.; Hammond, G. G. *Biochem. Med. Chem. Lett.* **1999**, *9*, 679.

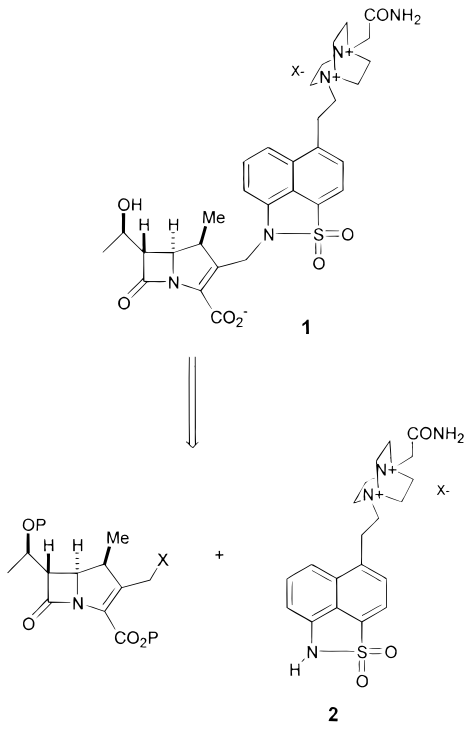
(2) (a) Wilkening, R. R.; Ratcliffe, R. W.; Wildonger, K. J.; Cama, L. D.; Dykstra, K. D.; DiNinno, F. P.; Blizzard, T. A.; Hammond, M. L.; Heck, J. V.; Dorso, K. L.; St. Rose, E.; Kohler, J.; Hammond, G. G. *Biochem. Med. Chem. Lett.* **1999**, *9*, 673. (b) Faraci, W. S.; Pratt, R. F. *Biochemistry* **1985**, *24*, 903. (c) Grabowski, E. J. J.; Douglas, A. W.; Smith, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 7, 268. (d) Perrone, E.; Jabes, D.; Alpegiani, M.; Andreini, B. P.; Bruna, C. D.; Nero, S. D.; Rossi, R.; Visentin, G.; Zarini, F.; Franceschi, G. *J. Antibiot.* **1992**, *45*, 589.

(3) Humphrey, G. R.; Miller, R. A.; Pye, P.; Rossen, K.; Ceglia, S. S.; Maliakal, A.; Volante, R. P.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **1999**, *121*, 11261.

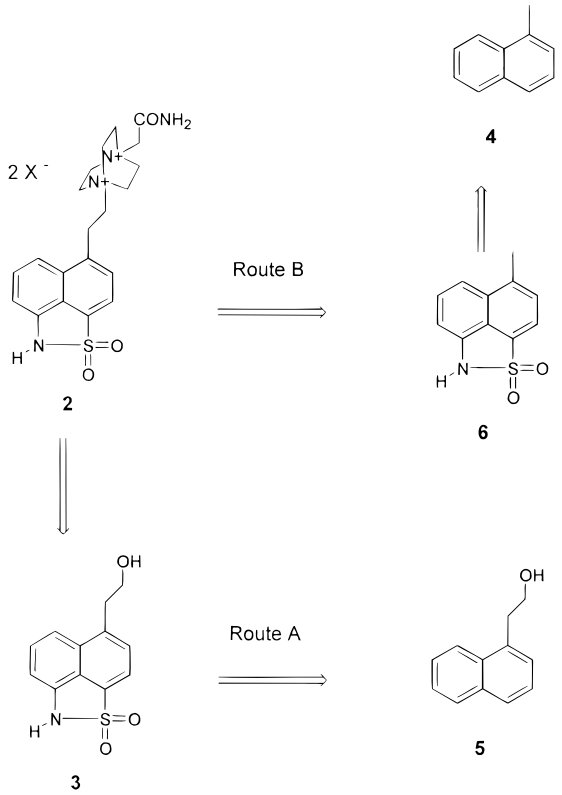
(4) At the time of writing, the cost of 1-methylnaphthalene was $4/kg and available in 55-gallon drum quantities.

10.1021/jo991490k CCC: $19.00
Published on Web 02/16/2000

Scheme 2

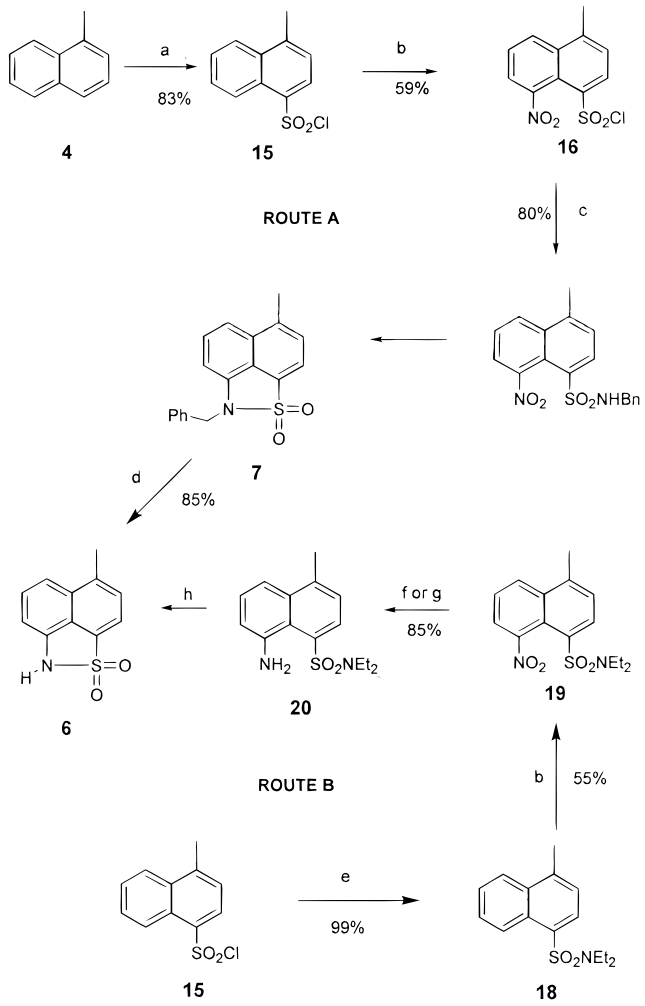


Scheme 3



Another option would be the preparation of naphthylethanol **5** from 1-methylnaphthalene **4**,[5] or from naphthylacetic acid.[6] However, a protecting group sequence would still be required. Thus, our approach was to use 1- methylnaphthalene as the key raw material, develop a practical methodology for the conversion to methyl-

Scheme 4[a]



[a] (a) 3 equiv of $ClSO_3H$; (b) HNO_3, H_2SO_4; (c) $BnNH_2$, K_2CO_3, 90 °C; (d) 10% Pd/C (50% wet), TEA, HCOOH, EtOH, 78 °C; (e) $HNEt_2$, IPA; (f) KO_2CH, 10% Pd/C; (g) 5% Pd/C, H_2; (h) HCl.

naphthosultam **6**, and last achieve functionalization through benzylic metalation to the naphthosultam ethanol **3**. Incorporation of the DABCO-acetamide fragment would then furnish our complete bis cation (1,8-naphthosultam) DABCO-acetamide **2** (route B).

Results and Discussion

Synthesis of the Methylnaphthosultam Core. Until now, synthetic strategies for the naphthosultam ring system have been limited to dehydration of the corresponding 1-amino-8-sulfonic acid using various phosphorus chloride reagents.[7] This ring-closure has been notoriously capricious, though recently patented processes claim to improve the methodology.[8] Alternatively, Merck Research Laboratories has uncovered a base-catalyzed intramolecular nucleophilic displacement reaction with a nitro leaving group to form the naphthosultam ring. Initially, we hoped to modify this strategy for the large-scale production of naphthosultam **6** (Scheme 4, route A).[9]

(5) Guggisberg, Y.; Faigl, F.; Schlosser, M. *J. Organomet. Chem.* **1991**, *415*, 1−6.

(6) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 38.

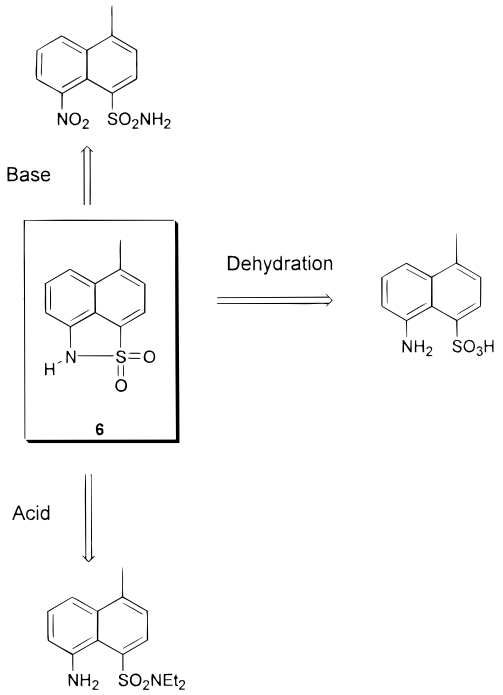
(7) Vesely, V.; Bubenik, H. *Collect. Czech. Chem. Commun.* **1939**, *11*, 412.

(8) (a) Korhummel, C. PCT Int. WO9821192A1. (b) Grondard, L.; Henriet, D. *P*CT Int. WO9736884A1.

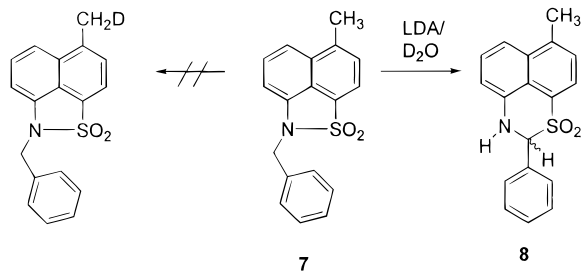
The chlorosulfonation of 1-methylnaphthalene proceeded in 83% isolated yield and >99:1 regioselectivity using chlorosulfonic acid. The chlorosulfonation was carried out by addition of a total of 3 equiv of chlorosulfonic acid to a suspension of 1-methylnaphthalene in trifluoroacetic acid (TFA). Addition of the first equivalent was carried out at 0−5 °C and gave rise to a rapid and exothermic formation of the sulfonic acid intermediate that was not isolated. After addition of the remaining chlorosulfonic acid and aging at 20 °C for 1 h, the reaction mixture was simply poured into cold water to crystallize the sulfonyl chloride **15** in 83% yield. Nitration of **15** proceeded smoothly with 1 equiv of fuming nitric acid in a mixture of 20% sulfuric acid in TFA.[10] The nitration gave rise to a 3:1 mixture of the required 8-nitro-isomer to the undesired 5-isomer. Carrying out the nitration under a number of other standard nitration conditions did not improve the regioselectivity. However, the minor regioisomer was easily removed by swishing the crude isolated solid with methyl *tert*-butyl ether or ethyl acetate/hexane, resulting in a 59% overall isolated yield of >99% isomerically pure 1,8-nitrosulfonyl chloride. The low cost of 1-methylnaphthalene starting material offset the inherent modest regioselectivity in this nitration. Formation of the sultam ring was achieved by direct addition of ammonia or benzylamine to the reaction mixture to form the nitrosulfonamides, respectively. The sulfonamides were cyclized by the addition of potassium carbonate and heating. In the case of the benzyl derivative, the yield (85%) and purity of the product **7** were superior to that of the ammonia derivative, and direct crystallization of the benzylsultam **7** was easily achieved from the reaction mixture by addition of water. Removal of the benzyl group under standard or transfer hydrogenation conditions furnished the key methyl NH naphthosultam **6**. The product was conveniently crystallized in >99% purity and 85% yield directly from the reaction mixture by the simple addition of water. This synthetic sequence was achieved without recourse to chromatography and consistently provided high-purity material.

During our scale-up demonstration, however, operational hazards analysis of the nitration reaction revealed that the **nitrosulfonyl chloride intermediate 16 was shock sensitive** and exhibited an extraordinarily high rate of temperature and pressure release (dT/dt = 17,-380 °C/min; dP/dt = 5234 psi/min) initiating at 42 °C.[11] In light of these findings, a revised synthesis of the key methyl naphthosultam **6** was evaluated (Scheme 4, route B). The methylnaphthalene sulfonyl chloride **15** was converted to the diethylsulfonamide **18** in quantitative yield by addition of diethylamine to a solution of the sulfonyl chloride **15** in 2-propanol. This substrate was then nitrated to give the nitrosulfonamide **19** under conditions similar to those used for the nitration of sulfonyl chloride **15**. Similar regiochemistry, rejection of the regioisomer, and isolated yield (55%) were observed. This intermediate did not possess the high-energy release of the nitrosulfonyl chloride, was not shock sensitive, and therefore was safely isolable. Cyclization of the nitrosulfonamide **19** to the required methylnaphthosultam was carried out using a novel one-pot hydrogenation−cyclization reaction. Reduction to the amine was accomplished cleanly under either standard hydrogen/catalyst or transfer hydrogenation conditions in quantitative yield. The intermediate aminosulfonamide (**20**) could be isolated or, more conveniently, was cyclized to the key methylnaphthosultam **6** upon acidification with hydrochloric acid and heating at reflux for 3 h. Crystallization directly from the reaction mixture was possible by simple addition of water and methylnaphthosultam **6** could be isolated in 85% yield (calculated from **19**) and in >99% purity. Thus, three different ways of forming the novel naphthosultam ring system have been explored with the newest methodology fulfilling all the requirements for a scalable synthesis (Scheme 5).

Scheme 5



Chain Extension of Methylnaphthosultam 6. Key to the use of methylnaphthalene as starting material was the chain extension of the sultam **6** to naphthosultam ethanol **3**. Lithiation of aromatic substrates have been extensively studied and have revealed that substituents on the ring have dramatic consequences for the regiochemical outcome of alkylation.[12] Attempted deprotonation of the N-protected sultam **7** with LDA or other bases gave no *C*-methyl benzylic lithiation; rather, the major product was an unusual rearrangement to an α-amino sulfone **8**, presumably from undesired directed metalation of the sultam.



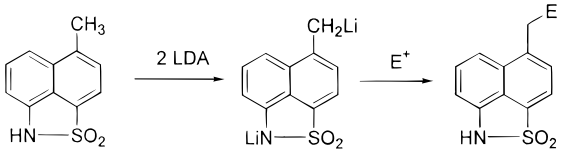
An example of this type of ring-expansion with a saccharin derivative has been previously reported.[13]

(9) Unpublished results. See ref 1, footnote 16.

(10) (a) Vesely, V. *Collect. Czech. Chem. Commun.* **1929**, *1*, 493, 504. (b) Steiger, R. E. *Helv. Chim. Acta* **1934**, *17*, 1142. (c) Steiger, R. E. *Helv. Chim. Acta* **1930**, *13*, 173.

(11) We thank Linda Tuma of the Operational Hazards Lab at Merck for obtaining these data.

Because of this complication and a desire to avoid any protecting group sequences, we envisioned generating a N,C-dianion and selectively alkylating on the carbon. Although there has been a large amount of literature dedicated to dianions in general, only a few examples of N,C-dianions could be found, and no examples involving *p*-methylsulfonamides could be located.[14] As a preliminary study, naphthosultam **6** was treated with LDA in THF at 0 °C, followed by addition of D_2O. Gratifyingly, clean incorporation of deuterium at the benzylic position occurred, as evidenced by NMR.[15] Although the dianion rapidly reacted with air, it proved to be quite thermally stable.[16] Table 1 shows a range of electrophiles that



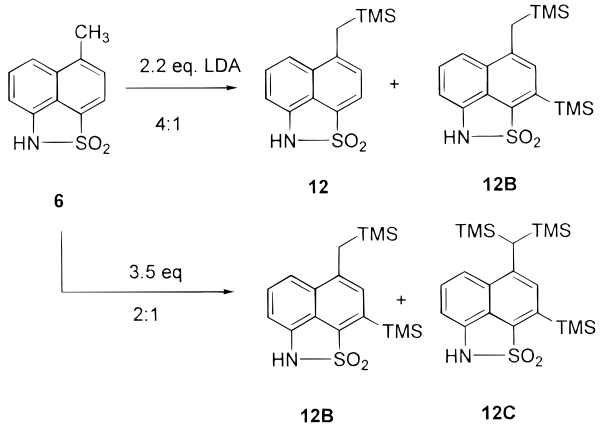
6

Table 1. Conversions and Yields of Electrophiles with 6[a]

electrophile	product	% conversion	% yield
MeI	**9**	99	92
paraformaldehyde	**3**	50	45
monomeric formaldehyde	**3**	70	65
DMF[b]	**3**	90	50−80
$ClCH_2I$	**10**	90	90
$(CH_3)_3CCHO$	**11**	95	93
TMSCl	**12**	98	83
PhCHO	**13**	98	87
CO_2	**14**	97−99	95

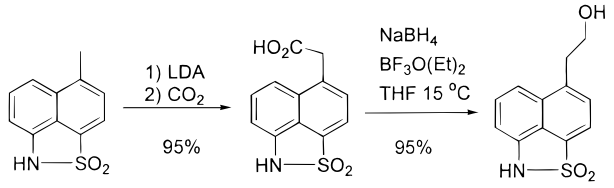
[a] See the Experimental Section for a general procedure. [b] After adding DMF, the reaction mixture was treated with sodium borohydride.

successfully reacted with dilithiated **6**. In all cases, an inverse addition of the dianion into the electrophile produced higher yields and more reproducible results than did a normal addition, presumably due to proton abstraction from the more acidic product by the highly basic dianion. Alkylation on nitrogen was not observed in any example under these conditions. Bis- and trissilylation (**12B** and **12C**, respectively) on carbon was observed during the quench with trimethylsilyl chloride and excess base, suggesting that further substitution of the naphthosultam skeleton through lithiation would be possible.



Aldehydes lacking acidic protons reacted cleanly with this dilithio-anion. However, in attempts to react with ketones and unsaturated carbonyl compounds, no useful yield of products could be obtained. No further optimization was done for these substrates, because they were without practical utility.

Critical to the synthesis of **2** was the hydroxymethylation of the dianion. The use of paraformaldehyde or monomeric formaldehyde[17] gave good yet variable yields of desired compound **3**. Variability in conversion and bisalkylation, which were dependent on quality of starting material and reagent, were significant. Reacting with DMF or other formyl synthons, followed by an in situ reduction, was similarly capricious. Alternatively, carbon dioxide consistently gave high conversions and isolated yields of acid **14**. After isolation, the intermediate was reduced in excellent yield to the desired hydroxyethylnaphthosultam **3** by a sodium borohydride/boron trifluoride reduction.[18] This carboxylation−reduction sequence provided significantly higher overall yield and purity than did the one-step hydroxymethylation process.



Completion of the Synthesis of 2. Completion of the synthesis of **2** required two more synthetic operations: (1) the preparation of DABCO-acetamide salt (DAT), and (2) its coupling with hydroxyethylnaphthosultam **3**. Because preliminary work had shown competitive displacement of the counteranion of DABCO-acetamide with the leaving group of hydroxyethylnaphthosultam, a weakly nucleophilic counteranion such as triflate was needed. Although two-step preparations of the DAT have been previously reported, an optimized one-pot process has now been achieved (Scheme 6).[19] In this revised procedure, DABCO, sodium triflate, and chloroacetamide are mixed together in acetonitrile, and simple filtration of the insoluble salts resulted in an essentially chloride-free DAT solution. The low solubility of sodium chloride and the chloride salt of DABCO acetamide in acetonitrile drove concurrent anion exchange/nucleophilic displace-

(12) (a) Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett.* **1990**, 747. (b) Schlosser, M. *Tetrahedron* **1998**, *54*, 2763.

(13) Zinnes, H.; Comes, R. A.; Shavel, J., Jr. *J. Org. Chem*. **1964**, *24*, 2068.

(14) (a) For general reviews on dianions in general, see Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509. (b)Thompson, C. M.; Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223. (c) For an example of a β-sultam dianion, see Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett*. **1989**, *30*, 2873. (d) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem*. **1968**, *33*, 900. (e) Watanabe, H.; Hauser, C. R. *J. Org. Chem*. **1968**, *33*, 4278.

(15) This type of benzylic dianion formation was precedented by the work on methyl-substituted benzoic acids: Creger, C. *J. Am. Chem. Soc*. **1970**, *92*, 1396.

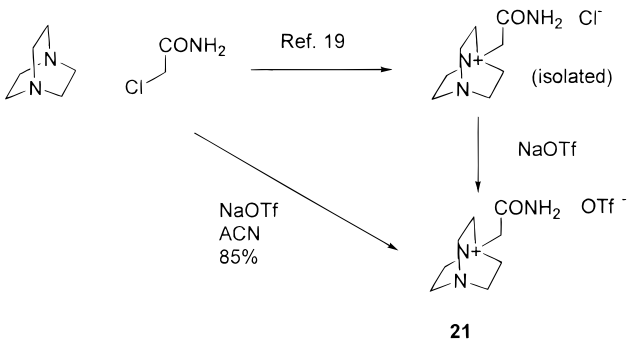
(16) For example, a naphthosultam dianion was prepared and allowed to stir under nitrogen at 20 °C, for 18 h, after which it was quenched into trimethylacetaldehyde. An identical result was obtained when a freshly prepared dianion solution was quenched into trimethylacetaldehyde.

(17) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1991**, 704.

(18) Attempted in situ reduction of the carboxylate with borohydride led to a reductive amination of diisopropylamine with the carboxylate; see Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766 for similar reductive aminations.

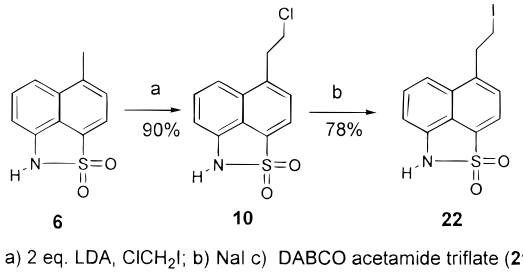
(19) Yasuda, N. et. al. *J. Org. Chem*. **1998**, *64*, 5438.

Scheme 6



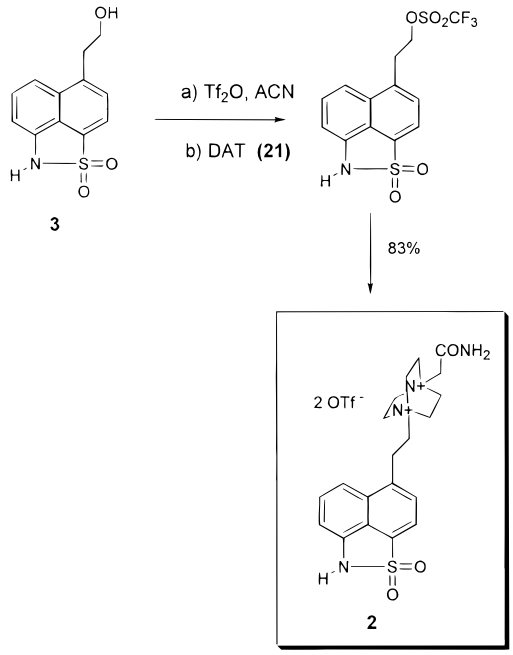
ment. The solution could be used directly in the next step, or the triflate salt isolated in 85% yield by addition of MTBE.

Initial experiments on the coupling of DAT with the naphthosultam fragment focused on the chloroethyl derivative **10**, available from the alkylation of the dianion of methylnaphthosultam **6** with chloroiodomethane. After exchange to the iodide, alkylation was achieved giving **2** as the iodo, triflate salt in 65% overall yield. Attempted coupling of this compound with the carbonate failed, and alternate counteranions were desired.



The preferred synthesis of **2** as the bis-triflate salt was achieved using an activation/displacement sequence from **3**. Selective triflation of the difunctional hydroxyethylnaphthosultam, without recourse to any protecting group, was desired. However, selective O-triflation could not be achieved under a variety of basic conditions.[20] In most cases, statistical mixtures of N-triflation, O-triflation, bistriflation, and starting material **3** were obtained. Alternatively, triflation in the absence of base was expected to selectively react with the more basic alcohol function.

(20) For a review on triflates, see Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.



The addition of 1 equiv of triflic anhydride into a solution of **3** in acetonitrile gave a 95% conversion to the monotriflate, as evidenced by reaction with tetrabutylammonium bromide. When reacted with 2 equiv of DAT, identical conversion was observed and, after crystallization, an 83% isolated yield of **2** was obtained. Under these low pH conditions, no evidence of N-triflation was observed, and <1% of the DABCO acetonitrile from dehydration of the acetamide was obtained. This operationally simple procedure has been successfully demonstrated on the multikilo scale, yielding high-purity (>99%) releasable side chain.

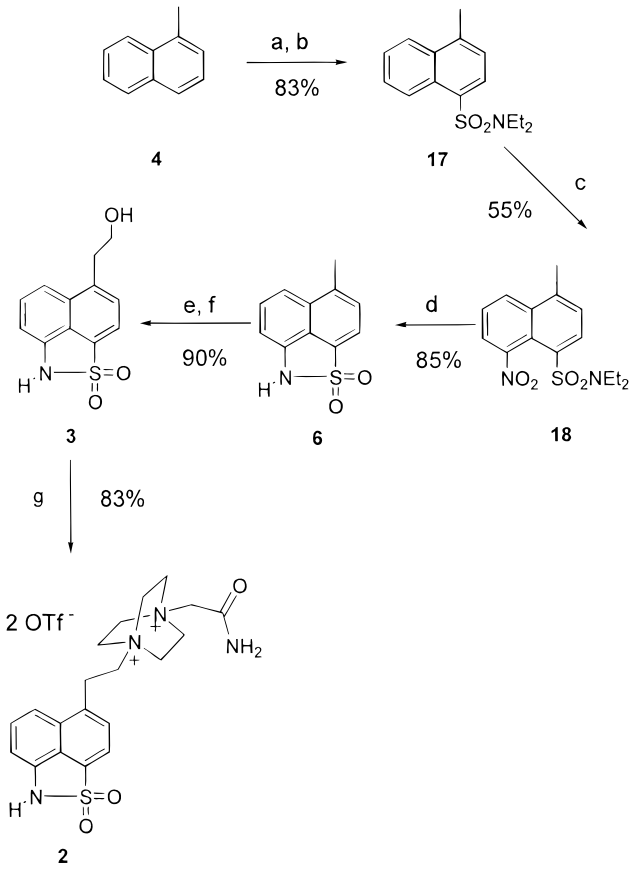
In summary, we have described a seven-step synthesis of **2** (Scheme 7), which proceeds in 29% overall yield. The synthesis was achieved without the use of any protecting groups, and features a new and operationally safe naphthosultam ring synthesis, a chemoselective chain extension of a novel methyl naphthosultam dianion and a chemoselective acid-catalyzed monotriflation. The synthesis has been reproducibly demonstrated on the multikilogram scale in high purity and has allowed for the production of side chain essential for the large-scale synthesis of the novel β-lactam antibiotic **1**.[3]

Experimental Section

General Considerations. All reactions were carried out under an atmosphere of dry N_2. All solvents were commercial grade and used without purification or drying. Melting points were measured with a Buchi 510 apparatus and are uncorrected. Low resolution mass spectroscopy was obtained from M Scan Inc. NMR spectra were recorded on a Bruker DPX-250 instrument (^{1}H NMR at 250 MHz, ^{13}C NMR at 63 MHz) or a Bruker DPX-400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz). The IR spectra were recorded on a Perkin-Elmer 781 instrument. New compounds were characterized by C, H, N analysis from Quantitative Technologies Inc.

4-Methyl-1-naphthalenesulfonyl Chloride (15). A 22 L three-neck flask fitted with mechanical stirrer, temperature probe, and nitrogen inlet was charged with 1-methylnaphthalene **4** (2.63 kg) and trifluoroacetic acid (13.2 L). The two-phase mixture was stirred and cooled to 5 °C using an ice−water bath. Chlorosulfonic acid (1.0 L) was added via an addition funnel over 30 min, maintaining the reaction temperature

Scheme 7



[a] (a) 2 equiv of $ClSO_3H$; (b) $HNEt_2$, IPA; (c) HNO_3, H_2SO_4; (d) KO_2CH, 5% Pd/C, HCl; (e) LDA, CO_2; (f) $NaBH_4$, BF_3OEt; (g) TF_2O, DAT.

between 5 and 10 °C. After complete addition, the slurry mixed for 10 min and warmed to 15 °C, and the remaining chlorosulfonic acid (1.93 L) was added over 15 min. The reaction temperature was allowed to increase to 20 °C during the addition and then maintained at 20 °C. The hydrogen chloride generated during sulfonation was trapped using a nitrogen sweep to a dilute sodium hydroxide solution. The slurry was stirred at 20 °C for 1 h and was then added to cold (5 °C) deionized water (19.7 L) at 10−25 °C over 15 min. The resultant slurry mixed at 15−20 °C for 30 min, was filtered, washed with water (9.5 L), and dried under a nitrogen stream overnight. Yield of **15:** 3.52 kg, 83%. mp 80−81 °C (lit. mp 81 °C).[21]

4-Methyl-8-nitro-1-naphthalenesulfonyl Chloride (16). (CAUTION: SHOCK SENSITIVE). A 72L flask fitted with nitrogen inlet, mechanical stirrer, addition funnel, and temperature probe was charged with 1-methylnaphthalene-4-sulfonyl chloride (**15**, 5.0 kg) and trifluoroacetic acid (50 L). The resultant slurry was cooled to 5 °C. Concentrated sulfuric acid (1.11 L) was added over 2 min. The reaction mixture was stirred at 5 °C for 10 min. Fuming nitric acid (1.0 L) was added to the slurry, maintaining the reaction temperature between 10 and 15 °C. The slurry was aged at 10−15 °C for 15 min. Water (40 L) was added to the slurry over 30 min, maintaining the internal temperature between 15 and 20 °C using an ice−water bath. The resultant slurry was aged at 20 °C for 30 min and filtered, and the cake was washed with 1:1 TFA/water (10 L) and water (5 L). The wet cake was slurried in ethyl acetate (20 L) at 20 °C for 1 h. Hexane (20 L) was added over 30 min and the slurry aged at 20 °C for 1 h and filtered. The cake was washed with 1:1 ethyl acetate/hexane (5 L) and dried under a nitrogen stream at rt overnight. The yield was 3.60 kg at 97 wt %; 3.49 kg pure basis, 59%.

(21) Baliga, B. *Can. J. Chem.* **1966**, *44*, 363.

16: ^{1}H NMR (400.25 MHz, d_6-acetone) δ 8.72 (d, J = 7.9 Hz, 1H), 8.66 (dd, J = 8.6, 1.1 Hz, 1H), 8.44 (dd, J = 7.6, 1.1 Hz, 1H), 7.9 (m, 2H), 2.96 (s, 3H); ^{13}C NMR (100.64 MHz, d_6-acetone) δ 147.7 (br), 146.9, 139.0, 136.1, 135.0, 132.2, 128.7, 128.4, 127.6, 120.0, 20.0; MS (EI) *m*/*e* (relative intensity) 250 (10) loss of Cl, 186 (90), 156 (60), 128 (100); IR (KBr) 3094, 1539, 1369, 1349, 1166, 668, 611, 560, 540 cm^{-1}. Anal. Calcd for $C_{11}H_8NO_4SCl$; C, 46.24; H, 2.82; N, 4.90; S, 11.22; Cl, 12.41; Found C, 46.34; H, 3.05; N, 4.75; S, 11.02; Cl, 12.25; mp 157−160 °C (dec).

***N*,*N*-Diethyl-4-methyl-1-naphthalenesulfonamide (18).** A 72 L flask fitted with mechanical stirrer, temperature probe, condenser, addition funnel, and nitrogen inlet was charged with methylnaphthalenesulfonyl chloride **15** (4.0 kg) and 2-propanol (6.2 L). Diethylamine (3.73 L) was added to the slurry over 10 min. An exotherm around 65 °C was noted. The starting material dissolved as the reaction progressed and was fully dissolved at complete reaction. No external cooling or heating was used during the reaction. The solution was cooled to 30 °C, and water (2 L) was then added. The mixture was seeded with sulfonamide product (2 g) and aged at 20 °C for 20 min. The remaining water (16.6 L) was added over 1 h and the resultant slurry mixed for 20 min. at 20 °C. The slurry was filtered and washed with water (12 L). The cake was dried under vacuum with a nitrogen sweep overnight. A total of 3.8 kg was obtained, which adjusted for purity at 95 wt % equaled 99% yield.

18: ^{1}H NMR (400.25 MHz, d_6-acetone) δ 8.72 (dd, J = 9.9, 1.9 Hz, 1H), 8.1(dd, J = 8.5, 1.4 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.7 (m, 2H), 7.49 (dd, J = 7.4, 0.8 Hz, 1H), 3.37 (q, J = 7.0 Hz, 4H), 2.76 (s, 3H), 1.07 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100.64 MHz, d_6-acetone) δ 141.0, 134.4, 133.5, 128.9, 128.7, 127.3, 126.7, 125.7, 125.1, 125.0, 41.0, 19.1, 13.4; MS (EI) *m*/*e* (relative intensity) 277 (35), 262 (55), 205 (70), 157 (20), 141 (100), 115 (40); IR (KBr) 2977, 1308, 1136, 942, 764, 707, 580 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; S, 11.56; Found C, 65.19; H, 6.87; N, 4.98; S, 11.43.; mp 67−68 °C.

***N*,*N*-Diethyl-4-methyl-8-nitro-1-naphthalenesulfonamide (19).** A 2 L flask fitted with nitrogen inlet, mechanical stirrer, addition funnel, and temperature probe was charged with *N*,*N*-diethyl-1-methyl-4-naphthalenesulfonamide (**18**, 30 g) and TFA (150 mL). The resultant solution was cooled to 15 °C, and concentrated sulfuric acid (30 mL) was added. The solution was cooled to −3 °C and fuming nitric acid (6.2 mL) added with rapid stirring over 30 min. The reaction temperature was maintained between −3 and +5 °C. Rapid stirring is essential for complete conversion. Water (375 mL) was added to the solution over 60 min while keeping the internal temperature less than 25 °C with an ice−water bath. **CAUTION! The initial 10% water charge should be added very slowly due to exotherm**. The resultant slurry was filtered and washed with water (100 mL). The cake was dried in a nitrogen stream until the residual water content was <35% w/w. A total of 28.6 g at 67 wt % was obtained; 19.2 g pure basis, 55% yield. Water content by Karl-Fisher titration was 7 wt %, **(19):** ^{1}H NMR (400.25 MHz, d_6-DMSO) δ 8.47 (d, J = 11.8 Hz, 1H), 8.23 (d, J = 7.0 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.8 (m, 1H), 7.69 (d, J = 7.7 Hz, 1H), 3.10 (q, J = 7.0 Hz, 4H), 2.78 (s, 3H), 0.95 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100.64 MHz, d_6-DMSO) δ 148.1, 141.2, 135.2, 134.3, 131.2, 130.7, 128.0, 126.3, 126.2, 121.1, 43.0, 20.4, 14.9; MS (EI) *m*/*e* (rel intensity) 250 (100) loss of NEt_2, 186 (85), 170 (55), 156 (80), 128 (100); IR (KBr) 2973, 1531, 1353, 1327, 1202, 1131, 1023, 955, 703, 560 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.89; H, 5.63; N, 8.69; S, 9.94; Found C, 55.89; H, 5.61; N, 8.58; S, 9.88; mp 164−165 °C.

6-Methyl-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (6). A 72 L flask was equipped with a N_2 inlet, thermocouple, and an overhead stirrer. To the flask were charged 2.20 kg of nitrodiethylsulfonamide naphthalene (**19**) and ethanol (20 L). Pd/C (10 wt %, 50 wt % water wet, 0.17 kg) was charged as a slurry in water (800 mL) and rinsed down with water (80 mL) and ethanol (6 L). To the resultant slurry was added potassium formate (1.74 kg) in one portion. The slurry was warmed to

60 °C for 1 h and then refluxed for 1 h. The reaction was considered complete when no starting material remained relative to the intermediate aminonaphthalene **20** (characterization included below), typically 2 h. Upon complete reaction, the mixture was cooled to 20 °C and concentrated hydrochloric acid (2.73 L) added over about 20 min. The resultant slurry was filtered through a pad of Solka-floc, and the cake was washed with 10% concentrated hydrochloric acid in ethanol (total of 13 L). The combined filtrates were recharged to the cleaned 72 L flask and heated to reflux (81 °C) for 3−4 h to achieve complete cyclization. The solution was cooled to 40 °C and concentrated to about 15 L (100 mmHg.). The slurry was cooled to 20 °C, and water (7.5 L) was added over 30 min. The slurry was cooled to 5 °C, mixed for 15 min, filtered, and finally washed with water (5 L). The crystalline solid was dried under a stream of nitrogen overnight. Obtained: 1.0 kg (85%)

6: ^{1}H NMR (250.1 MHz, d_6-DMSO) δ 11.35 (br s, 1H), 8.03 (d, J = 7.33 Hz, 1H), 7.64 (m, 3H), 6.94 (dd, J = 2.7 Hz, 5.17 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (62.5 MHz, CD_3OD) δ 141.9, 137.1, 131.7, 131.6, 130.3, 129.6, 121.9, 120.4, 117.0, 106.8, 18.7; MS (EI) *m/e* (rel intensity) 219 (100), 154 (30), 140 (24), 127 (17), 115 (10); IR (Nujol) 3260, 1590, 1625, 1290, 1155, 755 cm^{-1}. Anal. Calcd for $C_{11}H_9NSO_2$: C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 60.07; H, 4.16; N, 6.35; S, 14.27; mp 221−225 °C.

8-Amino-*N*,*N*-diethyl-4-methyl-1-naphthalenesulfonamide (20): ^{1}H NMR (400.25 MHz, d_6-DMSO) δ 7.66 (d, J = 7.5 Hz, 1H), 7.33 (m, 3H), 6.91 (d, J = 7.6 Hz, 1H), 6.28 (s, 2H), 3.3 (m, 4H), 2.6 (s, 3H), 1.11 (m, 6H); ^{13}C NMR (100.64 MHz, d_6-DMSO) δ 145.6, 141.2, 136.2, 134.0, 128.2, 126.4, 124.8, 117.6, 113.4, 112.9, 43.3, 21.2, 15.2; MS (EI) *m/e* (relative intensity) 292 (50), 219 (100), 157 (80), 129 (70), 128 (65); IR (KBr) 3476, 3386, 2971, 1647, 1572, 1461, 1294, 1126, 712 cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_2SO_2$: C, 61.62; H, 6.89; N, 9.58; S, 10.96. Found C, 61.67; H, 6.97; N, 9.33; S, 10.74; mp 126−128 °C.

6-Methyl-2-(phenylmethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (7). A 100 L flask was equipped with a N_2 inlet, thermocouple, addition funnel, and an overhead stirrer. The flask was charged with 2.00 kg of nitronaphthalene **16**, along with 18 L of DMF. Potassium carbonate (2.42 kg) was then charged followed by slow addition of benzylamine (0.79 kg). The solution changed from a yellow to a brownish color as the intermediate sulfonamide formed. The reaction mixture was heated to 90 °C until the starting material was consumed, typically 2 h. The solution was cooled to 25 °C, and 39 L of water was added over 1−2 h. The resultant slurry was filtered and washed with approximately 40 L water. The light brown powder was dried under vacuum at 40 °C overnight. A total of 2.17 kg (80% yield) was obtained.

7: ^{1}H NMR (250.1 MHz, CD_2Cl_2) δ 7.71 (d, J = 7.39 Hz, 1H), 7.27 (m, 8H), 6.34 (dd, J = 7.15 Hz, 0.62 Hz, 1H), 4.79 (s, 2H), 2.56 (d, J = 0.76 Hz, 3H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ 141.4, 136.9, 135.9, 130.4, 129.2, 129.1, 128.8, 128.3, 128.2, 127.9, 120.1, 119.5, 115.9, 104.0, 45.6, 18.9; MS (EI) *m/e* (rel intensity) 309 (20), 91 (100); IR (Nujol) 1630, 1590, 1500, 1290, 1170, 820, 795, 760 cm^{-1}. Anal. Calcd. for $C_{18}H_{15}NSO_2$: C, 69.88; H, 4.89; N, 4.53; S, 10.36. Found: C, 69.56; H, 4.85; N, 4.40; S, 10.37; mp 123−125 °C.

6-Methyl-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (6). To a 50 L flask equipped with a N_2 inlet, thermocouple, addition funnel, and an overhead stirrer was added 1.73 kg of *N*-benzylnaphthylsultam **7** and 17 L of ethanol. Triethylamine (850 g) was charged followed by 10% Pd/C (1.73 kg). Finally, formic acid (360 g) was charged via an addition funnel *slowly*, over 20−30 min. The reaction was heated to 80 °C until the starting material had been consumed. The reaction mixture was cooled to 25 °C and filtered through Celite to remove the Pd/C, washing the cake with 11 L of warm (30−40 °C) ethanol. The filtrate was then acidified with 6.6 L of 2 N HCl (pH 2−3), followed by slow addition of 31 L of water to crystallize out the product. The resultant slurry was cooled to 5 °C, filtered, and washed with 32 L of cold water. The product was dried under vacuum at 40 °C until <0.3 wt % water remained as analyzed by Karl-Fisher titration. Obtained: 1.04 kg of product (85% yield).

(2*R*,*S*)-2,3-Dihydro-7-methyl-2-phenylnaphtho[1,8-*de*]-1,3-thiazine 1,1-Dioxide (8). *N*-Benzyl-8-methylnaphthalene sultam (**7,** 1.0 g, 3.23 mmol) and 10 mL of dry THF were placed in a 50 mL flask and cooled to −30 °C. In a separate flask, diisopropylamine (0.72 g, 2.2 equiv) and 10 mL of THF were prepared and cooled to −30 °C. To this solution was slowly added 4.0 mL (2.0 equiv) of 1.6 M ^{n}BuLi. The resulting LDA solution was added slowly to the sultam solution over 20 min, maintaining the temperature <−20 °C. After complete LDA addition, a total of 28 mL of 2 N HCl was added to crystallize product. The resultant slurry was cooled to 0 °C, filtered, and washed with water to afford 0.80 g (80% yield) of product.

8: ^{1}H NMR (400.08 MHz, d_6-DMSO) δ 7.90 (d, J = 7.32 Hz, 1H), 7.80 (s, 1H), 7.71 (m, 2H), 7.56 (m, 6H), 7.22 (d, J = 6.73 Hz, 1H), 5.86 (s, 1H), 2.71 (s, 3H); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 141.3, 140.4, 133.0, 132.5, 130.1, 130.0, 128.7, 128.3, 127.9, 125.7, 119.4, 117.2, 114.9, 112.1, 75.1, 19.9. MS (EI) *m/e* (rel intensity) 309 (10), 275 (30), 245 (100), 230 (80), 160 (75). IR (Nujol) 3350, 1610, 1590, 1290, 1140, 1120, 830, 780, 750 cm^{-1}; HRMS calculated for $C_{18}H_{15}NO_2S$ = 309.0824, found 309.0796; mp 231−235 °C.

General Dianion Formation and Electrophile Addition. A 100 mL flask equipped with a nitrogen inlet, a stirrer, and a temperature probe was charged with anhydrous THF (50 mL), 1-Me-NH-naphthosultam **6** (2.5 g, 11.4 mmol) and diisopropylamine (3.0 g, 29.6 mmol). Three vacuum/purge cycles were then done to remove dissolved oxygen. The solution was cooled to −20 °C, and 10.7 g of *n*-butyllithium (1.6 M in hexane) was added dropwise, maintaining the internal temperature between −20 °C and 0 °C. The dark dianion solution was aged for 30 min at −15 °C.

Workup Procedure for CO_2 Addition (14). Bone-dry grade CO_2 was bubbled into −20 °C THF (400 mL) until approximately 45.6 mmol of CO_2 (2.0 g) was added. The dianion solution was added quickly to this carbonated solution while ensuring efficient mixing of the resulting slurry. After warming to 10 °C, 28 mL of 2 N HCl was slowly added to the solution. The solution was then concentrated atmospherically to about 28 mL to remove THF and initiate crystallization. The resultant slurry was aged at 5 °C for 30 min, filtered, washed with water (55 mL), and dried in a nitrogen stream. Obtained 2.94 gm at about 97 wt % = 2.85 g, 95% yield as a white solid.

Workup Procedure for Other Electrophiles. A separate 250 mL flask equipped with a stirrer, a nitrogen inlet, and a temperature probe was charged with THF (25 mL) and the electrophile and then degassed with a vacuum/nitrogen purge. The dianion was added to this solution and then mixed with 100 mL of ethyl acetate and 100 mL of water. The layers were cut, and the organic solution was dried over sodium sulfate. The organic layer was concentrated, and hexanes were added to crystallize out the naphthosultam products.

6-Ethyl-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (9): ^{1}H NMR (250.1 MHz, d_6-DMSO) δ11.33 (br s, 1H), 8.06 (d, J = 7.45 Hz, 1H), 7.63 (m, 3H), 6.93 (dd, J = 6.95, 0.8 Hz, 1H), 3.12 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 146.6, 135.9, 130.2, 129.8, 129.4, 127.6, 120.4, 120.2, 115.7. 105.9, 25.2, 15.6; MS (EI) *m/e* (rel intensity) 233 (100), 218 (25), 154 (20); IR (Nujol) 3300, 1625, 1590, 1495, 1380, 1305, 1150, 1110, 840, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NSO_2$: C, 61.78; H, 4.75; N, 6.00; S, 13.74. Found: C, 61.66; H, 4.71; N, 5.97; S, 13.50; mp 175−179 °C.

2*H*-Naphth[1,8-*cd*]isothiazole-6-ethanol 1,1-dioxide (3): ^{1}H NMR (250.1 MHz, CD_3CN) δ 8.43 (br s, 1H), 7.85 (d, J = 7.42 Hz, 1H), 7.56 (m, 3H), 6.89 (d, J = 7.22 Hz, 1H), 3.76 (t, J = 6.54 Hz, 2H), 3.23 (t, J = 6.52 Hz, 2H), 2.67 (br s, 1H): ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 142.5, 135.8, 130.3, 130.1, 129.7, 129.5, 120.4, 119.9, 116.1, 105.8, 61.9, 35.8; MS (EI) *m/e* (rel intensity) 249 (100), 218 (85), 155 (50), 127 (30); IR (Nujol) 3530, 3200, 1640, 1580, 1490, 1300, 1285, 1170, 825, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NSO_3$: C, 57.82; H, 4.45; N,

5.62; S, 12.86. Found: C, 57.65; H, 4.65; N, 5.57; S, 12.47; mp 175−177 °C.

6-(2-Chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (10): ^{1}H NMR (400.3 MHz, d_6-DMSO) δ 8.01 (d, J = 7.5 Hz, 1 H), 7.8 (d, J = 7.3 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.65 (m, 1H), 7.01 (d, J = 7.3 Hz, 1H), 3.99 (t, J = 7.0 Hz, 2H); 3.65 (t, J = 7.0 Hz, 2H);^{13}C NMR (62.5 MHz, d_6-acetone)-140.25, 135.90, 131.57, 130.03, 129.67, 129.35, 120.75, 119.18, 115.59, 105.97, 44.17, 34.89; MS (EI) *m/e* (rel intensity) 269 (35) chlorine isotope, 267 (100), 218 (80), 154 (30); IR (KBr) 3187, 1498, 1359, 1296, 1148, 1111, 831, 752 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76; N, 5.23; S, 11.98, Cl, 13.24. Found C, 53.93; H, 3.83; N, 5.04; S, 11.99; Cl, 12.94; mp 148−151 °C.

(α-(1,1-Dimethylethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (11): ^{1}H NMR (250.1 MHz, CD_2Cl_2) δ 7.94 (d, J = 7.45 Hz, 1H), 7.67 (m, 3H), 7.12 (br s, 1H), 7.00 (dd, J = 7.20, 0.6 Hz, 1H), 3.57 (m, 2H), 3.01 (dd, J = 13.6, 10.7 Hz, 1H) 1.55 (br s, 1H), 1.13 (s, 9H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ 143.6, 135.2, 130.8, 130.2, 129.9, 129.2, 121.8, 119.9, 117.4, 107.2, 80.3, 35.8, 35.2, 25.9; MS (EI) *m/e* (rel intensity) 305 (20), 219 (50), 155 (100); IR (Nujol) 3450, 3295, 1625, 1590, 1495, 1360, 1320, 1150, 830, 795, 760 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NSO_3$: C, 62.93; H, 6.27; N, 4.59; S, 10.5. Found: C, 62.69; H, 6.28; N, 4.49; S, 10.29; mp: 196−199 °C.

(6-[(Trimethylsilyl)methyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (12): ^{1}H NMR (250.1 MHz, d_6-DMSO) δ 11.28 (br s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.59 (m, 3H), 6.91 (d, J = 7.06 Hz, 1H), 2.77 (s, 2H), 0.00 (s, 9H); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 144.8, 135.7, 129.2, 128.9, 128.0, 127.5, 120.6, 120.0, 116.9, 105.7, 23.8, −1.1; MS (EI) *m/e* (rel intensity) 291 (80), 212 (30), 201 (95), 73 (100); IR (Nujol) 3240, 1630, 1585, 1495, 1145, 1120, 860, 840, 795, 750 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NSO_2Si$: C, 57.70; H, 5.88; N, 4.81; S, 11.00. Found: C, 57.30; H, 5.83; N, 4.67; S, 10.84; mp 205−208 °C.

8-Trimethylsilyl-6-[(trimethylsilyl)methyl]-2*H*-naphth-[1,8-*cd*]isothiazole 1,1-dioxide (12B): ^{1}H NMR (250.1 MHz, CD_2Cl_2) δ 7.48 (m, 3H), 6.87 (dd, J = 6.8, 1.1 Hz, 1H), 6.87 (br s, 1H), 2.62 (s, 2H), 0.45 (s, 9H), −0.04 (s, 9H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ 144.5, 137.4, 136.6, 134.8, 131.5, 129.8, 123.4, 119.3, 108.4, 108.1, 25.8, 1.3, 0.0; MS (EI) *m/e* (rel intensity) 363 (70), 273 (90), 227 (20), 73 (100); IR (Nujol) 3200, 1625, 1560, 1160, 1140, 850, 825, 750 cm^{-1}. Anal. Calcd. for $C_{17}H_{25}NSO_2Si_2$: C, 56.15; H, 6.93; N, 3.85; S, 8.82. Found: C, 56.25; H, 6.96; N, 3.77; S, 8.77; mp: 154−157 °C.

12C was not isolated; however, an NMR was obtained using an LC NMR. The data have been included in the Supporting Information.

(α-Phenyl-2*H*-naphth[1,8-*cd*]isothiazole-6-ethanol 1,1-dioxide) (13): ^{1}H NMR (250.1 MHz, d_6-DMSO) δ 11.32 (br s, 1H), 8.03 (d, J = 7.45 Hz, 1H), 7.43(m, 8H), 6.92 (d, J = 7.05 Hz, 1H), 5.46 (d, J = 3.26 Hz, 1H), 4.93 (s, 1H), 3.41 (m, 2H); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 145.7, 141.8, 135.7, 130.3, 130.2, 129.5, 128.4, 127.3, 126.3, 125.8, 120.3, 119.6, 116.3, 105.7, 73.5, 42.4; ^{13}C NMR (62.5 MHz in CD_3OD) δ 145.9, 142.6, 137.5, 132.4, 132.1, 131.4, 130.7, 129.7, 128.9, 127.5, 122.5, 120.4, 117.4, 107.0, 76.0, 43.8; MS (EI) *m/e* (rel intensity) 325 (5), 307 (30), 219 (60), 155 (100), 107 (55), 77 (35); IR (Nujol) 3500, 3020, 1625, 1595, 1495, 1380, 1150, 1110 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NSO_3$: C, 66.44; H, 4.65; N, 4.30; S, 9.85. Found: C, 66.40; H, 4.71; N, 4.25; S, 9.75; mp: 191−194 °C.

2*H*-Naphth[1,8-*cd*]isothiazole-6-acetic acid 1,1-dioxide (14): ^{1}H NMR (250.1 MHz, d_6-DMSO) δ 12.66 (br s, 1H), 11.42 (br s, 1H), 8.10 (d, J = 7.38 Hz, 1H), 7.77 (d, J = 7.43 Hz, 1H), 7.63 (m, 2H), 6.96 (dd, J = 5.13, 2.70 Hz, 1H), 4.12 (s, 2H); ^{13}C NMR (62.5 MHz, d_6-DMSO) δ 172.4, 137.8, 135.8, 131.2, 130.5, 130.3, 130.1, 120.3, 120.0, 116.2, 106.0, 38.0; MS (EI) *m/e* (rel intensity) 263 (100), 218 (50), 154(20); IR (Nujol) 3320, 1695, 1630, 1590, 1310, 1280, 1255, 1220, 1145, 805, 740 cm^{-1}. Anal. Calcd for $C_{12}H_9NSO_4$: C, 54.75; H, 3.45; N, 5.32; S, 12.18. Found: C, 54.74; H, 3.55; N, 5.35; S, 12.13; mp: 247−250 °C.

2*H*-Naphth[1,8-*cd*]isothiazole-6-ethanol 1,1-Dioxide (3). The dried sultam carboxylic acid **14** (1.14 kg) was slurried in THF (18 L) and cooled to 15 °C. To this solution was added $NaBH_4$ (327 g), followed by *slow* addition of BF_3 etherate. The addition of BF_3 etherate caused vigorous evolution of gas. The slurry was aged for about 1 h. MeOH (1.2 L) was *slowly* added to quench excess borane, followed by slow addition of 11 L of 2 N HCl. After aging for 30 min to ensure homogeneity, the reaction mixture was distilled at atmospheric pressure to concentrate and then cooled to 55 °C, seeded, and cooled to 15 °C. The slurry was filtered, washed with 10 L water, and dried under a stream of nitrogen. Obtained: 1007 g of **3** (4.04 mol, 93% yield) as a white solid.

1-(2-Amino-2-oxoethyl)-4-aza-1-azoniabicyclo[2.2.2]-octane salt with trifluoromethanesulfonic Acid (1:1) (21). To a 250 mL RB flask under a nitrogen blanket containing DABCO (1.93 g, 17.2 mmol) and acetonitrile (100 mL) at 25 °C were added NaOTf (2.69 g, 15.6 mmol) and 2-chloroacetamide (1.46 g, 15.6 mmol). The reaction mixture was heated to reflux (82 °C) for 2−3 h. The crude reaction mixture was cooled to 25 °C, filtered through Solka Floc to remove the insoluble chloride salts, and washed with an additional 15 mL of acetonitrile. The filtrate and wash were combined and concentrated under reduced pressure to 15 mL, and then *tert*-butyl methyl ether (30 mL) was slowly added at 25 °C with stirring; the slurry was then aged for 20 min. The product was filtered and washed with an additional 10 mL of *tert*-butyl methyl ether. The product was dried in vacuo (25 °C) with a nitrogen sweep to give 4.45 g, 89% yield of DAT; <0.3 wt % Cl^- by analysis with capillary zone electrophoresis.

1-(2-Amino-2-oxoethyl)-4-[2-(1,1-dioxido-2*H*-naphth-[1,8-*cd*]isothiazol-6-yl)ethyl]-1,4-diazoniabicyclo[2.2.2]-octane Salt with Trifluoromethanesulfonic Acid (1:2) (2). A solution (1100 μg/mL water as determined by Karl-Fischer titration) of naphthosultam ethanol (2370 g) in acetonitrile (27.9 kg) was cooled to 0 °C, and then triflic anhydride (2548 g) added slowly while keeping the temperature <5 °C. The reaction was aged 0.5 h at <5 °C. DAT was added (5765 g), and the reaction was allowed to warm to ambient temperature. Crystallization of the product occurred after stirring at room temperature for approximately 2−3 h. The crude reaction mixture was then solvent switched to methanol and concentrated to approximately 24 L, cooled to 5 °C, filtered, and washed with cold methanol (3 × 4 L, approximately 6% loss in mother liquors). **2**: Yield 83%, 5.08 kg; ^{1}H NMR (400.25 MHz, d_6-DMSO) δ 8.16 (d, J = 7.4 Hz, 1H), 8.04 (br s, 1H), 7.71 (m, 4H), 6.98 (d, J = 6.9 Hz, 1H), 4.3 (s, 2H), 4.15 (m, 12H), 3.85 (m, 2H), 3.65 (m, 2H); ^{13}C NMR (100.64 MHz, d_6-DMSO) δ 165.1, 138.1, 136.2, 131.8, 130.7, 129.9, 129.8, 120.4, 120.3, 121.2 (q, J = 322.3 Hz), 115.6, 106.4, 63.4, 61.8, 51.8, 50.9, 24.7; MS (EI) *m/e* (relative intensity) 401.1(100); IR(KBr) 3438, 3348, 3220, 3040, 1702, 1262, 1151, 1031, 1031, 640 cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_4O_9S_3F_6$: C, 37.71; H, 3.74; N, 8.00; F, 16.27; S 13.73. Found C, 37.77; H, 3.84; N, 7.91; F, 17.00; S, 14.24; mp>250 °C (dec).

Supporting Information Available: Spectral data of **8** and **12C**. This material is available free of charge via the Internet at http://pubs.acs.org.

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