Practical Synthesis of Anti-Methicillin-Resistant *Staphylococcus Aureus* (MRSA) Carbapenem L-742,728

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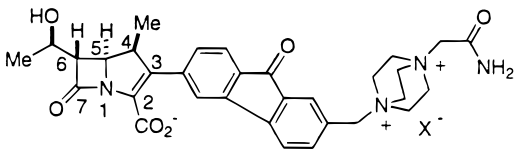
Anti-MRSA carbapenem, L-742,728, has been prepared in large quantity using the Suzuki−Miyaura cross-coupling as the key reaction. Three approaches have been examined by varying the coupling reaction between carbapenem nucleus **A** and side chains **B**, **BC**, and **BCD**, wherein **BCD** represents the fully elaborated side chain. The coupling of **A** with **BCD** offers the advantage of convergence and requires fewer chemical steps after installation of the thermally unstable carbapenem skeleton. This key reaction highlights the versatility and efficiency of the Suzuki−Miyaura reaction. This approach offers a general method for the preparation of the 3-aryl carbapenems, which possess strong antibacterial activity against resistant strains.

Introduction

The ubiquitous use of antibiotics for the treatment of infectious disease has resulted in many bacterial strains acquiring resistance to multiple drugs. One of the most serious resistant strains is the methicillin-resistant *Staphylococcus aureus* (MRSA).[1] First observed in Australia in the 1980s,[2] MRSA has become a worldwide problem, especially in areas where potent antibiotics have been heavily used. In such MRSA infections, vancomycin has become the primary treatment despite its adverse side effects. The search for alternative therapies is driven by the expected emergence of vancomycin-resistant MRSA.[3] Indeed the transfer of vancomycin resistance to *S. aureus* from a resistant *Enterococcus* has been demonstrated in the laboratory.[4]

Recently, Merck scientists have reported anti-MRSA activity in carbapenems bearing aromatic substituents at the 3-position.[5] The most recent candidate to emerge from this program is L-742,728 (**1**),[6] the large-scale synthesis of which we report here.



L-742,728 (**1**)

Results and Discussion

The antibacterial **1** is a cationic zwitterionic β-methyl carbapenem which can be retrosynthetically divided into four sections: the β-methyl carbapenem skeleton (**A**), a functionalized methylfluorenone (**B**), doubly quaternized 1,4-diazabicyclooctane (DABCO) (**C**), and acetamide (**D**) (Scheme 1). The carbapenem skeleton derives from the readily available diazo compound **2**.[7] The methylfluorenone can be prepared from 4-bromobenzonitrile (**3**) and 4-toluidine (**4**).

The key step in the synthesis is the coupling between the carbapenem core **A** and the side chain. Two aspects

(1) (a) *Methicillin Resistant Staphylococcus aureus*; University of Tokyo Press: Tokyo, 1986. (b) Brumfitt, W.; Hamilton-Miller, J. *N. Eng. J. Med.* **1989**, *320*, 1188.

(2) McDonald, O. J. *Med. J. Australia* **1982**, *1*, 445.

(3) Very recently, vancomycin resistant MRSA has been reported. Michel, M.; Gutmann, L. *Lancet* **1997**, *349*, 1901.

(4) Noble, W. C.; Virani, Z.; Cree, R. G. A. *FEMS Microb. Lett.* **1992**, *93*, 195.

(5) Previously, we reported this class of carbapenem as 2-aryl carbapenem based on the traditional numbering system in β-lactam chemistry. In this report, we use the IUPAC numbering system as depicted in L-742,728 (**1**). (a) Greenlee, M. L.; Cama, L. D.; DiNinno, F. P.; Heck, J. V. U.S. Pat. 5034384, 1991. (b) DiNinno, F.; Dykstra, K. D.; Greenlee, M. L.; Rano, T. A.; Guthikonda, R. N.; Schmitt, S. M.; Meurer, L. C.; Cama, L. D.; Sasor, M. F.; Laub, J. B.; Rouen, G. P.; Lee, W.; Muthard, D. A.; Hammond, M. L.; Heck, J. V.; Salzmann, T. N.; Kahan, J. S.; Huber, J. L.; Sundelof, J. G.; Dorso, K.; Kohler, J.; Gerkens, L.; Pelak, B.; St. Rose, E.; Jackson, J. J.; Hajdu, R.; Kropp, H.; Hammond, G. G.; Overbye, K. M.; Silver, L. L. The 4th International Conference on Chemical Synthesis of Antibiotics and Related Microbial Products, Nashville, IN, September 1994. (c) Sasor, M. F.; Cama, L. D.; Greenlee, M. L.; DiNinno, F.; Heck, J. V. The 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Paper #F 50, Orlando, FL, October 1994. (d) Huber, J. L.; Dorso, K.; Gerckens, L.; St. Rose, E.; Kohler, J.; Dufresne, S.; Kahan, J.; Shungu, D.; Kropp, H. The 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Paper #F 54, Orlando, FL, October 1994. (e) Rylander, M.; Rollof, J.; Norrby, S. R. The 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Paper #F 56, Orlando, FL, October 1994. (f) Dykstra, K. D.; DiNinno, F. The 6th Symposium on the Latest Trends in Organic Synthesis, Blacksburg, VA, October 1994. (g) Meurer, L. C.; Guthikonda, R. N.; Huber, J. L.; DiNinno, F. *BioMed. Chem. Lett.* **1995**, *5*, 767. (h) DiNinno, F.; Muthard, D. A.; Salzmann, T. N.; Huber J.; Kahan, J.; Kropp, H. *BioMed. Chem. Lett.* **1995**, *5*, 945. (i) Laub, J. B.; Greenlee, M. L.; DiNinno, F.; Huber, J. L.; Sundelof, J. G. The 210th National Meeting of the American Chemical Society, Abstract #MEDI 210, Chicago, IL, August 1995. (j) Chambers, H. F. *Antimicrob. Agents Chemother.* **1995**, *39*, 426. (k) Rylander, M.; Rollof, J.; Jacobsson, K.; Norrby, S. R. *Antimicrob. Agents Chemother.* **1995**, *39*, 1178. (l) Norrby, S. R. *Antimicrob. Therapy II* **1995**, *79*, 745. (m) Yasuda, N. 1995 International Chemical Congress of Pacific Basin Societies, Honolulu, HI, December 1995.

(6) (a) Greenlee, M. L.; DiNinno, F.; Hammond, M. L. U.S. Pat. 5,451,579, 1995. (b) Greenlee, M. L.; Laub, J. B.; Rouen, G. P.; DiNinno, F.; Cama, L. D.; Hammond, M. L.; Huber, J. L.; Sundelof, J. G.; Hammond, G. G. The 211th National Meeting of the American Chemical Society, Abstract #MEDI0178, New Orleans, LA, March 1996.

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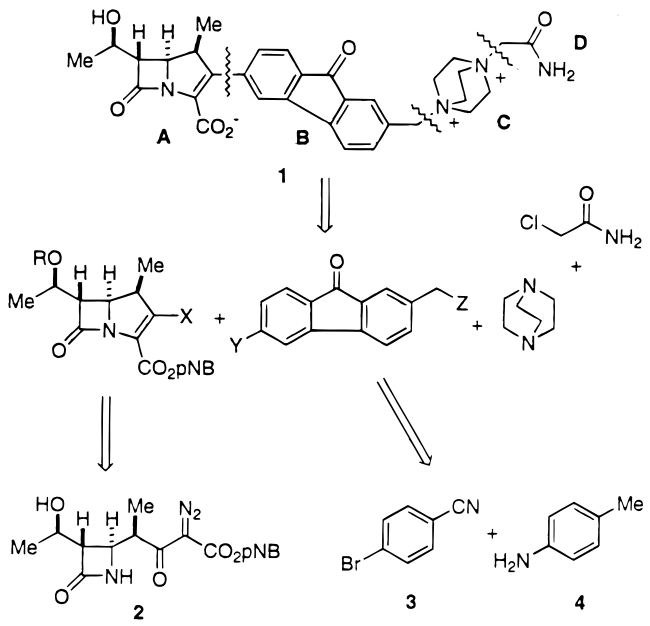
Scheme 1

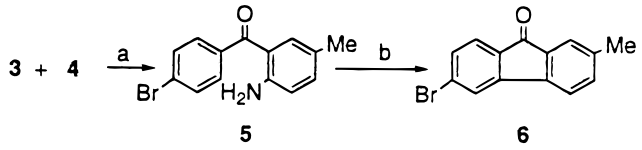


were considered: coupling convergence and method. Three different approaches were explored, namely, **A** + **B**; **A** + **BC**, and **A** + **BCD**. The coupling of **A** with the simpler side-chain **B** was expected to be the easiest to achieve. On the other hand, coupling with the more complex, quaternized side chains (**BC** or **BCD**) would minimize the number of steps involving unstable carbapenem intermediates.

Previously, introduction of the side chain has efficiently been accomplished by a Stille cross-coupling reaction between a carbapenem enol triflate and an aryl stannane.[5b,g,8] We judged this method to be unsuitable for large-scale pharmaceutical synthesis due to the toxicity of the organotin byproducts and the difficulty in removing them from coupled products. Recent reports from these laboratories disclosed mild conditions in which the Suzuki−Miyaura cross-coupling served as a successful replacement for the Stille reaction in the cross-coupling of a carbapenem enol triflate with simple boronic acids.[9] With this method, the byproduct boric acid is easily removed by aqueous extraction and poses no toxicological concern. For the present synthesis, we sought to apply the Suzuki−Miyaura cross-coupling method to this more complex side chain.

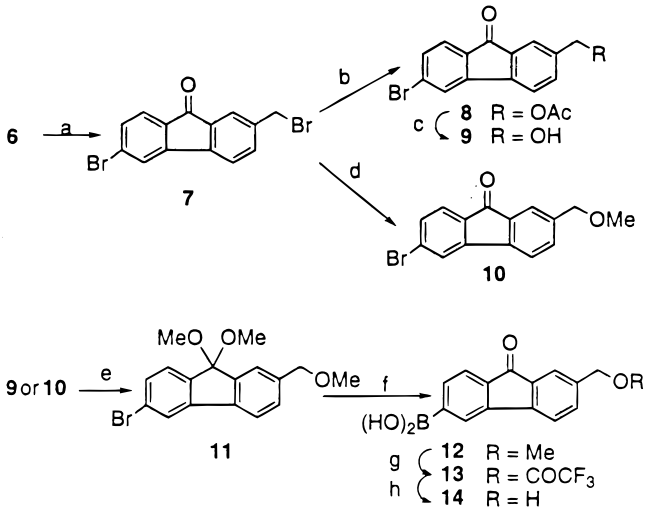
Preparation of 2-Methylfluorenone (6). All side-chain coupling partners were prepared from 2-methylfluorenone (**6**) as a common intermediate. Employing a modified Sugasawa reaction,[10] amino benzophenone **5** was obtained from **3** and **4** as a PhCl solution in excellent yield (Scheme 2). Diazotization of **5**, followed by Pschorr cyclization under standard radical conditions, gave a ca. 1:1 mixture of 2-methyl- and 4-methylfluorenone, due to a 1,5 hydrogen transfer.[11] The hydrogen transfer was successfully suppressed by carrying out the cyclization under acidic conditions. Solid $NaNO_2$ was slowly added to the PhCl solution of **5** and superphosphoric acid[12] at 80 °C to provide **6** without accumulation of a potentially explosive diazonium intermediate. In this way, **6** was prepared in two steps in an overall yield of 70%.

Scheme 2[a]



[a] (a) BCl_3, $AlCl_3$, PhCl, 130−134 °C. (b) $NaNO_2$, H_3PO_4, 80 °C.

Scheme 3[a]



[a] (a) NBS, VAZO-52, AcOH, CH_2Cl_2. (b) NaOAc, DMF. (c) NaOMe. (d) MeOH, 100 °C. (e) $CH(OMe)_3$, concentrated H_2SO_4, MeOH. (f) B(O-*i*-Pr)$_3$, *n*-BuLi, THF/toluene/hexanes, <−70 °C. (g) TFA. (h) NaOH, THF, H_2O; then aqueous HCl.

Preparation of Simple Side-Chain Boronic Acid B (14). In three steps, benzyl alcohol **9** was prepared from common intermediate **6** (Scheme 3). All transmetalation attempts on either **9** or O-protected versions failed due to the reactivity of the carbonyl group. Protection as the dimethylketal **11** was achieved by heating **9** with a large excess of $CH(OMe)_3$ in MeOH in the presence of 1 equiv of concentrated H_2SO_4. Benzyl methyl ether formation is inevitable during the ketalization, so preparation of **11** was modified to a route via methyl ether **10** [**6** → **7** → **10** → **11**], reducing the number of chemical steps.

Halo-transmetalation of **11** to boronic acid **12** was accomplished by addition of *n*-BuLi to a solution of **11** and B(O-*i*-Pr)$_3$ below −70 °C, followed by acidic hydrolysis. Solvolysis of the methyl ether of **11** with hot TFA, followed by hydrolysis, gave the simple side-chain fragment **14** in an overall yield of 45% in seven steps from **3**.

Preparation of Elaborated Side-Chains BC and BCD (19, 20). To access further functionalized coupling

(7) Compound **2** is readily available from (2*R*)-[(3*S*,4*S*)-3-[(1*R*)-*tert*-butyldimethylsilyloxyethyl]azetidinone-4-yl]propionic acid, which is now commercially available from Kanegafuchi, Japan, Nippon Soda, Japan, and Takasago, Japan. For recent preparation of the propionic acid; see: Jones, D. K.; Liotta, D. C.; Choi, W.-B.; Volante, R. P.; Reider, P. J.; Shinkai, I.; Churchill, H. R. O.; Lynch, J. E. *J. Org. Chem.* **1994**, *59*, 3749 and references therein.

(8) Rano, T. A.; Greenlee, M. L.; DiNinno, F. *Tetrahedron Lett.* **1990**, *31*, 2853 and references therein.

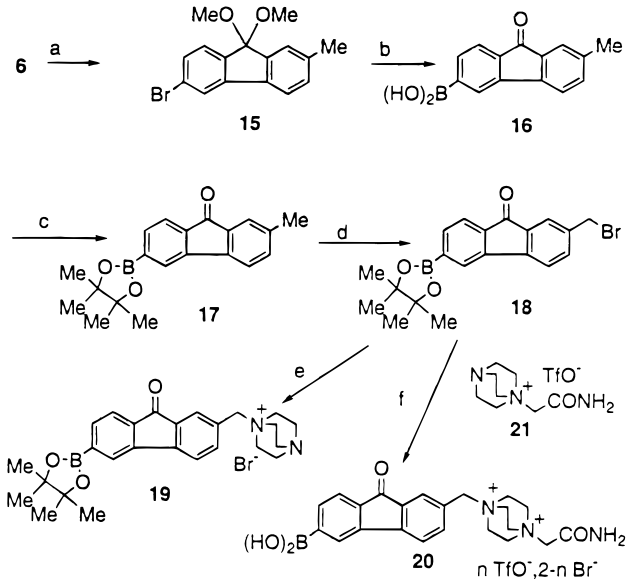
(9) (a) Yasuda, N.; Xavier, L.; Rieger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U.-H. *Tetrahedron Lett.* **1993**, *34*, 3211. (b) Narukawa, Y.; Nishi, K.; Onoue, H. *Tetrahedron* **1997**, *53*, 539 and references therein.

(10) Douglas, A. W.; Abramson, N. L.; Houpis, I. N.; Karady, S.; Molina, A.; Xavier, L. C.; Yasuda, N. *Tetrahedron Lett.* **1994**, *35*, 6807 and references therein.

(11) Karady, S.; Abramson, N. L.; Dolling, U.-H.; Douglas, A. W.; McManemin, G. J.; Marcune, B. *J. Am. Chem. Soc.* **1995**, *117*, 5425.

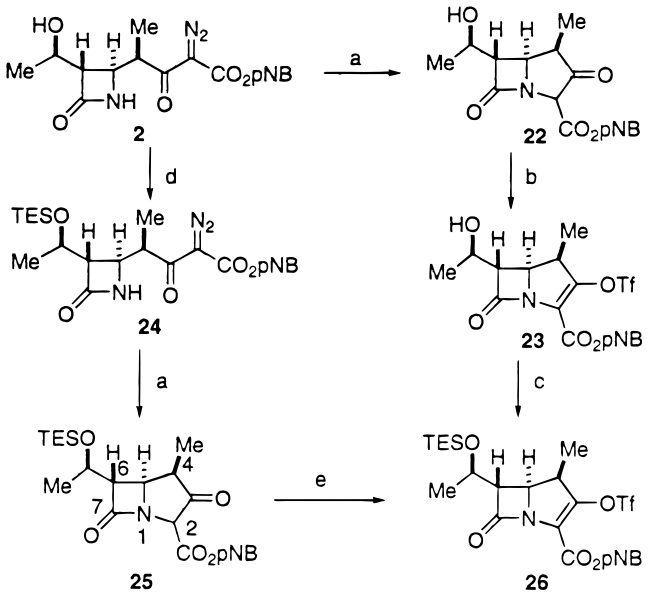
(12) Purchased from Aldrich Co. Ltd.

Scheme 4[a]



[a] (a) $CH(OMe)_3$, concentrated H_2SO_4, MeOH; then TEA. (b) B(O-*i*-Pr)$_3$, *n*-BuLi, THF/toluene/hexanes. <−70 °C; then dilute H_2SO_4. (c) Pinacol, PhCl, 133 °C. (d) Dibromodimethylhydantoin, VAZO-52, 37−39 °C. (e) DABCO, *t*-BuOMe/MeOH. (f) **21**, MeCN/MeOH, 28−30 °C.

Scheme 5[a]



[a] (a) $Rh_2(C_7H_{15}CO_2)_4$, $ZnBr_2$, CH_2Cl_2. (b) Et_3N, Tf_2O, CH_2Cl_2, −78 °C. (c) Et_3N, TESOTf, CH_2Cl_2, −78 °C. (d) Imidazole, TESCl, *i*-PrOAc/THF. (e) Et_3N, *i*-Pr_2NH, Tf_2O, CH_2Cl_2, −40 °C.

partners **19** and **20**, 2-bromomethyl-9-fluorenone-6-boronic acid derivative **18** was considered an ideal intermediate (Scheme 4). Methylfluorenoneboronic acid **16** was prepared from **6** in two steps under the previously used ketalization/transmetalation conditions (vide supra) in good yield. Direct bromination of **16** failed due to solubility problems. Consequently, **16** was first converted to its more soluble pinacol ester **17**, allowing smooth bromination to **18**.

Mono-quaternized boronic acid pinacol ester **19** was obtained in excellent yield from **18** and DABCO. Finally, doubly quaternized boronic acid **20** was prepared by reacting **18** with DABCO *N*-acetamide triflate salt **21**, prepared from DABCO and chloroacetamide, followed by boronic ester hydrolysis. Crystallization of **20** in the presence of triflate kept the amount of bromide counteranion below 0.6 equiv, a factor which affected the subsequent Suzuki−Miyaura coupling reaction (vide infra).

Preparation of Carbapenem Enol Triflate (26). The carbapenem coupling partner was the triethylsilyl (TES) protected enol triflate **26**. The TES protective moiety was chosen to balance the stability of the protected carbapenem enol triflate with the need for mild deprotection conditions.

In our initial approach to **1**, enol triflate **26** was prepared from diazo compound **2** according to the previously reported method (Scheme 5).[6,8,9] Rhodium-catalyzed cyclization of **2** gave the β-keto ester **22** which was not isolated because it is not crystalline. A small amount of $ZnBr_2$ was added prior to cyclization to inhibit base-catalyzed epimerization of the β-methyl substituent in **22**.[13] The unprotected enol triflate **23**, generated from **22** by addition of Et_3N and Tf_2O, is extremely unstable even at −78 °C. Immediate in situ protection of the secondary alcohol with the TES group provided the more stable protected enol triflate **26**, which was then used in situ for cross-coupling.

While efficient for multigram synthesis, this sequence did not perform well on large scale. The exothermic character of both the triflation and silylation steps required very slow additions to maintain the temperature below −70 °C, and during this time significant decomposition of the unprotected enol triflate **23** occurred.

To bypass the most unstable intermediate **23**, we opted to silylate the secondary alcohol prior to cyclization. While other bases gave mixtures of N- and O-silylated products, selective O-silylation of **2** was achieved with imidazole and TESCl to afford **24** as a crystalline solid. Rhodium-catalyzed cyclization of **24** gave a solution of β-keto ester **25** as a 97:3 mixture of β and α epimers at C-2.

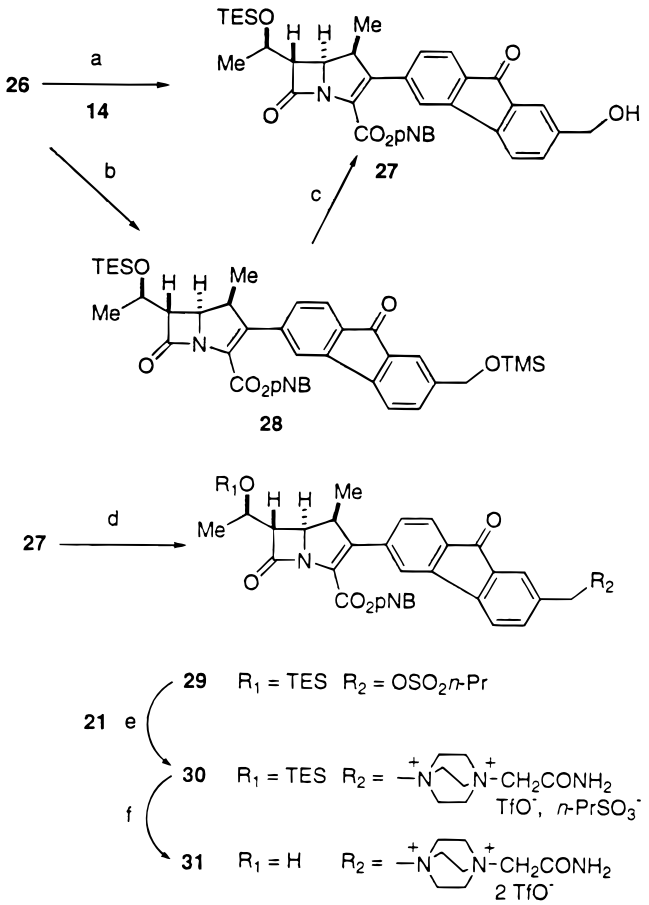
Triflation of **25** was not as straightforward as it was with **23**. The use of Et_3N (or other 3° amines) as the base gave **26** in only 82% HPLC assay yield. On the other hand, diisopropylamine (or other 2° or 1° amines) gave initially high yields but poor stability even at −78 °C. Optimum results were achieved with a combination of 1 equiv of diisopropylamine and 0.35 equiv of Et_3N. Under these conditions, vinyl triflate **26** was formed in 98% yield with good stability. The reaction can be carried out at temperatures as high as −40 °C, and scales up without difficulty.

Cross-Coupling Reactions. Initial cross-coupling efforts employed the simple fluorenone boronic acid **14** (Scheme 6). The previously developed conditions ($Pd(dba)_2$ and aqueous KOH)[9a] were successful, with the only modification being the substitution of DMF for THF because of the low solubility of **14**. The problem with this method for scale-up is that the product (**27**) could not be isolated as a crystalline solid without chromatography.

In an attempt to increase its solubility, boronic acid **14** was reacted with 3 equiv of *N*,*O*-bis(trimethylsilyl)-

(13) Liu, T. M.−H.; Lynch, J. E.; Volante, R. P. U.S. Pat. 5,493,018, 1996.

Scheme 6[a]



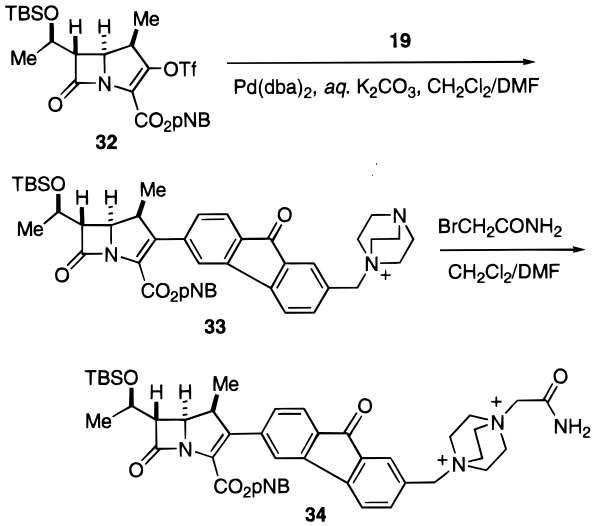
[a] (a) $Pd_2(dba)_3$·$CHCl_3$, aqueous KOH, CH_2Cl_2/DMF. (b) **14** + BSA; $Pd(dba)_2$, Et_3N, H_2O, CH_2Cl_2/THF. (c) pH 4.0, aqueous THF. (d) *n*-$PrSO_2Cl$, Et_3N, CH_2Cl_2. (e) NaI, CH_3CN. (f) pH 2.2−2.4, aqueous THF; then pH 6.5, NaOTf, H_2O.

acetamide (BSA) in THF.[14] The resulting homogeneous solution of fully silylated material was effective for cross-coupling with vinyl triflate **26** in CH_2Cl_2/THF. The TMS-containing product **28** crystallized well from methanol and could be isolated without chromatography. However, the usual cross-coupling conditions employing aqueous inorganic base caused substantial desilylation of the fluorenone hydroxymethyl position and so limited the isolated yield. Milder conditions employing 2 equiv of Et_3N as base and only 2 equiv of water limited the desilylation and allowed isolation of **28** without chromatography in 80% yield. Subsequent desilylation of **28** at pH 4.0 gave **27** in high yield.

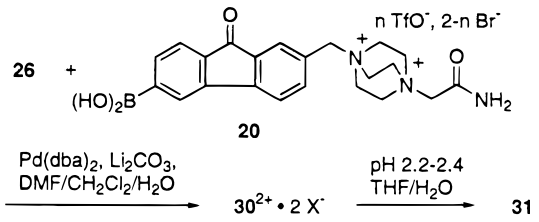
The alcohol **27** was converted to the final intermediate, *p*-nitrobenzyl (pNB)-protected L-742,728 (**31**), in three steps via the *n*-propanesulfonate **29**, in greater than 80% yield. Isolation of intermediates **27** and **30** was difficult because of poor crystallinity. In addition, this scheme suffers from multiple steps involving the sensitive carbapenem unit.

To minimize post-coupling elaboration, we next investigated reaction of the mono-quaternized-DABCO-containing side chain, as the pinacol boronate bromide salt **19** (Scheme 7). Model studies employed the *tert*-butyldimethylsilyl (TBS)-protected enol triflate **32**, which is stable enough to isolate and need not be generated in situ. The coupling of **32** and **19** proceeded smoothly in DMF/CH_2Cl_2 to give **33**. The acetamide moiety was

Scheme 7



Scheme 8

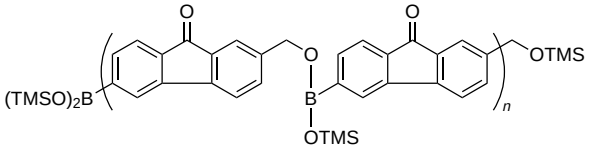


appended in situ by treatment with bromoacetamide to give the TBS/pNB-protected L-742,728 (**34**) in good yield.

Encouraged by the successful coupling of **19**, we next moved to the more ambitious goal of coupling vinyl triflate **26** with the doubly quaternized boronic acid **20**. This approach initially proved fruitless, primarily due to the difficult solubility properties of **20** and its borate salts. As a result of the highly charged character of **20**, a solvent mixture of DMF and water was essential for the reaction. The countercation of the base was also critical for success. Lithium carbonate was found to be the best base, with potassium and cesium carbonates being much worse. This trend is the opposite of the usual cation influence observed by us[9] and others,[15] and it correlates with borate solubility.

A further critical factor turned out to be the quantity of bromide ion; bromide typically constituted a portion of the counterion to the boronic acid **20**. The highest coupling rate was observed with ca. 0.2 molar equiv of bromide. Either larger or smaller quantities slowed the reaction, and no coupling occurred in the absence of halide.

(14) Silylation of the boronic acid **14** proved not to be a trivial task. The slow addition of **14** to a solution of BSA in THF at 40 °C was required to prevent formation of oligomeric boronic esters (**a**), which would give **27** after the coupling and workup.



(15) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

With the proper choice of solvents and base, high-yielding coupling occurred at 30−35 °C. Because the TES-containing product **30** was difficult to isolate (vide supra), it was desirable to proceed directly into desilylation. To do so, it was necessary to change the solvent to THF and remove the DMF to a level below 0.5%. Higher amounts of DMF led to unacceptable levels of β-lactam hydrolysis during desilylation. The CH_2Cl_2 was first removed by vacuum distillation. Then THF was added, and the solution was extracted thoroughly with aqueous NaCl. Desilylation was carried out by addition of water and acidifying to pH 2.3 with aqueous TfOH. When desilylation was complete, **31** was crystallized by neutralization, addition of NaOTf, and slow addition of water. This sequence has been carried out on a multikilogram scale, and **31** is typically isolated in a yield of 60% over the four steps from diazo compound **24**.

Preparation of L-742,728. Removal of the 4-nitrobenzyl protective moiety from **31** was accomplished by hydrogenolysis with Pt_2O below 10 °C. Purification of crude **1** was achieved by a chromatography on HP20s[16] polystyrene resin. The aqueous eluent was treated with NaCl followed by acetone, crystallizing **1** as the chloride salt which was isolated in ca. 65% yield. The highly crystalline sulfate salt was obtained by addition of sodium sulfate to an aqueous solution of the chloride salt.

Conclusion

The potent antibacterial L-742,728 was synthesized in 31−36% yield over six steps from the diazo intermediate **2**. The centerpiece of the synthesis was the highly complex Suzuki−Miyaura coupling of the dicationic boronic acid **20** with in situ prepared carbapenem vinyl triflate **26**, a convergent approach which minimized the number of steps involving unstable carbapenem intermediates.

Experimental Section

General. Reactions were carried out under an atmosphere of dry N_2. Reagents and solvents were dried over 3- or 4-Å molecular sieves. In many cases, the α-carbon of the boronic acids could not be observed due to its long relaxation time.

(2-Amino-5-methylphenyl)(4-bromophenyl)methanone (5). A precooled (−20 °C) solution of 4-toluidine (**4**; 19.5 g, 0.182 mol) in dry PhCl (50 mL) was added to precooled (−5 °C) BCl_3 (26.0 g, 0.222 mol) in dry PhCl (75 mL) over 5 min, maintaining the internal temperature below 25 °C. After 1 h at room temperature, the toluidine−BCl_3 complex slurry was added to a solution of 4-bromobenzonitrile (**3**; 18.0 g, 99 mmol) and $AlCl_3$ (15.0 g, 113 mmol) in PhCl (95 mL) at reflux over a 2 h period. After an additional 2 h at 130−134 °C, the mixture was cooled to 70 °C. The mixture was quenched into the preheated H_2O (300 mL) at 60 °C, rinsing with PhCl (30 mL). After 1 h at 80−85 °C, the mixture was cooled to 60 °C. The mixture was diluted with H_2O (630 mL) and PhCl (180 mL) and stirred at 60 °C for 0.5 h. The organic layer was separated at 60 °C, cooled to 20−25 °C, washed with H_2O (250 mL) and 5 w/v % aqueous $NaHCO_3$ (250 mL), and then azeotropically dried to give a solution of **5** (495 mL, 27.5 g; 96%). This solution was used directly in the next reaction. Analytically pure **5** was obtained by crystallization from EtOAc/hexane: mp 111−112 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.58 (m, 4H), 7.20−7.11 (m, 2H), 6.69 (d, J = 8 Hz, 1H), 2.19 (s, 3H); HRMS calcd for $C_{14}H_{12}BrNO$ 289.0140, found 289.0102. Anal. Calcd: C, 57.96; H, 4.13; N, 4.82. Found: C, 57.82; H, 4.06; N, 4.80.

6-Bromo-2-methyl-9*H*-fluoren-9-one (6). To a warm (80−82 °C) two-phase mixture of a PhCl solution of **5** (29.0 g, 100 mmol, 200 mL) and superphosphoric acid (93 g, 996 mmol) was added solid $NaNO_2$ (10.3 g, 149 mmol) in 10 equal portions every 15 min, keeping the reaction temperature at 80−82 °C with vigorous stirring. After an additional 2 h at 80−82 °C, the mixture was cooled to 60 °C and diluted with PhCl (55 mL). Water (150 mL) was added to the mixture over a 0.5 h period, maintaining the temperature at 60 °C. The organic layer was separated, washed with 5 w/v % aqueous Na_2CO_3 (150 mL) three times at 60 °C, concentrated in vacuo to a volume of ca. 170 mL, and diluted with dry PhCl (80 mL) at 60−70 °C. To the hot solution was added 15 g of silica gel at 60−70 °C, and the mixture was stirred for 0.5 h at the same temperature. The mixture was filtered, and the silica gel cake was washed with hot (60 °C) PhCl (200 mL). The filtrate and washings were combined, and the solvent was switched to *n*-BuOH. From ca. 150 mL of *n*-BuOH solution, crystals were precipitated at 0 °C, filtered, washed with cold *n*-BuOH (30 mL) followed by cold (0−5 °C) hexane (100 mL), and dried to give **6** (19.9 g; 73%): mp 159−160 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.56 (d, J = 1.3 Hz, 1H), 7.47−7.44 (m, 2H), 7.37 (dd, J = 7.9, 1.6 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.27 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 192.9, 146.3, 140.5, 140.2, 135.3, 134.4, 132.9, 131.5, 129.6, 125.4, 125.2, 123.5, 120.4, 21.4; HRMS calcd for $C_{14}H_9BrO$ 271.9836, found 271.9832. Anal. Calcd for $C_{14}H_9BrO$: C, 61.57; H, 3.29. Found: C, 61.53; H, 3.12.

6-Bromo-2-(bromomethyl)-9*H*-fluoren-9-one (7). To mixture of **6** (50 g, 183 mmol), NBS (35.7 g, 200 mmol), and AcOH (5.0 mL) in CH_2Cl_2 (500 mL) was added a solution of VAZO-52[17] (2.5 g; 10 mmol) in CH_2Cl_2 (100 mL) over a 1 h period, maintaining reflux temperature. The reaction was completed in 12 h at reflux. The mixture was heated to reflux for 1 h with added THF (350 mL). The mixture was cooled to 0 °C. The product was filtered, washed with a mixture of THF and CH_2Cl_2 (1:1) and then THF, and dried to give **7** (57.8 g; 90%) as yellowish crystals: mp 236−237 °C; ^{1}H NMR (DMF-d_7, 70 °C, 400 MHz) δ 8.08 (d, J = 1.6 Hz, 1H), 7.89 (m, 1H), 7.77−7.74 (m, 2H), 7.62 (dd, J = 7.9, 1.6 Hz, 1H), 7.57 (dd, J = 7.9, 0.6 Hz, 1H), 4.81 (s, 2H); ^{13}C NMR (DMF-d_7, 70 °C, 100 MHz) δ 192.0, 146.6, 143.6, 141.5, 136.7, 135.2, 133.8, 133.1, 130.2, 126.1, 125.4, 125.3, 122.6, 33.7. Anal. Calcd for $C_{14}H_8Br_2O$: C, 47.77; H, 2.29. Found: C, 47.44; H, 2.34.

2-[(Acetoxy)methyl]-6-bromo-9*H*-fluoren-9-one (8). A suspension of **7** (1.7 g, 4.8 mmol) and KOAc (580 mg; 5.8 mmol) in DMF (25 mL) was stirred at 100 °C for 1 h. The reaction mixture was diluted with EtOAc, washed four times with H_2O and twice with saturated aqueous NaCl, dried over $MgSO_4$, and chromatographed on a silica gel column to give **8** (1.04 g; 66%): mp 148−149 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.68−7.58 (m, 2H), 7.56−7.38 (m, 4H), 5.10 (s, 2H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 192.0, 170.7, 145.6, 142.8, 138.0, 134.5, 134.3, 132.8, 132.1, 129.8, 125.5, 124.0, 123.9, 120.6, 65.4, 20.9. Anal. Calcd for $C_{16}H_{11}BrO_3$: C, 58.03; H, 3.35. Found: C, 58.08; H, 3.34.

6-Bromo-2-(hydroxymethyl)-9*H*-fluoren-9-one (9). To a suspension of **8** (1.18 g; 3.5 mmol) in a mixture of MeOH (102 mL) and THF (23 mL) was added 0.054 M NaOMe in MeOH (6.6 mL, 0.35 mmol) at room temperature. After 1.25 h, the mixture was neutralized with 0.2 M pH 7 phosphate buffer and concentrated in vacuo. The residual was dissolved in EtOAc, washed with H_2O and saturated aqueous NaCl successively, dried over $MgSO_4$, and concentrated in vacuo to give **9** (1.00 g; 100%): mp 191−192 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 7.90−7.33 (m, 6H), 5.38 (t, J = 5.0 Hz, 1H), 4.51 (d, J = 5.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 191.9, 145.9, 145.1, 141.1, 133.4, 132.9, 132.3, 131.6, 129.2, 125.3, 124.1, 121.9, 121.4, 62.4. Anal. Calcd for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14. Found: C, 57.79; H, 3.30.

6-Bromo-2-(methoxymethyl)-9*H*-fluoren-9-one (10). A slurry of **7** (20 g, 57 mmol) in MeOH (200 mL) was heated in

(16) Trademark of Mitsubishi Chemical Co. Ltd.

(17) 2,2′-Azobis(2,4-dimethylvaleronitrile). Trademark of E. I. Du Pont De Nemours & Co. Inc.

the sealed tube at 100 °C for 24 h. The reaction mixture was used in the next reaction without further purification. Analytically pure **10** was obtained by filtration of the resulting slurry: mp 100 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 7.93 (d, J = 1.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.49−7.38 (m, 4H), 4.40 (s, 2H), 3.31 (s, 3H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 191.6, 145.6, 141.7, 140.7, 133.9, 133.4, 132.2, 131.8, 129.2, 125.3, 124.3, 122.7, 121.5, 72.8, 57.6. Anal. Calcd for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66. Found: C, 59.27; H, 3.63.

6-Bromo-9,9-dimethoxy-2-(methoxymethyl)-9*H*-fluorene (11). To the slurry of **10** (57 mmol) in MeOH (200 mL) were added concentrated H_2SO_4 (4.6 mL, 85.7 mmol) and $CH(OMe)_3$ (93.5 mL, 855 mmol) under ice-cooling. The mixture was then heated to reflux (60 °C). The reaction was completed in 1.5 h and cooled to 10 °C. After addition of Et_3N (47.7 mL; 340 mmol), the mixture was concentrated in vacuo, diluted with toluene (400 mL), and washed with 1 M aqueous NaOH (400 mL). The aqueous layer was extracted with toluene (200 mL). The combined organic phases were washed with H_2O (200 mL) twice and azeotropically dried to give a toluene solution of **11** (57 mL, 18.2 g; 92%). Analytically pure **11** was isolated as colorless crystals by silica gel column chromatography in the presence of Et_3N: mp 57 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.72 (brs, 1H), 7.59−7.48 (m, 2H), 7.46−7.33 (m, 3H), 4.51 (s, 2H), 3.42 (s, 3H), 3.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 142.0, 141.8, 140.5, 139.0, 138.0, 130.4, 129.4, 125.9, 124.1, 123.9, 123.4, 120.3, 107.3, 74.4, 58.2, 51.6. Anal. Calcd for $C_{17}H_{17}BrO_3$: C, 58.47; H, 4.91. Found: C, 58.47; H, 4.57.

[2-(Methoxymethyl)-9-oxo-9*H*-fluoren-6-yl]boronic Acid (12). Compound **12** was prepared from **11** by the method described for **16** in typically 95−99% yield. Analytically pure **12** was obtained by recrystallization from hot aqueous DMF: mp 249−251 °C (dec); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.41 (s, 2H, exchangeable with D_2O), 8.05 (s, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.54−7.47 (m, 3H), 4.39 (s, 2H), 3.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 193.3, 143.6, 142.6, 139.9, 135.2, 134.8, 134.3, 133.6, 126.1, 122.9, 122.8, 120.7, 72.9, 57.7. Anal. Calcd for $C_{15}H_{13}BO_4$: C, 67.21; H, 4.89. Found: C, 67.01; H, 4.87.

[2-(Hydroxymethyl)-9-oxo-9*H*-fluoren-6-yl]boronic Acid (14). A solution of **12** (70.8 g, 264 mmol) in TFA (710 mL) was heated to reflux for 36 h to give a solution of trifluoroacetate **13**. The solution was concentrated, diluted with H_2O (500 mL), and concentrated again. The residue was dissolved in THF (1.5 L) and 1 M aqueous NaOH (1 L) and stirred at room temperature for 1 h. Sodium salts were precipitated out by addition of THF (1.85 L) followed by aging at 5 °C overnight. The precipitates were filtered at 0 °C and washed with THF (1.1 L). The resulting solid was dissolved in a mixture of MeOH (550 mL) and H_2O (2.2 L). Insoluble material was filtered off. The filtrate was adjusted to pH 1.8 with 2 M aqueous HCl at room temperature and stirred at 5 °C. The precipitates were collected by filtration at 5 °C, washed with H_2O (1 L), and dried at 80 °C in vacuo to give **14** (60.3 g; 90.0%) as a yellowish crystalline solid: mp > 250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.41 (s, 2H), 8.06 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.56−7.52 (m, 3H), 5.42 (t, J = 5.7 Hz, 1H), 4.52 (d, J = 5.7 Hz, 2H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 193.5, 144.3, 142.9, 142.8, 135.1, 134.8, 133.5, 133.2, 125.9, 122.8, 122.0, 120.6, 62.3. Anal. Calcd for $C_{14}H_{11}BO_4$: C, 66.19, H, 4.36. Found: C, 65.95; H, 4.44.

6-Bromo-9,9-dimethoxy-2-methyl-9*H*-fluorene (15). To a solution of **6** (50 g, 183 mmol) in MeOH (500 mL) were added concentrated H_2SO_4 (15 mL, 274 mmol) and $CH(OMe)_3$ (300 mL, 2.7 mol) sequentially at 0−5 °C. The mixture was heated at reflux (56−58 °C) until the reaction was completed (typically 1.5−2.5 h). After the reaction mixture was cooled to 10 °C, Et_3N (153 mL, 1.1 mol) was added to the mixture, maintaining the temperature below 20 °C. The solution was concentrated in vacuo to ca. 225 mL. The mixture was diluted with toluene (1 L), and 1 M aqueous NaOH (1 L) was added. The organic layer was separated. The aqueous layer was extracted with toluene (0.5 L). The combined organic solution was washed with water (250 mL) and azeotropically dried to give a 150 mL toluene solution of **15** (58.4 g; 100%). The solution was used in the next reaction without further purification. Analytically pure **15** was isolated by concentration of the solution, followed by trituration with hexanes: mp 79−80 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.67 (d, J = 0.7 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.38−7.36 (m, 2H), 7.33 (m, 1H), 7.19 (dd, J = 7.8, 0.7 Hz, 1H), 3.30 (s, 6H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 142.3, 142.0, 140.2, 138.8, 135.9, 130.8, 130.0, 125.9, 125.3, 124.1, 123.2, 120.2, 107.4, 51.6, 21.7. Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.21; H, 4.74. Found: C, 60.19; H, 4.79.

(2-Methyl-9-oxo-9*H*-fluoren-6-yl)boronic Acid (16). To the solution of **15** (58.4 g, 183 mmol) in toluene (150 mL) were added $B(O\text{-}i\text{-}Pr)_3$ (62 mL, 265 mmol) and dry THF (550 mL). To this solution was slowly added *n*-BuLi solution in hexanes (1.6 M, 160 mL, 256 mmol) over a 3−7 h period, maintaining the temperature below −70 °C. The reaction was completed in 0.5 h after completion of addition. The mixture was warmed to 15 °C and slowly poured into aqueous 1 M KOH (600 mL) at about 20 °C. The mixture was washed with *t*-BuOMe (200 mL) and filtered through a medium sintered glass funnel. To the filtrate, diluted with *i*-PrOH (200 mL), was added 1 M aqueous H_2SO_4 (ca. 550 mL), keeping the temperature at 55−60 °C, until the pH became 3−4. After 2 h at 55−60 °C, the resulting slurry was aged at 15−20 °C. Crystals were filtered, washed with water, and dried to give **16** (43.0 g; 98%) as yellowish crystals: mp >250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.37 (s, 2H), 8.02 (s, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.61 (m, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.42−7.35 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 193.7, 142.9, 141.8, 139.1, 135.8, 134.9, 134.7, 133.7, 125.8, 124.6, 122.8, 120.7, 20.9. Anal. Calcd for $C_{14}H_{11}BO_3 \cdot 0.25H_2O$: C, 69.33; H, 4.78. Found: C, 69.60; H, 4.89.

2-(Bromomethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-fluoren-9-one (18). A suspension of **16** (23.8 g, 100 mmol) and pinacol (12.0 g, 101 mmol) in PhCl (560 mL) was heated and distilled until the reaction temperature increased to ca. 133 °C. The mixture was then heated at reflux for a 1 h period to give a solution of pinacol ester **17**. To the resulting solution were added AcOH (1.05 g, 17 mmol), dibromodimethylhydantoin (14.8 g, 52 mmol), and VAZO-52 (1 g, 4 mmol) at 20 °C. The mixture was heated at 37−39 °C. The reaction was completed in 15−20 h. The mixture was cooled to 0 °C and aged for 1 h. The precipitates were filtered and washed with cold PhCl (50 mL). The filtrate and washings were combined, concentrated to ca. 100 mL in vacuo, and diluted with hexanes (500 mL). The slurry was stirred at 0−5 °C for 4 h. The precipitate was filtered, washed with hexanes (100 mL), and dried in vacuo to give **18** (35.5 g; 89% based on HPLC purity). This compound was a mixture of 2-methyl, 2-dibromomethyl, and **18**. The typical purity of **18** was 90 wt % and it was used in the next reaction without further purification: mp 147−150 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 7.98 (s, 1H), 7.87 (m, 1H), 7.68−7.63 (m, 3H), 7.57 (dd, J = 7.3, 0.6 Hz, 1H), 4.76 (s, 2H), 1.32 (s, 12H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 192.6, 143.7, 142.6, 139.6, 136.3, 136.0, 135.8, 133.7, 126.5, 124.7, 123.2, 121.7, 84.2, 33.7, 24.7. Anal. Calcd for $C_{20}H_{20}BBrO_3$: C, 60.19; H, 5.05. Found: C, 60.57; H, 4.99.

1-[[9-Oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-fluoren-2-yl]methyl]-4-aza-1-azoniabicyclo[2.2.2]-octane Bromide (19). To a slurry of **18** (2.0 g, 4.5 mmol, 90 wt %) in *t*-BuOMe (25 mL) was added a solution of DABCO (0.60 g; 5.35 mmol) in MeOH (10 mL) at room temperature. After 2 h at room temperature, the solid was filtered, washed with *t*-BuOMe (10 mL) twice, and dried to give **19** (2.07 g; 92%) as yellowish solid: mp >250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.14−8.03 (m, 2H), 7.83−7.74 (m, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 4.69 (s, 2H), 3.51−3.27 (m, 6H), 3.15−2.91 (m, 6H), 1.33 (s, 12H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 192.6, 145.4, 142.3, 140.5, 136.5, 135.7, 133.6, 128.6, 128.5, 126.8, 123.4, 122.0, 84.3, 65.4, 51.5, 44.7, 24.7.

1-(2-Amino-2-oxoethyl)-4-aza-1-azoniabicyclo[2.2.2]-octane Trifluoromethanesulfonate (21). To a precooled (5 °C) solution of DABCO (12.3 g, 0.11 mol) in MeCN (65 mL) was added a solution of 2-chloroacetamide (9.35 g, 0.10 mol)

in MeCN (210 mL) over a 0.5−2 h period, keeping the temperature below 15 °C. The reaction was completed at 20−25 °C in 8−10 h. The slurry was filtered, washed with MeCN (100 mL), and dried to give the chloride salt (20.0 g; 97%): ^{1}H NMR (D_2O, 250 MHz) δ 4.13 (s, 2H), 3.71 (t, J = 7.4 Hz, 6H), 3.26 (t, J = 7.4 Hz, 6H); ^{13}C NMR (CD_3OD, 63 MHz) δ 166.7, 63.5, 54.3, 46.0. The chloride salt (11.3 g, 55 mmol) was added portionwise to a solution of NaOTf (9.9 g, 57 mmol) in MeCN (180 mL) at 20 °C. After 2−4 h at 40−45 °C, the mixture was filtered through Solka Floc, rinsing with MeCN (20 mL) at 40 °C. The filtrate and washings were combined to obtain a solution of **21** (96−98%) in MeCN and used for the next reactions. Analyticaly pure **21** was obtained by crystallization from EtOH: mp 174−175 °C; ^{1}H NMR (D_2O, 250 MHz) δ 4.04 (s, 2H), 3.65 (t, J = 7.5 Hz, 6H), 3.22 (t, J = 7.5 Hz, 6H); ^{13}C NMR (CD_3OD, 63 MHz) δ 166.6, 121.8 (q, J = 319 Hz), 63.3, 54.3, 45.9. Anal. Calcd for $C_9H_{16}F_3N_3O_4S$: C, 33.85; H, 5.05; N, 13.16. Found: C, 34.00; H, 5.03; N, 13.15.

1-(2-Amino-2-oxoethyl)-4-[(6-borono-9-oxo-9*H*-fluoren-2-yl)methyl]-1,4-diazoniabicyclo[2.2.2]octane Bromide Trifluoromethanesulfonate (20). A slurry of **21** (17.6 g, 55 mmol), **18** (20 g, 45 mmol; 90 wt %) in MeCN (200 mL), and MeOH (200 mL) was stirred at 28−30 °C for 12−15 h. To the mixture was added 0.5 M aqueous KOTf (200 mL, 100 mmol) over 1 h at 20−25 °C. The mixture was concentrated in vacuo to ca. 400 mL. After water (300 mL) was added, the mixture was further concentrated to ca. 250 mL. The product was precipitated out at 20 °C, filtered, washed with 0.2 M aqueous LiOTf (50 mL, 100 mmol), and dried. A slurry of the crude product in *t*-BuOMe (200 mL) was refluxed for 20 min and cooled to 20 °C. The mixture was filtered, washed with *t*-BuOMe (200 mL), and dried to give **20** (27.3 g; 95%): mp >250 °C; ^{1}H NMR (DMSO-d_6 + D_2O, 250 MHz) δ 8.13 (brs, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.81 (dd, J = 7.4, 1.2 Hz, 1H), 7.78−7.72 (m, 2H), 7.62 (d, J = 7.4 Hz, 1H), 4.79 (s, 2H), 4.27 (s, 2H), 4.16−4.00 (m, 6H), 4.00−3.85 (m, 6H); ^{13}C NMR (DMSO-d_6 + D_2O, 63 MHz) δ 193.5, 164.8, 147.0, 143.2 (br), 142.5, 140.9, 136.8, 135.3, 134.6, 128.8, 127.4, 127.2, 123.9, 122.3, 121.0 (q, J = 321 Hz), 67.0, 62.1, 52.1, 50.7. Anal. Calcd for $C_{23}H_{26}BBrF_3N_3O_7S\cdot0.5H_2O$: C, 42.81; H, 4.22; N, 6.51; S, 4.97. Found: C, 42.67; H, 4.09; N, 6.26; S, 4.74. The bis triflate salt was prepared by treatment with AgOTf followed by crystallization from MeOH: mp >250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.44 (brs, 2H), 8.20 (s, 1H), 8.00 (brs, 1H), 7.95 (d, J = 7.4 Hz, 1H), 7.89−7.79 (m, 2H), 7.78−7.68 (m, 2H), 7.64 (d, J = 7.4 Hz, 1H), 4.79 (s, 2H), 4.29 (s, 2H), 4.07 (m, 6H), 3.91 (m, 6H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 192.8, 164.6, 146.4, 142.0, 140.3, 136.2, 134.8, 134.1, 128.3, 127.4, 126.9, 123.2, 121.7, 120.7 (q, J = 319 Hz), 66.3, 61.5, 51.5, 50.2.

(4-Nitrophenyl)methyl [2*R*-[2α(*R),3*β*(*R**)]]-α-Diazo-*γ*-methyl-*β*,4-dioxo-3-[1-[(triethylsilyl)oxy]ethyl]-2-azetidinebutanoate (24).** To a vigorously stirred solution of alcohol **2** (15.0 g, 38.4 mmol) and imidazole (4.7 g, 69.0 mmol) in a mixture of *i*-PrOAc (90 mL) and THF (20 mL) was slowly added TESCl (9.0 mL, 53.6 mmol), maintaining a temperature of 18−22 °C. After being stirred for 2 h at 20 °C, the mixture was poured into a mixture of heptane (30 mL) and 0.01 M phosphate buffer (100 mL; pH 6.8) at room temperature. The organic layer was separated and washed with 0.01 M phosphate buffer three times. The organic solution was concentrated and **24** was isolated from a mixture of heptane (ca. 97%) and *i*-PrOAc (ca. 3%) at 0 °C as crystalline solid (18.0 g; 93%): mp 64 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.22 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 6.14 (s, 1H), 5.33 (s, 2H), 4.20−4.07 (m, 1H), 3.94−3.81 (m, 2H), 2.92 (dd, J = 4.9, 1.5 Hz, 1H), 1.18 (d, J = 6.3 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.9 Hz, 9H), 0.60−0.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 194.1, 168.2, 160.6, 147.9, 141.9, 128.7, 123.9, 76.0, 65.5, 65.2, 61.2, 51.9, 43.3, 22.6, 12.3, 6.7, 4.8. Anal. Calcd for $C_{23}H_{32}N_4O_7Si$: C, 54.75; H, 6.39; N, 11.10. Found: C, 54.65; H, 6.32; N, 11.07.

(4-Nitrophenyl)methyl [4*S*-[4α,5*β*,6*β*(*S)]]-4-Methyl-7-oxo-3-[2-(hydroxymethyl)-9-oxo-9*H*-fluoren-6-yl]-6-[1-[(triethylsilyl)oxy]ethyl]-1-azabicyclo[3.2.0]heptan-2-carboxylate (27). Coupling of 26 and 14.** A solution of the diazo alcohol **2** (20.0 g, 51.2 mmol) in dry CH_2Cl_2 (200 mL) was heated to reflux for 4 h in the presence of rhodium octanoate (199 mg, 0.26 mmol) and $ZnBr_2$ (118 mg, 0.52 mmol) and then cooled to −78 °C. To this solution were added Et_3N (6.82 mL, 48.9 mmol) and Tf_2O (48.9 mmol) keeping the reaction temperature below −73 °C. After 30 min at −78 °C, Et_3N (7.85 mL, 56.4 mmol) and TESOTf (12.7 mL, 56.4 mmol) were sequentially added, again below −73 °C to give a solution of triflate **26**. After the mixture was stirred an additional 1 h at −78 °C, a solution of boronic acid **14** (13.0 g; 51.2 mmol) in DMF (110 mL) was added to the cold mixture, followed by $Pd_2(dba)_3\cdot CHCl_3$ (1.08 g, 1.04 mmol) and 6 M aqueous KOH (25.6 mL, 153.6 mmol). The reaction mixture was then warmed to 30 °C. After 1 h at 30−35 °C, the mixture was cooled and diluted with EtOAc (300 mL). The precipitate was filtered, and the mixture was concentrated to ca. 200 mL. The solution was diluted with EtOAc (300 mL) and washed with H_2O (300 mL). The aqueous layer was back extracted with EtOAc (50 mL). The organic extracts were combined, dried over $MgSO_4$, and purified by silica gel column chromatography (1.5 L; EtOAc:hexanes from 37:63 to 50:50) to give **27** (26.6 g, containing 2.5 wt % EtOAc; 77%) as amorphous solid. Analytically pure **27** was obtained by crystallization from a mixture of *t*-BuOMe and heptane: mp 85−87 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.92 (m, 2H), 7.57−7.50 (m, 2H), 7.43−7.24 (m, 5H), 7.15 (dd, J = 7.5, 1.1 Hz, 1H), 5.19 (d, J = 13.5 Hz, 1H), 5.08 (d, J = 13.5 Hz, 1H), 4.63 (s, 2H), 4.40 (dd, J = 10.3, 3.0 Hz, 1H), 4.33−4.22 (m, 1H), 3.52−3.34 (m, 2H), 3.10 (br, 1H), 1.26 (d, J = 6.1 Hz, 3H), 1.10 (d, J = 7.3 Hz, 3H), 0.93 (t, J = 7.2 Hz, 9H), 0.63−0.54 (m, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 192.8, 175.1, 160.0, 148.7, 147.1, 143.7, 143.1, 142.5, 141.9, 139.7, 134.1, 133.9, 132.9, 128.8, 128.2, 127.2, 123.6, 123.2, 122.6, 121.0, 120.1, 65.5, 65.3, 64.0, 60.6, 55.5, 44.1, 22.3, 15.5, 6.6, 4.7. Anal. Calcd for $C_{37}H_{40}N_2O_8Si$: C, 66.45; H, 6.03; N, 4.19. Found: C, 66.12; H, 6.18; N, 4.05.

(4-Nitrophenyl)methyl [4*S*-[4α,5*β*,6*β*(*S)]]-4-Methyl-7-oxo-3-[9-oxo-2-[[(trimethylsilyl)oxy]methyl]-9*H*-fluoren-6-yl]-6-[1-[(triethylsilyl)oxy]ethyl]-1-azabicyclo[3.2.0]heptan-2-carboxylate (28).** To a solution of bis(trimethylsilyl)acetamide (BSA) (1.485 kg, 7.30 mol) in THF (15 L) was added **14** (996 g, 3.92 mol) in 10−20 portions over 2 h. The resulting solution was stirred at 35 °C for 30 min and then cooled to 0 °C. Simultaneously, a solution of **26** was prepared from **2** (1.50 kg, 3.84 mol) by Rh(II)-catalyzed cyclization (14.9 g of rhodium octanoate, 8.85 g of $ZnCl_2$, 15 L of CH_2Cl_2) followed by the sequential additions of Et_3N (536 mL, 3.84 mol), Tf_2O (646 mL, 3.84 mol), Et_3N (669 mL, 4.80 mol), and TESOTf (956 mL, 4.23 mol) as described in the above example. The THF solution of silylated **14** was added to the −78 °C solution of **26**. To the resulting −40 °C mixture were added H_2O (138 mL, 7.68 mol), $Pd(dba)_2$ (66.3 g, 115 mmol), and Et_3N (1.02 L, 7.30 mol), and the solution was warmed to 30 °C. When the reaction was complete (2−3 h), the solution was cooled to room temperature. The mixture was diluted with hexanes (9 L) and washed with aqueous NaCl twice. The solution was filtered through Solka Floc. The solvent was then evaporated with concurrent addition of methanol (final volume 6 L), inducing crystallization. The crystals were filtered and dried to give **28** (2.0 kg; 70%). On a smaller scale (20 g) this procedure gave a somewhat higher yield of 81%: mp 142−145 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.04 (m, 2H), 7.64−7.58 (m, 2H), 7.47−7.32 (m, 5H), 7.19 (dd, J = 7.5, 1.3 Hz, 1H), 5.27 (d, J = 13.6 Hz, 1H), 5.13 (d, J = 13.6 Hz, 1H), 4.69 (s, 2H), 4.41 (dd, J = 10.3, 3.1 Hz, 1H), 4.37−4.25 (m, 1H), 3.52−3.40 (m, 1H), 3.37 (dd, J = 5.8, 3.1 Hz, 1H), 1.29 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 7.4 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.67−0.56 (m, 6H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 192.9, 175.1, 160.1, 148.9, 147.5, 144.1, 143.1, 142.6, 142.2, 139.7, 134.4, 134.3, 132.6, 128.9, 128.3, 127.3, 123.9, 123.5, 122.5, 120.9, 120.2, 65.8, 65.4, 63.9, 60.9, 55.7, 44.3, 22.5, 15.7, 6.8, 4.9, −0.5. Anal. Calcd for $C_{40}H_{48}N_2O_8Si_2$: C, 64.84; H, 6.53; N, 3.78. Found: C, 64.84; H, 6.59; N, 3.65.

Compound 27, from Desilylation of 28. A solution of **28** (3.45 kg, 4.66 mol) in a mixture of THF (55.2 L) and 0.05 M phthalic acid potassium acid salt aqueous solution (22.1 L;

pH 4.0) was stirred at room temperature for 16 h. To the solution was added solid NaCl (5.52 kg); the resulting organic layer was separated and washed with saturated aqueous $NaHCO_3$ (22 L) followed by saturated aqueous NaCl (22 L). The organic layer was concentrated in vacuo to about 4 L. The solution was diluted with *t*-BuOMe (50 L) and washed with 2.5 wt % aqueous NaCl (22 L). Further concentration of the organic layer gave a solution in *t*-BuOMe (20 L). Compound **27** was crystallized by the addition of heptane (60 L). Filtration and drying gave 2.90 kg, 93%.

(4-Nitrophenyl)methyl [4*S*-[4α,5*β*,6*β*(*S)]]-4-Methyl-7-oxo-3-[9-oxo-2-[[(propylsulfonyl)oxy]methyl]-9*H*-fluoren-6-yl]-6-[1-[(triethylsilyl)oxy]ethyl]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (29).** To a −20 °C solution of **27** (1.4 kg, 2.09 mol) in dry CH_2Cl_2 (14 L) were added Et_3N (0.321 L, 2.30 mol) and *n*-$PrSO_2Cl$ (0.235 L, 2.09 mol). After 30 min at −20 °C, the reaction solution was added to 0.25 M MOPS buffer at pH 6.8 (14 L). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to ca. 7 L. By addition of MeCN and vacuum concentration, the mixture was converted to a solution in 14 L of MeCN and used directly for the next reaction. Alternatively, by evaporation of the CH_2Cl_2, **29** could be isolated as an amorphous solid: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.95 (brd, J = 8.6 Hz, 2H), 7.60−7.53 (m, 2H), 7.48−7.32 (m, 5H), 7.21 (m, 1H), 5.22 (d, J = 13.6 Hz, 1H), 5.15 (s, 2H), 5.08 (d, J = 13.6 Hz, 1H), 4.40 (dd, J = 10.3, 3.0 Hz, 1H), 4.27 (m, 1H), 3.47 (dq, J = 10.3, 7.4 Hz, 1H), 3.37 (dd, J = 5.5, 3.0 Hz, 1H), 3.12−3.02 (m, 2H), 1.84 (m, 2H), 1.25 (d, J = 6.1 Hz, 3H), 1.10 (d, J = 7.4 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.9 Hz, 9H), 0.64−0.51 (m, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 191.8, 174.9, 159.9, 148.3, 147.1, 144.1, 143.1, 142.1, 139.9, 135.2, 134.7, 134.4, 133.8, 129.4, 128.1, 127.3, 124.0, 123.7, 123.2, 121.4, 120.5, 69.7, 65.5, 65.2, 60.7, 55.4, 52.4, 44.0, 22.2, 17.0, 15.5, 12.6, 6.6, 4.7. Anal. Calcd for $C_{40}H_{46}N_2O_{10}SSi$: C, 62.00; H, 5.98, N, 3.61, S, 4.14. Found: C, 62.05; H, 6.03; N, 3.59; S, 4.30.

[4*S*-[4α,5*β*,6*β*(*S)]]-1-(2-Amino-2-oxoethyl)-4-[[6-[4-methyl-2-[[[(4-nitrophenyl)methyl]oxy]carbonyl]-7-oxo-6-[1-[(triethylsilyl)oxy]ethyl]-1-azabicyclo[3.2.0]hept-2-en-3-yl]-9-oxo-9*H*-fluoren-2-yl]methyl]-1,4-diazaniabicyclo-[2.2.2]octane 1-Propanesulfonate Trifluoromethanesulfonate (30).** To a solution of **29** (containing 2.09 mol) in MeCN (14 L) were added **21** (801 g, 2.51 mol) and NaI (16 g, 0.11 mol). The solution was stirred at 28−29 °C for 20 h in the dark. To the resulting suspension was added *t*-BuOMe (14 L). The solids were collected by filtration, washed with *t*-BuOMe, and dried to give crude **30** (2.19 kg, 93%). This solid was used for the next reaction without further purification: ^{1}H NMR (acetone-d_6 + D_2O, 250 MHz) δ 8.00−7.57 (m, 6H), 7.57−7.28 (m, 4H), 5.18 (d, J = 13.4 Hz, 1H), 5.08 (d, J = 13.4 Hz, 1H), 4.95 (brs, 2H), 4.63−4.02 (m, 16H), 3.66−3.39 (m, 2H), 2.65 (m, 2H), 1.62 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H), 0.98−0.74 (m, 12H), 0.64−0.43 (m, 6H); ^{13}C NMR (acetone-d_6 + D_2O, 63 MHz) δ 193.0, 176.3, 165.3, 160.7, 149.1, 147.5, 146.4, 143.4, 143.3, 141.4, 141.0, 134.9, 133.9, 131.1, 129.0, 128.7, 127.7, 127.4, 124.4, 123.6, 122.9, 122.6, 120.8 (q, J = 319 Hz), 68.0, 65.8, 65.6, 62.7, 61.0, 55.4, 53.6, 52.7, 51.3, 44.2, 22.0, 18.6, 15.6, 13.2, 6.8, 5.0. Anal. Calcd for $C_{49}H_{62}F_3N_5O_{14}S_2Si$: C, 53.78; H, 5.71; N, 6.40; S, 5.86. Found: C, 53.62; H, 5.79; N, 6.31; S, 5.94.

[4*S*-[4α,5*β*,6*β*(*S)]]-1-(2-Amino-2-oxoethyl)-4-[[6-[6-(1-hydroxyethyl)-4-methyl-2-[[[(4-nitrophenyl)methyl]oxy]-carbonyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl]-9-oxo-9*H*-fluoren-2-yl]methyl]-1,4-diazaniabicyclo[2.2.2]-octane 1-Propanesulfonate Trifluoromethanesulfonate (31).** A solution of **30** (2.19 kg, 1.95 mol) in a mixture of THF (9.24 L) and H_2O (4.62 L) was stirred at 23−25 °C, maintaining a pH of 2.3−2.4 by addition of 1 M aqueous TfOH and saturated aqueous $NaHCO_3$. After 4 h, NaOTf (402 g, 2.34 mol) was added and the pH was adjusted to 6.4 with saturated aqueous $NaHCO_3$. Crystallization was induced by addition of H_2O (ca. 40 L). The crystals were isolated by filtration, washed with 20 v/v % aqueous THF (5 L), and dried to give **31** (1.85 kg; 90% yield; typical purity was 92−95%; containing 0.3−1 equiv of $PrSO_3^-$ residue).

[4*S*-[4α,5*β*,6*β*(*S)]]-1-(2-Amino-2-oxoethyl)-4-[[6-[4-methyl-2-[[[(4-nitrophenyl)methyl]oxy]carbonyl]-7-oxo-6-[1-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-1-azabicyclo-[3.2.0]hept-2-en-3-yl]-9-oxo-9*H*-fluoren-2-yl]methyl]-1,4-diazaniabicyclo[2.2.2]octane (34).** To a solution of vinyl triflate **32** (304 mg, 0.50 mmol), prepared from **2** by a method similar to that described for the preparation of **26**, and pinacol boronate **19** (256 mg, 0.50 mmol) in a mixture of CH_2Cl_2 (2 mL) and DMF (1.1 mL) was added $Pd(dba)_2$ (12 mg, 0.02 mmol) and 3 M aqueous K_2CO_3 (0.333 mL, 1 mmol). The mixture was stirred at 32 °C for 2.5 h to give a solution of DABCO salt **33**. To this reaction mixture was added bromoacetamide (83 mg, 0.6 mmol), and the mixture was stirred at 32 °C for 1.5 h. The mixture was then stirred at room temperature overnight with additional bromoacetamide (24 mg, 0.17 mmol). The reaction mixture was filtered and diluted with THF to 25 mL. Analysis by HPLC indicated the presence of **34** (0.41 mmol, 82%). HPLC assay: Inertsil ODS 4.6 × 250 mm; MeCN:0.02 M $HNEt_3OAc$ buffer (pH 4.5); 50:50 for 0−5 min; 50:50 to 90:10 over 5−15 min; 90:10 for 15−25 min; flow rate 1.0 mL/min; UV detection at 254 nm; t_R(**32**) = 24 min; t_R(**33**) = 16.3 min; t_R(**34**) = 11.7 min. An authentic sample of **34** was prepared as the propanesulfonate trifluoromethanesulfonate salt from coupling **32** with **14**, followed by conversion to **34** by the same sequence used to make **30** from **27**. Amorphous solid: ^{1}H NMR (acetone-d_6 + D_2O) δ 7.88 (d, J = 8.6 Hz, 2H), 7.84−7.69 (m, 2H), 7.67−7.58 (m, 2H), 7.50−7.40 (m, 3H), 7.31 (d, J = 7.7 Hz, 1H), 5.19 (d, J = 7.7 Hz, 1H), 5.08 (d, J = 7.7 Hz, 1H), 4.95 (brs, 2H), 4.50 (brs, 2H), 4.47−4.12 (m, 14H), 3.64−3.43 (m, 2H), 2.68 (m, 2H), 1.63 (m, 2H), 1.15 (d, J = 6.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H), 0.77 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (acetone-d_6 + D_2O) δ 193.0, 176.5, 165.3, 160.7, 149.0, 147.5, 146.4, 143.4, 143.3, 141.4, 141.0, 134.9, 133.8, 131.0, 129.0, 128.7, 127.7, 127.4, 124.3, 123.6, 123.0, 122.6, 120.8 (q, J = 319 Hz), 68.0, 65.8, 65.5, 62.7, 61.0, 55.2, 53.6, 52.7, 51.3, 44.1, 25.8, 21.9, 18.6, 18.1, 15.6, 13.2, −4.5, −5.2. Anal. Calcd for $C_{45}H_{55}N_5O_8Si^{2+}\cdot 1.3CF_3O_3S^-\cdot 0.7C_3H_7O_3S^-$: C, 52.75; H, 5.48; N, 6.35; S, 5.82. Found: C, 52.50; H, 5.24; N, 6.32; S, 5.70.

Preparation of 31 from 24 and 20. A mixture of **24** (30.0 g; 59.5 mmol), rhodium octanoate (0.23 g; 0.30 mmol), and $ZnBr_2$ (0.13 g; 0.60 mmol) in CH_2Cl_2 (120 mL) was heated to reflux under nitrogen for 90 min. The resulting solution of **25** was cooled to −50 °C, and to it was added a mixture of diisopropylamine (7.79 mL, 59.5 mmol) and Et_3N (2.90 mL, 20.8 mmol) dropwise. After 15 min, Tf_2O (10.5 mL, 62.4 mmol) was added, maintaining the reaction temperature below −40 °C, and the mixture was stirred at this temperature for 1 h to give a solution of **26**. Simultaneously, boronic acid **20** (33.9 g, 52.9 mmol) and Li_2CO_3 (6.26 g, 84.7 mmol) were suspended in a mixture of DMF (184 mL) and H_2O (74 mL) at 30 °C. To this suspension was added the cold mixture containing **26**, rinsing with DMF (30 mL). The combined reaction mixture was warmed to 30 °C after addition of $Pd(dba)_2$ (1.30 g, 2.26 mmol). The reaction was typically complete in 8 h. The CH_2Cl_2 was removed from the reaction mixture in vacuo. The mixture was filtered through Solka Floc, rinsing with 1:1 DMF/H_2O (43 mL). After dilution with THF (300 mL), the solution was washed three times with 20 wt % aqueous NaCl, with THF being added before the second and third washing. The solution was concentrated in vacuo to give 265 mL of 90:10 THF/water containing 50.4 mmol of **30**. After addition of water (96 mL), the pH of the solution was adjusted to 2.4 with 1.0 M aqueous TfOH at room temperature. After 1 h of stirring, the pH was readjusted to 5 with 1.0 M. aqueous $NaHCO_3$. Aqueous NaOTf (45 mL of 2.0 M) was then added, and the pH was adjusted to 6.5. Addition of water (554 mL) induced crystallization. After 8 h of stirring at room temperature and 2 h at 5 °C, the mixture was filtered and the crystals were washed with water followed by MeOH. Vacuum drying gave **31** (36.8 g; 94 wt %; 58% overall yield): ^{1}H NMR (acetone-d_6 + D_2O, 250 MHz) δ 7.85−7.72 (m, 4H), 7.68 (d, J = 7.7 Hz, 1H), 7.58 (brs, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.32−7.24 (m, 3H), 5.11 (d, J = 13.1 Hz, 1H), 5.04 (d, J = 13.1 Hz, 1H), 4.96 (brs, 2H), 4.49 (brs, 2H), 4.47−4.34 (m, 7H), 4.28−4.19 (m, 6H), 4.14 (q,

J = 6.3 Hz, 1H), 3.56 (dq, J = 10.1, 7.4 Hz, 1H), 3.45 (dd, J = 6.3, 3.1 Hz, 1H), 1.23 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 7.4 Hz, 3H); ^{13}C NMR (acetone-d_6 + D_2O) δ 193.0, 177.2, 165.2, 160.9, 150.1, 147.4, 146.6, 143.2, 143.0, 142.0, 141.0, 134.9, 133.8, 130.8, 129.6, 128.6, 127.8, 127.3, 124.4, 123.7, 123.0, 122.6, 120.8 (q, J = 319 Hz), 68.2, 66.2, 65.3, 62.7, 60.4, 56.4, 52.7, 51.4, 44.7, 21.1, 15.3. Anal. Calcd for $C_{41}H_{41}F_6N_5O_{14}S_2$: C, 48.96; H, 4.11; N, 6.96. Found: C, 48.61; H, 4.21; N, 6.78.

[4*S*-[4α,5*β*,6*β*(*S)]]-1-(2-Amino-2-oxoethyl)-4-[[6-[2-carboxy-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-en-3-yl]-9-oxo-9*H*-fluoren-2-yl]methyl]-1,4-diazoniabicyclo[2.2.2]octane Hemisulfate (1; L-742,728 Hemisulfate).** A suspension of **31** (206 g, 95 wt % pure; 195 mmol) in a mixture of 0.025 M MOPS buffer (pH 7.0; 6 L) and *i*-PrOH (6 L) was hydrogenated at 5−10 °C under 100 psi of hydrogen in the presence of PtO_2 (6 g) for 5 h 45 min. The reaction mixture was diluted with THF (5 L) and filtered through a pad of Solka Floc, rinsing with 2 L of cold saturated aqueous NaCl. After addition of solid NaCl (1.5 kg), the combined solution was washed three times with wet *i*-AmOH (12 L) at 5 °C. The aqueous solution contained 132 mmol of **1** in 6 L (68%). Chromatography on HP20s resin at 5 °C, eluting with acetone/water, followed by addition of NaCl and acetone/methyl ethyl ketone crystallized **1** as the chloride salt (76.2 g; 64%): ^{1}H NMR (D_2O; 400 MHz) δ 7.49 (d, J = 7.8 Hz, 1H), 7.31−7.27 (m, 4H), 7.29 (d, J = 7.8 Hz, 1H), 4.71 (d, J = 13.3 Hz, 1H), 4.65 (d, J = 13.3 Hz, 1H), 4.49 (s, 2H), 4.37−4.29 (m, 8H), 4.11 (m, 6H), 3.52 (dd, J = 5.7, 2.7 Hz, 1H), 3.47 (dq, J = 9.0, 7.1 Hz, 1H), 1.36 (d, J = 6.4 Hz, 3H), 1.09 (d, J = 7.1 Hz, 3H); ^{13}C NMR (D_2O, 101 MHz) δ 194.5, 177.5, 169.4, 166.1, 146.8, 143.6, 142.4, 141.0, 136.4, 135.3, 135.1, 132.5, 130.6, 128.4, 126.7, 125.1, 122.8, 121.7, 68.4, 65.7, 63.2, 59.0, 56.9, 53.1, 51.5, 42.0, 21.0, 16.9. The chloride salt was converted to the hemisulfate dihydrate by addition of K_2SO_4 solution to the aqueous chloride salt. Anal. Calcd for $C_{32}H_{35}N_4O_6^+ \cdot 0.5SO_4^{2-} \cdot 2H_2O$: C, 58.62; H, 5.99; N, 8.54; S, 2.44. Found: C, 58.57, H, 5.90, N, 8.43, S, 2.56.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **19** and **20** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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