Macrocyclic Bisindolylmaleimides: Synthesis by Inter- and Intramolecular Alkylation

Margaret M. Faul,* Leonard L. Winneroski, Christine A. Krumrich, Kevin A. Sullivan, James R. Gillig,† David A. Neel,† Christopher J. Rito,† and Michael R. Jirousek†

Lilly Research Laboratories, A Division of Eli Lilly and Company, Chemical Process Research and Development Division and Endocrine Discovery Research, Indianapolis, Indiana 46285-4813

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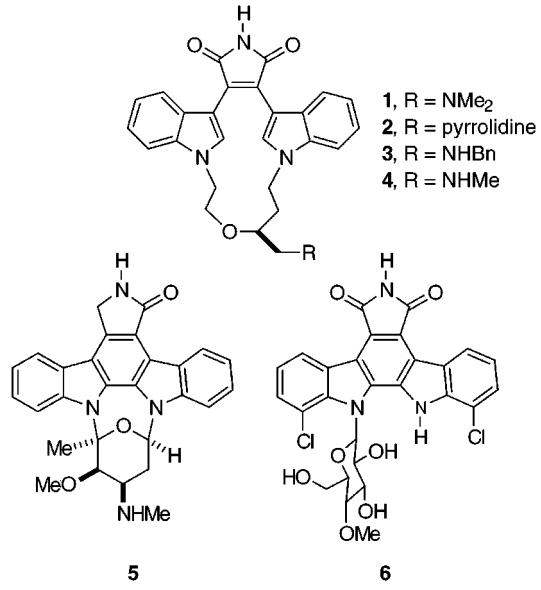
Macrocyclic bisindolylmaleimides **1**−**4** have been identified as competitive reversible inhibitors of PKC β_1 and β_2 and are being advanced to the clinic for evaluation as a treatment of retinopathy associated with diabetic complications. Highly convergent and stereoselective syntheses of **1**−**4** have been developed. The key synthetic step involves intermolecular alkylation of symmetrical bisindolylmaleimide **9** with chiral bisalkylating agent **8c** and is amenable to the preparation of multikilogram quantities of these compounds. The synthetic sequence to **1**, the most active compound, proceeds in 11 steps and 26% overall yield (>98% ee) from (*R*)-1-chloro-2,3-propanediol. No chromatographic purifications are required throughout the process and the final product is isolated in >97% purity after crystallization from DMF/MeOH. Synthesis of **1**−**4** by intramolecular alkylation proved less efficient, requiring 17 steps and affording **1**−**4** in lower overall yields of 6.0−8.5%.

Introduction

Hyperglycemia is the major cause of retinopathy and nephropathy in patients with diabetes mellitus.[1] One theory has attributed the adverse effects of hyperglycemia to the activation of protein kinase C (PKC), a family of serine/threonine specific kinases, consisting of at least 11 isozymes, which regulate vascular function.[2] Recently, Ishii and co-workers provided support for the hypothesis that activation of the β_2 isoform of PKC in vascular tissue is a key step in the cascade of events through which glucose triggers diabetic complications.[3] In the development of new therapies for the treatment of diabetic complications, we have identified a family of macrocyclic bisindolylmaleimides **1**−**4** that are competitive reversible inhibitors of PKC β_1 and β_2 (Chart 1).[4] Of this class, **1** was determined to be the most active compound, exhibiting nanomolar inhibition of PKC β and at least 60-fold selectivity for PKC β versus PKC α. In addition, **1** is several orders of magnitude more selective for inhibition of PKC β in comparison to the other ATP dependent kinases. This represents a significant improvement over the naturally occurring indolocarbazoles, such as staurosporine (**5**)[5] and rebeccamycin (**6**),[6] which are known to be inhibitors of PKC but have little selectivity in vitro for both ATP dependent kinases and the individual PKC isozymes.

Chart 1



5 **6**

The encouraging biological and pharmacological properties of **1**−**4** resulted in selection of these compounds for clinical evaluation. In support of these studies, a synthetic route that would be amenable to the preparation of multikilogram quantities of **1**−**4** was required. This paper describes the first full disclosure of our synthetic approaches to the synthesis of this class of compounds.[7]

† Endocrine Discovery Research.

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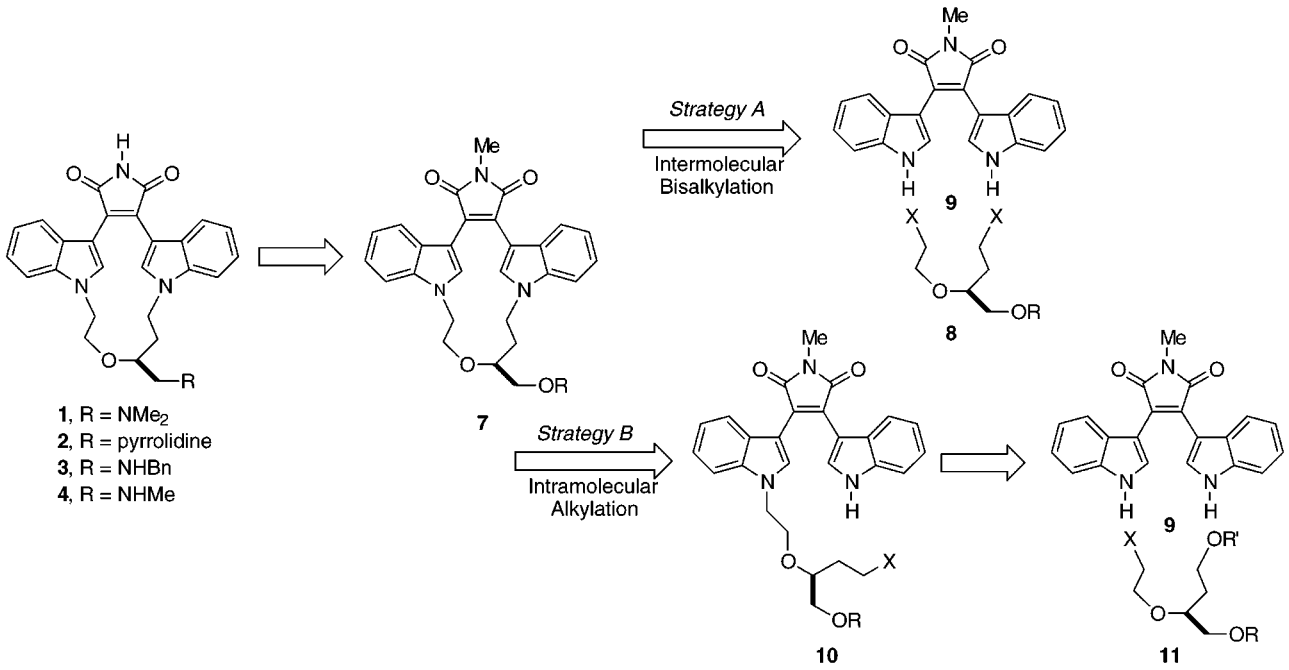
Scheme 1



Results and Discussion

Retrosynthetic Analysis. Acyclic bisindolylmaleimides can be prepared by reaction of indolyl-3-glyoxylyl chlorides with indole-3-acetic acids[8] or indole-3-acetimidate esters.[9] These methods, however, were not applicable to the synthesis of **1**−**4** due to the low yields and difficult chromatographic purifications required. In the design of a scalable synthetic route to **1**−**4**, several key issues were considered. In addition to ensuring stereochemical control and obtaining high yield for reactions, special emphasis was devoted to practical issues including avoiding all chromatographic purifications and the use of hazardous reagents and/or reaction conditions.

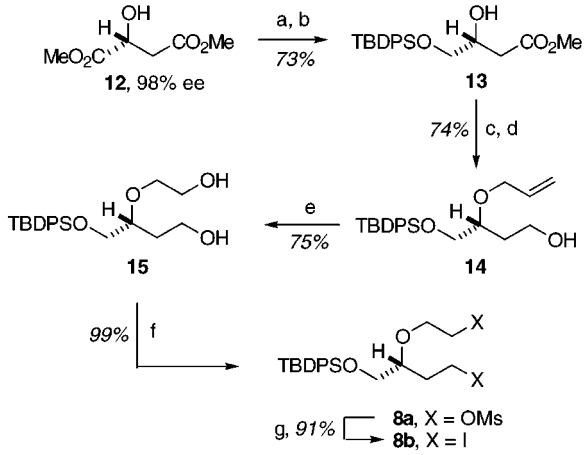
Our retrosynthetic analysis of **1**−**4** is shown in Scheme 1. The 14-membered macrocycle **7** was selected as the penultimate intermediate to be converted into **1**−**4** by hydrolysis and ammonolysis of the *N*-methylmaleimide, followed by deprotection/activation of the alcohol and displacement with the appropriate amine. Two approaches to **7** were examined based upon alkylation of symmetrical bisindolylmaleimide **9**, readily prepared in 65−70% yield by coupling indolylmagnesium bromide with 3,4-dichloro-*N*-methylmaleimide.[10] The intermolecular approach involved formation of macrocycle **7** in one step by reaction of **9** with chiral bisalkylating agent **8** (strategy A). In the intramolecular approach (strategy B), a four-step sequence via **10** was required to generate **7**. A comparison of both synthetic approaches for the synthesis of **1**−**4** will be outlined and the optimum synthesis of the bisalkylating agent **8** and alkylating agent **11** described.

Synthesis of the Alkylating Agents. (i) Synthesis of Chiral Bisalkylating Agent **8**. Three optically active starting materials for the synthesis of **8** were evaluated and their suitability for large scale preparation assessed:

(a) Dimethyl (*S*)-maleate: Allylation of alcohol **13**, obtained from dimethyl (*S*)-maleate (**12**) in 73% yield (98% ee),[11] with allyl trichloroacetimidate/CF_3SO_3H (cat.)[12] followed by DIBAL-H reduction of the ester afforded **14** in 74% yield. The allylation reaction had to be performed using acid catalysis, since silyl migration was observed when basic conditions were employed. Ozonolysis/$NaBH_4$ reduction of olefin **14** afforded diol **15** in 75% yield. Conversion of **15** into bismesylate **8a**, followed by a double Finkelstein reaction with NaI, yielded bisiodide **8b** in 91% yield (Scheme 2).

Synthesis of **8** from dimethyl (*S*)-maleate was thus achieved in seven steps and 36% overall yield (98% ee).

Scheme 2[a]



[a] Key: (a) BMS−$NaBH_4$, THF, 0 °C; (b) TBDPSCl, imidazole, CH_2Cl_2; (c) $H_2C{=}CHCH_2OCNHCCl_3$, C_6H_{12}, cat. CF_3SO_3H, rt; (d) DIBAL-H, THF, −78 to −20 °C; (e) O_3, MeOH, −78 °C, then $NaBH_4$; (f) MsCl, Et_3N, Et_2O, 0 °C; (g) NaI, acetone, 10% $NaHCO_3$.

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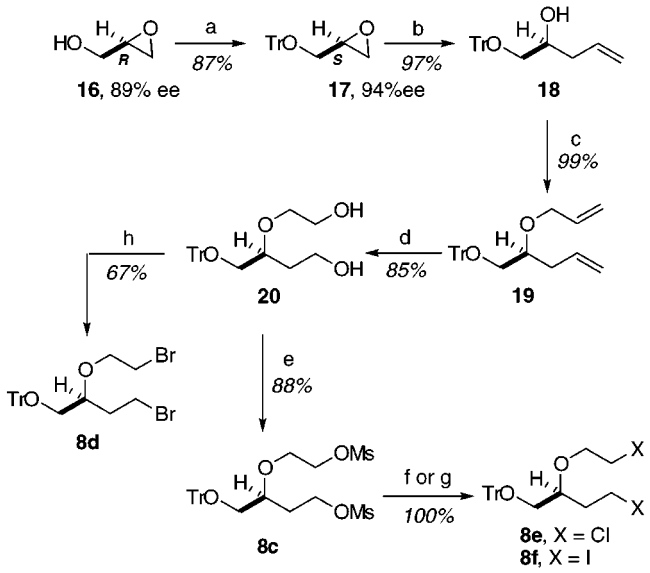
Scheme 3[a]



[a] Key: (a) TrCl, Et_3N, CH_2Cl_2; (b) vinylmagnesium bromide, 5 mol % Cu(I), −30 °C, THF; (c) allylbromide, KOBu^t, THF; (d) O_3, CH_2Cl_2:MeOH 1:1, −50 °C, followed by $NaBH_4$; (e) MsCl, Et_3N, CH_2Cl_2; (f) Bu_4NI, toluene, reflux; (g) $Bu_4NCl{\cdot}H_2O$, toluene, reflux; (h) Br_2, $P(PhO)_3$, pyridine.

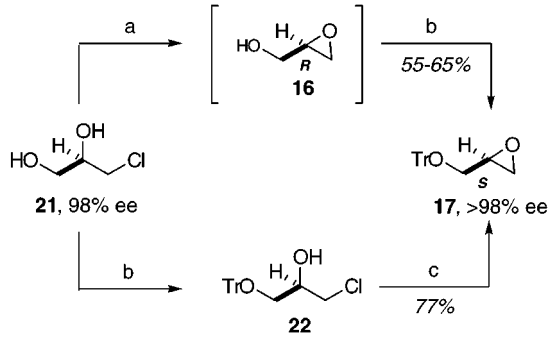
Preparation of kilogram quantities of **8** by this route was difficult because all intermediates were oils requiring chromatographic purification. In addition, the need to perform the allylation under acidic conditions required an additional step to prepare allyltrichloroacetimidate. A precursor that could be allylated under basic conditions with a commerically available allylating agent (e.g., allyl bromide) would be more desirable. Therefore, an alternative approach to **8** was explored.

(b) (*R*)-Glycidol and (*R*)-chloro-2,3-propanediol: Glycidol and its derivatives are versatile C_3 synthons.[13] An extremely efficient synthesis of **8** from (*R*)-glycidol (**16**), using triphenylmethyl (trityl) as the protecting group, was developed (Scheme 3). This synthesis eliminated the problems of silyl migration, allowed the allylation reaction to be performed under basic conditions, and afforded three crystalline intermediates that facilitated large-scale purification. Trityl could not be employed as a protecting group with dimethyl (*S*)-maleate since it was removed under the acidic conditions of the allylation reaction.

We developed a general procedure for the synthesis of (*S*)-trityl glycidol (**17**) in 87% yield, 94% enantioselectivity, by reaction of **16** (89% ee)[14] with TrCl/Et_3N in CH_2Cl_2 followed by recrystallization from Pr^{i}OH. However, macrocyclic bisindolylmaleimides **1**−**4** prepared from **17** were also only of 94% ee, and material with this low optical purity was not acceptable for use in clinical trials. Thus, two alternative approaches to **17** from (*R*)-1-chloro-2,3-propanediol (**21**) (>98% ee)[15] were examined (Scheme 4).

Treatment of **21** with K_2CO_3 or Cs_2CO_3 in CH_2Cl_2 generated (*R*)-(+)-glycidol (**16**) in situ. However, while **17** could be isolated in 98% ee following treatment of **16**

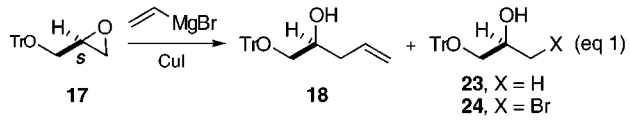
Scheme 4[a]



[a] Key: (a) K_2CO_3 or Cs_2CO_3 in CH_2Cl_2; (b) TrCl, Et_3N, CH_2Cl_2; (c) KOH in EtOH.

with TrCl/Et_3N, the chemical yield was only 55−65%. A more efficient synthesis of **17** involved first converting **21** into (*R*)-3-chloro-1-*O*-trityl-1,2-propanediol (**22**) then cyclizing this intermediate using KOH in EtOH. This afforded **17** in 77% overall yield and >98% ee from **21**.

Regioselective opening of epoxide **17** was examined with a number of reagents. Vinylmagnesium bromide (2 equiv) with 5 mol % CuI was the optimal reagent, affording a 97% yield of **18**.[16] This reaction was performed at −30 °C, since **23** and **24** were generated as impurities when the reaction was conducted at higher temperatures or when fewer equivalents of vinylmagnesium bromide or CuI were employed (eq 1). In fact, in



the absence of CuI, bromide **24** was the major product (75%). Suprisingly, reaction of **17** with vinylmagnesium chloride and 5 mol % CuI at −30 °C afforded only the reduced product **23** in 89% yield. Although higher order cuprates [(vinyl)$_2$CuCNLi$_2$, (vinyl)CuCN(thienyl)Li$_2$][17] also gave **18** in >95% yield, they introduced 2 equiv of copper into the reaction that on a large scale presented disposal problems.

Allylation of **18** was achieved using allyl-Br with NaH or KOBu^t in THF and afforded **19** in 99% yield (Scheme 3).[18,19] Allylation under phase-transfer conditions, using NaOH and either TBAB or TBAF in CH_2Cl_2 or toluene, was less efficient, providing only 66−80% yield of **19**.[20] Ozonolysis of **19** in 1:1 CH_2Cl_2:MeOH at −50 °C, followed by quench of the reaction mixture into a 0.05 N solution of $NaBH_4$ in NaOH, gave diol **20** as an oil in 85% yield.[21] Higher temperatures in the ozonolysis of **19** led to generation of TrOMe as a major byproduct. Treatment of **20** with MsCl/Et_3N in CH_2Cl_2 afforded bismesylate **8c** in 88% yield after crystallization from heptane:EtOAc. Reaction of **20** with $(PhO)_3PBr_2$ complex, generated in

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(14) (*R*)-(+)-Glycidol (**16**) was purchased in 89% enantioselectivity from Diasco.

(15) (*R*)-1-Chloro-2,3-propanediol (**21**) was purchased in >98% enantioselectivity from Diasco.

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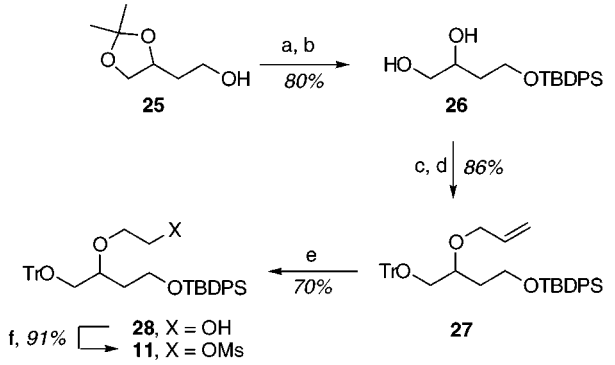
Scheme 5[a]



[a] Key: (a) TBDPSCl, 10 mol % DMAP, Et_3N, CH_2Cl_2; (b) *p*-TsOH, MeOH; (c) TrCl, Et_3N, CH_2Cl_2; (d) NaH, allylbromide, THF, 45 °C; (e) O_3/$NaBH_4$, CH_2Cl_2:MeOH 1:1, −50 °C; (f) MsCl, Et_3N, CH_2Cl_2.

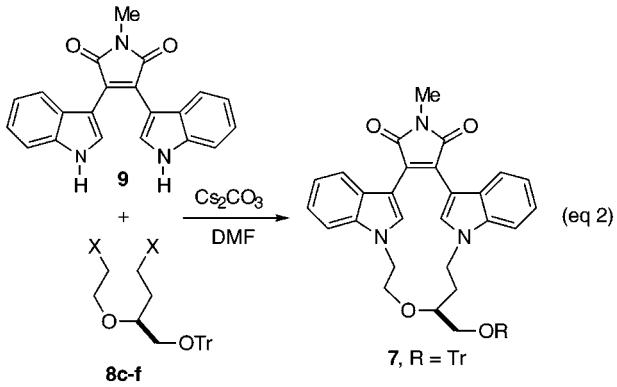
situ using 2 equiv of pyridine as a base to prevent detritylation, yielded a 67% yield of bisbromide **8d** after crystallization from EtOH.[22] Bischloride **8e** and bisiodide **8f** were prepared in quantitative yield by treatment of **8c** with the corresponding tetrabutylammonium halides in toluene at reflux.[23]

In summary, bisalkylating agents **8c**−**f** were prepared from (*R*)-1-chloro-2,3-propanediol (**21**) in 45−52% overall yield and >98% enantioselectivity. Their syntheses provided three crystalline intermediates eliminating the need for any chromatographic purification. The success of each of these bisalkylating agents in the intermolecular alkylation reaction was examined.

(ii) Synthesis of Alkylating Agent 11. Synthesis of racemic **11** was developed using racemic malic acid. *O*-Silylation of 1,2,4-triol acetonide **25**,[24] derived from malic acid, with TBDPSCl and DMAP (10 mol %), followed by ring cleavage of the acetonide with *p*-TsOH in methanol, afforded diol **26** in 80% yield.[25] Selective protection of the primary alcohol of **26** using TrCl/Et_3N in CH_2Cl_2, followed by allylation with allyl bromide and NaH, afforded **27** in 86% yield. Ozonolysis/$NaBH_4$ reduction of olefin **27** and mesylation of alcohol **28** afforded alkylating agent **11** in seven steps and in 44% overall yield from acetonide **25** (Scheme 5).

Formation of the 14-Membered Macrocycle 7. (i) Strategy A: Intermolecular Alkylation. On the basis of literature precedent in the synthesis of macrocyclic thioethers,[26,27] the initial conditions examined to generate the 14-membered macrocycle **7** involved simultaneous addition of bisalkylating agent **8c** or **8f** and bisindolylmaleimide **9** into a solution of Cs_2CO_3 (6 equiv) in DMF over 72 h (eq 2, Table 1, entries 1 and 2). To prevent undesirable oligomerizations, the reaction was performed at high dilution (0.0083 M). Macrocycle **7** was isolated in 56% and 48% yield using **8c** and **8f**, respectively. Since our goal was to develop a synthesis to supply multikilogram quantities of **1**−**4**, a reaction performed at high dilution over extended reaction times was undesirable. It was determined that the reaction volume could be reduced 4-fold with no reduction in yield of **7**. In fact, addition of **8c** or **8f** to a suspension of **9** in DMF (0.0029 M) and Cs_2CO_3 (6.0 equiv) over 60 h afforded **7** in an improved yield of 66% and 67% yield, respectively (Table 1, entries 3 and 4). However, further increases in concentration led to a decreased yield of **7** to 53% using **8c** (Table 1, entry 5). More significantly, the addition time could be reduced 10-fold, from 60 to 6 h, to afford **7** in 54% yield (Table 1, entry 6). The lower yield for entry 6 was due to isolation of **7** directly from the reaction by crystallization using DMF/acetonitrile.[28]

Table 1. Effect of Addition Time and Concentration on Intermolecular Alkylation of 9 (eq 2)



entry	reagent	X	molarity[a]	addn time (h)[b]	yield of **7**[c] (%)
1	**8c**	OMs	0.0083	72	56
2	**8f**	I	0.0083	72	48
3	**8c**	OMs	0.029	60	66
4	**8f**	I	0.029	60	67
5	**8c**	OMs	0.058	60	53
6	**8c**	OMs	0.029	6[d]	54[e]
7	**8d**	Br	0.029	60	68
8	**8e**	Cl	0.029	60	56

[a] Based on bisindolylmaleimide **9**. [b] All reactions were performed with 1.2 equiv of bisalkylating agent, 6.0 equiv of Cs_2CO_3, and 1.0 equiv of **9** at 50 °C unless otherwise indicated. [c] Yield of **7** after chromatographic purification, unless noted otherwise. [d] Reaction at 100 °C. [e] Reaction used 2.5 equiv of Cs_2CO_3. Yield of **7** isolated directly from the reaction by crystallization from DMF/acetonitrile.

The optimum bisalkylating agent was determined on the basis of ease of synthesis and reactivity in the alkylation reaction. Although the reaction with **9** and bisbromide **8d** afforded **7** in 68% yield (Table 1, entry 7), bischloride **8e** was less reactive and afforded only a 56% yield of **7** (Table 1, entry 8). On the basis of the reaction efficiency, bisalkylating agents **8c**, **8d**, and **8f** were comparable in terms of reactivity. However, the stability of these reagents was different. While **8d** could be stored at room temperature for extended periods of time, crystallization of this compound was variable and dependent on the purity of **20**. Although bisalkylating agents **8c** and **8f** decomposed rapidly over 24 h, they were stable indefinitely at −5 °C. On the basis of these results, the bismesylate **8c** was selected as the optimum alkylating agent for preparation of **7**, since it was readily prepared as a crystalline solid in 52% yield and five steps from (*R*)-1-chloro-2,3-propanediol.

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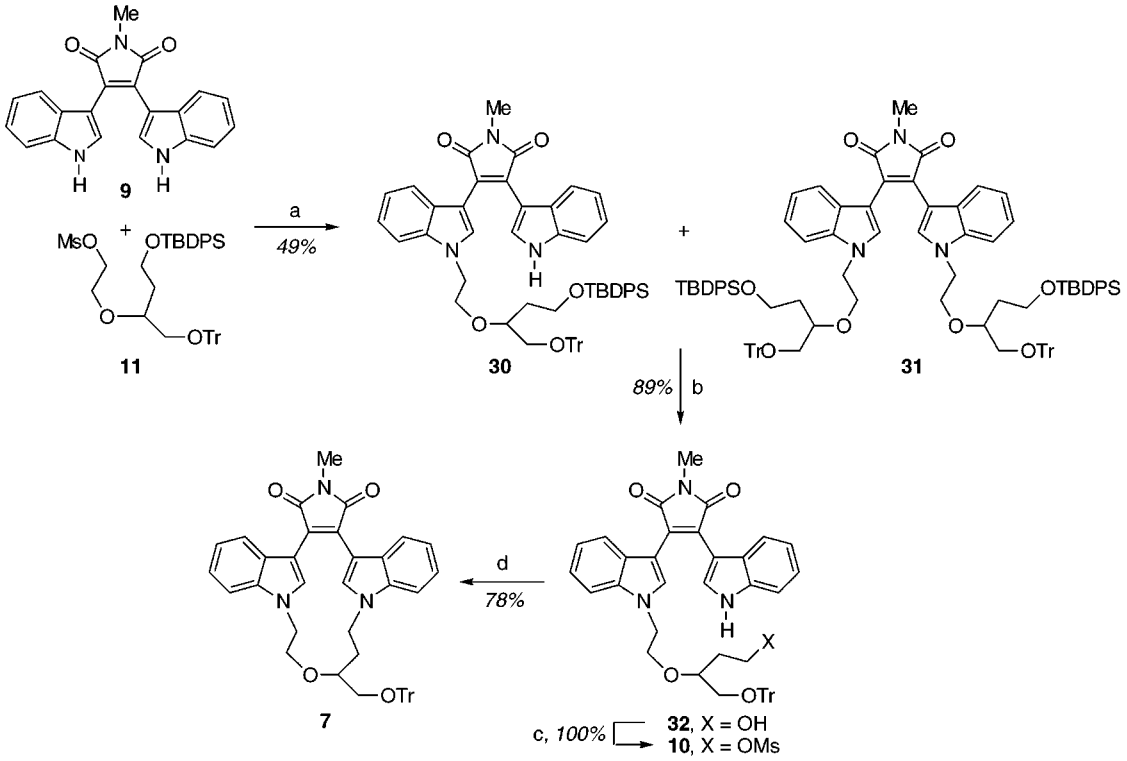
(28) On large scale yield of **7** by crystallization from DMF/acetonitrile varied from 55 to 68%.

Scheme 6[a]



[a] Key: (a) Cs_2CO_3, DMF, 60 °C, 24 h; (b) 1 M TBAF, THF, 0 °C, 1.5 h; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; (d) Cs_2CO_3, DMF, 100 °C, 6 h.

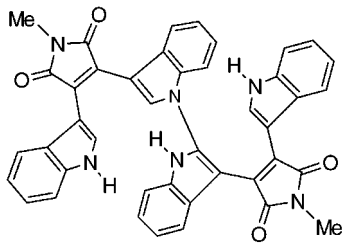
Table 2. Alternative Solvents and Bases Employed in the Intermolecular Alkylation Reaction of 8c with 9

entry	solvent	base	yield of **7**[b] (%)
1	CH_2Cl_2	Cs_2CO_3	0
2	THF	Cs_2CO_3	0
3	ACN	Cs_2CO_3	22[c]
4	DMF	K_2CO_3	40[d]
5	DMF	NaH	34
6	THF	NaH	0
7	toluene	KOH	16[e]
8	H_2O	NaOH	6[f]

[a] All reactions were performed with 1.2 equiv of bisalkylating agent, 6.0 equiv of Cs_2CO_3, and 1.0 equiv of **9** at 50 °C unless otherwise indicated. [b] Yield of **7** after chromatographic purification. [c] Addition time was 0 h, **8c** was insoluble in ACN. [d] Addition time 72 h, reaction time 144 h. [e] Reaction run with 5 mol % of 18-crown-6.[29] [f] Reaction run with 1 equiv of phase-transfer catalyst Aliquot 336.[30]

Alternative solvents and bases were examined in the intermolecular alkylation reaction, although the yields of **7** were significantly lower than those obtained using Cs_2CO_3/DMF (Table 2). Use of less polar solvents resulted either in no reaction (CH_2Cl_2, THF) or reduced yields of **7** (CH_3CN, 22%) (Table 2, entries 1−3). Intermolecular alkylation with other bases (K_2CO_3, NaH) or under phase-transfer catalysis (18-crown-6, aliquot 336) provided **7** in low yield (6−40%) (Table 2, entries 4−8). These results supported the use of DMF and Cs_2CO_3 as the optimal solvent and base for formation of **7**.

While a yield of 55−65% for formation of a 14-membered macrocycle is significant, the intermolecular alkylation was examined in more detail to try to determine what was happening to the remainder of the material. Analysis of the reaction using an internal standard revealed that the in situ reaction yield was 65−70%, indicating some loss of product during the crystallization. However, HPLC and LC/MS examination of the unpurified reaction mixture indicated no dimer, trimer, or polymer formation. Macrocycle **7** and bisindolylmaleimide **9** were found to be stable to the reaction conditions, although after extended reaction times, in the absence of bisalkylating agents **8c**−**f**, **9** formed the autooxidation product **29** in 10−15% yield. No additional impurities have been isolated from this reaction.



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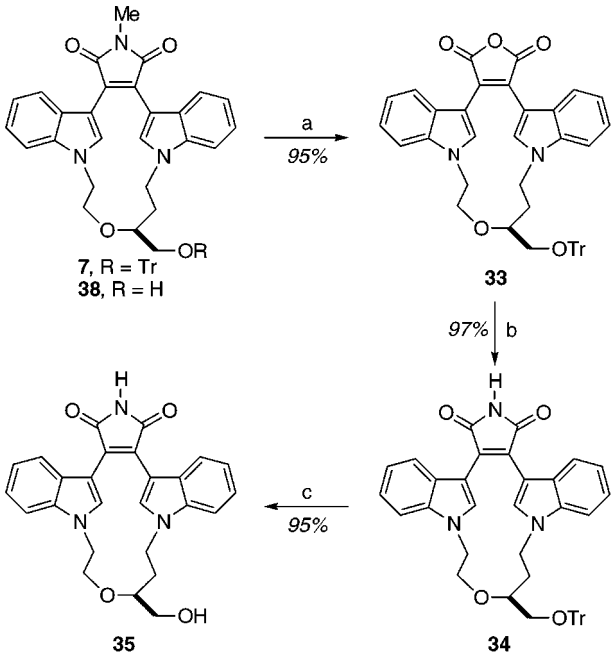
(ii) Strategy B: Intramolecular Alkylation. Cs_2CO_3, the optimal base in the intermolecular approach, was also employed in the intramolecular reaction sequence. To minimize dialkylation, 2 equiv of **9** was used. Thus, reaction of **11** with 2 equiv of **9** using Cs_2CO_3 (1 equiv) in DMF (0.058 M) at 60 °C afforded, after chromatography, monoalkylated product **30** in 49% yield and dialkylated product **31** in 10% yield. The alkylation reaction was sluggish, requiring 24 h to consume all of **11** (Scheme 6).

Desilyation of **30** to **32** and conversion into mesylate **10** was achieved in 89% and 100% yield, respectively, under standard conditions. Intramolecular alkylation of **10** was performed, using conditions identical to those established in the intermolecular approach, by syringe pump addition of a DMF solution of **10** (0.013 M) into a suspension of Cs_2CO_3 in DMF at 100 °C over 6 h.

Scheme 7[a]



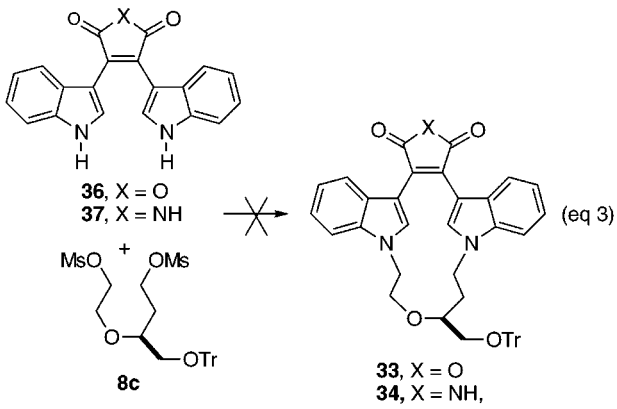
[a] Key: (a) 10 N KOH, EtOH, reflux, 19 h; (b) DMF, HMDS/MeOH, 80 °C, 7 h; (c) 6 N HCl, EtOH, reflux 2 h.

Cyclization of **10** was extremely rapid, affording a 78% yield of **7**. Interestingly, although **10** is a presumed intermediate in the intermolecular reaction, it was never observed, suggesting that in the latter case the second alkylation is extremely rapid relative to the first alkylation.

Synthesis of the key macrocycle **7** by inter- and intramolecular alkylation of **9** has been achieved. The intermolecular approach (strategy A) afforded **7** in 66% yield, while the intramolecular approach (strategy B) required four steps and proceeded in a lower overall yield of 34%. While in the intramolecular approach dialkylation of **9** proved problematic, no oligomerization products have been observed to date in the intermolecular case. In fact, alkylation of **9** by **8c** has proved to be an extremely efficient method for formation of the 14-membered macrocycle for this class of compounds. This approach has proved successful in preparation of multikilogram quantities of **7**, the key intermediate in the synthesis of **1**−**4**.

Conversion of 7 into Macrocyclic Bisindolylmaleimides 1−4. Conversion of *N*-methylmaleimide **7** to maleimide **34** was accomplished by hydrolysis and ammonolysis (Scheme 7). Literature methods for the hydrolysis are generally performed at high dilution (>100 mL of solvent/g of maleimide) in aqueous or ethanolic solvent, using excess 5 N KOH (>100 equiv).[31] However, we found that hydrolysis of **7** to the dicarboxylate and subsequent conversion to the anhydride **33** could be achieved using 10 N KOH (5 equiv) in EtOH (7.5 mL/g of **7**) at reflux for 19 h. The intermediate dicarboxylate was neutralized/cyclized with citric acid, and **33** was isolated in 95% yield after crystallization from EtOH.[32]

Maleimides are readily available from the corresponding anhydrides by heating at high temperature in the presence of ammonia or an ammonium source.[33] Treatment of **33** with hexamethyldisilazane and MeOH (in DMF at 80 °C for 7 h) afforded a 97% yield of **34** after crystallization from EtOH. Other ammonia sources (NH_4OH, NH_4OAc) provided **34** in 95% yield, although longer reaction times (24−48 h) and higher temperatures (85 °C) were required for complete conversion. Attempts to prepare **33** or **34** directly, by intermolecular alkylation of the corresponding bisindolylmaleic anhydride **36** or maleimide **37** with bismesylate **8c**, were unsuccessful (eq 3). Detritylation of **34** was achieved using either HCl(g)



in CH_2Cl_2 at −25 °C for 1 h or 6 N HCl in EtOH at reflux for 2 h and afforded alcohol **35** in 95% yield (>98% ee). Alcohol **35** was insoluble in organic solvents and was isolated by trituration from CH_2Cl_2, which also removed all tritylated byproducts generated during the deprotection.

Conversion of *N*-methylmaleimide **7** into alcohol **35** was accomplished in 87% yield and in three extremely efficient steps, each of which provided crystalline intermediates. In an attempt to reduce the number of steps, methods were examined that would eliminate both the imide methyl and trityl alcohol protecting groups simultaneously. However, standard dealkylation conditions (TMSCl/NaI, BBr_3, LiI/PhOCOCl) afforded only the detritylated product **38**. Derivatives of **9** with alternative imide protecting groups, e.g., benzyl, BOM, and MOM, were also examined but, as reported by a number of other research groups,[34] deprotection was difficult and the reaction sequence was not competitive with the hydrolysis/ammonolysis procedure outlined above.

The synthesis of **1**−**4** was completed by activation of alcohol **35** via mesylate **39** and displacement with amine. Reaction of **35** with Ms_2O/pyridine in THF followed by crystallization from THF/H_2O afforded **39** in quantitative yield. MsCl with Et_3N or pyridine was not selective, yielding **39** in only 60% and 15% yield, respectively, presumably due to competitive mesylation of the imide nitrogen.

A number of conditions were examined for displacement of mesylate with amine (Table 3). Reaction of **39**

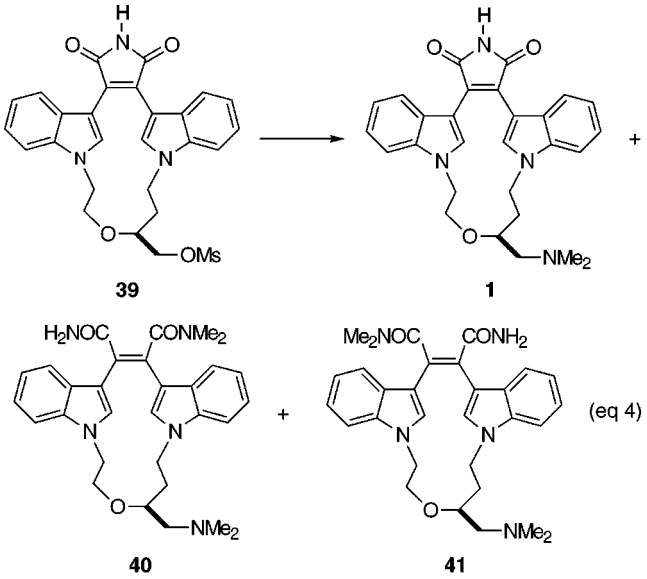
(29) Santaniello, E.; Farachi, C.; Ponti, F. *Synthesis* **1979**, 617.
(30) Bocchi, V.; Casnati, G.; Dossena, A.; Villani, F. *Synthesis* **1976**, 414.
(31) Sandler, S. R.; Karo, W. *Organic Functional Group Preparation*; Academic Press: London, 1972; Vol. 3, Chapter 7.
(32) Neutralization with strong acid was unsuccessful due to competitive detritylation.
(33) Davis, P. D.; Bit, R. A. *Tetrahedron Lett.* **1990**, *31*, 5201.
(34) A number of methods to deprotect imide nitrogens have been reported: (a) PMB: (i) Akiyama, T.; Kumegawa, M.; Takesue, Y.; Nishimoto, H.; Ozaki, S. *Chemistry Lett.* **1990**, 339. (ii) Van Aerschot, A.; Jie, L.; Herdewijn, P. *Tetrahedron Lett.* **1991**, *32*, 1905. (b) BOM: Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552.

Table 3. Formation of Macrocyclic Bisindolylmaleimides 1−4

entry	amine[a]	solvent	base (equiv)	yield (%) (product)	**40**/**41**[d] (%)
1	Me_2NH[b]	THF/H_2O	200	61 (**1**)[d]	32
2	Me_2NH[c]	THF/H_2O	100	73 (**1**)[d]	20
3	Me_2NH	THF/H_2O	50	80 (**1**)[d]	10
4	Me_2NH	DMF	50	91 (**1**)[d]	3
5	Me_2NH	DMF	25	92 (84,[e] **1**)	3
6	pyrrolidine	DMF	25	68 (**2**)[f]	
7	pyrrolidine	DMA	25	83 (**2**)	
8	$BnNH_2$	DMA	25	95 (**3**)[g]	
9	$MeNH_2$	DMA	25	85 (**4**)[h]	

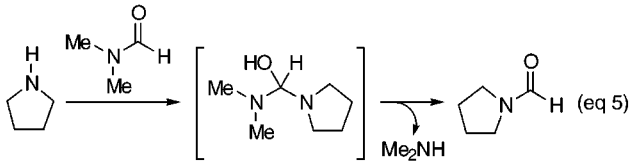
[a] All reactions were carried out at 65 °C for 17 h unless otherwise indicated. [b] Reaction performed at 60 °C. [c] Reaction time 42 h. [d] Determined by HPLC analysis. [e] Crystallized directly from the reaction using DMF/MeOH. [f] Contaminated with 10−15% **1**. [g] Reaction time 30 h. [h] Contaminated with 20% of **44**.

with a 40% aqueous solution of Me_2NH (200 equiv) in THF at 60 °C for 24 h afforded **1** in 61% in situ yield (Table 3, entry 1). Two impurities, identified as regioisomers **40** and **41**, were also formed in 32% yield by attack of Me_2NH at the imide carbonyls (eq 4).[35] Since



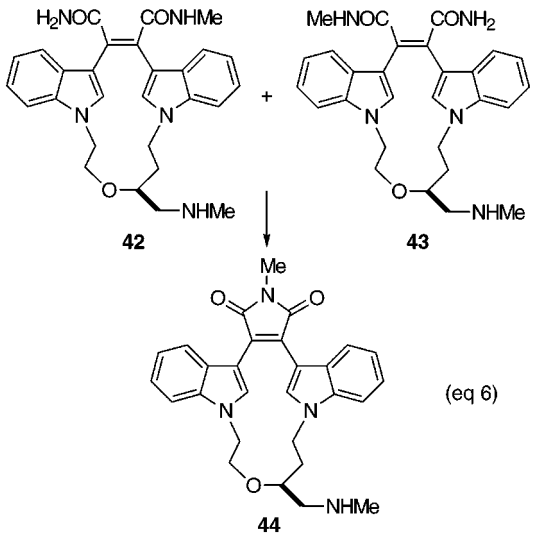
material of >97% homogeneity was required to evaluate **1** in clinical trials, conditions were examined to eliminate these impurities. The yield of **1** increased to 80%, and formation of **40** and **41** was reduced to 10% when less Me_2NH (50 equiv) was employed (Table 3, entry 3). However, the reaction was sluggish in THF/H_2O due to the poor solubility of **39** and **1** in this solvent mixture and alternative reaction solvents were examined. DMF was found to be optimal, having a high solubility for both starting materials and product. Upon treatment of **39** with Me_2NH (50 or 25 equiv) in DMF, at 65 °C for 17 h, **1** was formed with an in situ yield of 91%, containing only 3% of **40** and **41** (Table 3, entries 4 and 5). Initially, purification of **1** was problematic due to the poor solubility of this compound in most organic solvents. However, we found that **1** could be isolated directly from the reaction in 84% yield and >97% purity by crystallization from DMF/MeOH. This completed a very efficient synthesis of **1** that has been employed to prepare multikilogram quantities of material.

Although DMF was the optimum solvent for reaction of **39** with Me_2NH it proved problematic when other amines were employed. Upon reaction of **39** with pyrrolidine (25 equiv) in DMF at 65 °C for 17 h only a 68% yield of **2** was obtained contaminated with 10−15% of **1** (Table 3, entry 6). Formation of **1** was due to transformylation of pyrrolidine with DMF under the reaction conditions, resulting in formation of Me_2NH that competed with pyrrolidine for reaction with **39** (eq 5). To



eliminate this competing reaction, treatment of **39** with amines other than Me_2NH was performed using *N*,*N*-dimethylacetamide (DMA) as solvent. Thus, reaction of **39** with pyrrolidine or $BnNH_2$ in DMA afforded the corresponding macrocyclic bisindolylmaleimides **2** and **3** in 81% and 95% yield, respectively (Table 3, entries 7 and 8). Interestingly, no maleimide ring-opened byproducts were observed in either of these reactions.

In contrast, reaction of **39** with $MeNH_2$ (25 equiv) in DMA at 65 °C for 17 h afforded an 85% yield of bisindolylmaleimide **4** contaminated with 20% of the *N*-methylmaleimide derivative **44** (Table 3, entry 9). The latter compound was generated by cyclization of **42** and **43** formed by attack of $MeNH_2$ at either imide carbonyl (eq 6). Cyclization to **44** was rapid, and regioisomers **42** and **43** were not observed in the reaction.



Conclusion

An 11-step synthesis of macrocyclic bisindolylmaleimides **1**−**4**, potent inhibitors of PKC β, has been achieved in 17−26% yield (>98% ee) from (*R*)-1-chloro-2,3-propanediol (**21**) and bisindolylmaleimide, (**9**). Synthesis of **1**, the most active member of this series, on greater than 1 kg scale has been completed using this chemistry. No chromatographies were required throughout this process,

(35) Impurities **40** and **41** could not be separated and were isolated by chromatography as a mixture of regioisomers. FD-MS indicated a molecular weight of 513, with a smaller peak at *m*/*z* 468 corresponding to **1**. HRMS could not be obtained since ES-MS and EI-MS only gave a *m*/*z* of 468, indicating that reclosure of the imide ring was extremely facile. IR spectra of the regioisomeric mixture gave no carbonyl frequency greater than 1667 cm^{-1}, indicating that no cyclic imide was present.

and **1** was isolated in >97% homogeneity by crystallization from DMF/MeOH. The key steps in this synthesis were (i) an efficient five-step synthesis of bisalkylating agent **8c** in 52% yield as a crystalline solid from (*R*)-1-chloro-2,3-propanediol, (ii) intermolecular alkylation of symmetrical bisindolylmaleimide **9** by **8c** to form the 14-membered macrocycle **7** in 66% yield after crystallization from DMF/acetonitrile, (iii) a highly efficient three-step hydrolysis, ammonolysis, deprotection sequence for conversion of **7** into alcohol **35** that proceeded in 87% yield, and (iv) conversion of **35** into macrocyclic bisindolylmaleimides **1**−**4** in 65−95% yield via mesylate **39**. The synthesis described herein should allow for the synthesis of large quantities of any member of this series via the intermolecular alkylation approach.

Experimental Section

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F254 plates (Merck) using reagent-grade solvents. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ^{1}H NMR were performed at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral and combustion analysis were performed by the Eli Lilly and Co. Physical Chemistry Department.

(*R*)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-(2-propenyloxy)-1-butanol (14). To a solution of alcohol **13** (29.0 g, 0.078 mol) in cyclohexanes (400 mL) was added allyl trichloroacetimidate (31.5 g, 0.156 mol) in cyclohexanes (30 mL). Trifluoromethanesulfonic acid (1.45 mL, 0.016 mol) was then added portionwise over 40 min. The reaction was stirred at room temperature for 2.5 days. After removal of the solids by filtration, the filtrate was washed with saturated aqueous sodium bicarbonate solution (4 × 200 mL) and saturated aqueous sodium chloride (2 × 200 mL), dried (Na_2SO_4), and filtered. The cyclohexane were removed in vacuo and the resultant oil purified by silica pad filtration using hexanes, followed by 9:1 hexanes−EtOAc, to give 30.7 g of a yellow oil that contained approximately 20% allyl trichloroacetimidate. This material was used directly without further purification.

To a solution of the allyl ester (28.5 g, 0.069 mmol), isolated from the above reaction, in anhydrous THF (1 L) under nitrogen at −78 °C was added via cannula DIBAL-H (1 M solution in toluene, 276 mL, 0.276 mol). The reaction was stirred for 40 min at −78 °C and then allowed to warm to −5 °C. After 3 h, the reaction was complete as determined by TLC (3:1 hexanes−EtOAc). The reaction was quenched with 20% aqueous methanol (320 mL) while the temperature was maintained at − 5 °C. Celite was added, and the mixture was stirred for 30 min and then filtered. The THF was removed in vacuo and the resulting residue partitioned between Et_2O (500 mL) and water (250 mL). The aqueous layer was extracted with Et_2O (3 × 200 mL), and the combined organic layers were washed with 20% citric acid solution (2 × 200 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give an oil that was purified by silica pad filtration using 95:5 hexanes−EtOAc followed by 3:1 hexanes−EtOAc to give 22 g (74%) of **14** as a clear oil: $[\alpha]^{20}_D$ +21.12°; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4H), 7.47−7.37 (m, 6H), 5.92−5.81 (m, 1H), 5.25−5.12 (m, 2H), 4.16−4.10 (m, 1H), 3.99−3.93 (m, 1H), 3.79−3.61 (m, 5H), 1.86−1.81 (m, 2H), 1.06 (s, 9H); MS (FD) *m*/*z* calcd for $C_{23}H_{32}O_3Si$ 384, found 385 (M + 1). Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.58; H, 8.52.

(*R*)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-(2-hydroxyethoxy)-1-butanol (15). A solution of olefin **14** (21.4 g, 0.056 mol) in methanol (500 mL) at −78 °C was treated with ozone for 20 min. The reaction was quenched with $NaBH_4$ (12.6 g, 0.334 mol) and after 20 min allowed to warm to room temperature. After 1 h, methanol was removed in vacuo and the residue partitioned between Et_2O (600 mL) and water (300 mL). The aqueous layer was re-extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed with 0.1 N HCl (200 mL) and saturated aqueous sodium chloride (200 mL). The material was dried (Na_2SO_4), filtered, and evaporated in vacuo to give an oil that was purified by preparative chromatography on a Waters Prep 2000 LC, using a solvent gradient of 9:1 hexanes−EtOAc to 1:4 hexanes−EtOAc, to give 16.3 g (75%) of **15** as a clear oil: $[\alpha]^{20}_D$ +7.47°. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.66 (m, 4H), 7.47−7.36 (m, 6H), 3.83−3.52 (m, 9H), 2.82−2.78 (m, 1H), 2.69−2.66 (m, 1H), 1.79−1.71 (m, 2H), 1.06 (s, 9H); MS (FD) *m*/*z* calcd for $C_{22}H_{32}O_4Si$ 388, found 389 (M + 1). Anal. Calcd for $C_{22}H_{32}O_4Si$: C, 68.00; H, 8.30. Found: C, 68.00; H, 8.48.

(*R*)-3-[2-[(Methylsulfonyl)oxy]ethoxy]-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-butanol, Methanesulfonate Ester (8a). To a solution of diol **15** (8.1 g, 0.021 mol) in Et_2O (500 mL) under nitrogen at 5 °C was added triethylamine (8.7 mL, 0.063 mol) followed by methanesulfonyl chloride (4.84 mL, 0.063 mol). The reaction was stirred at 5 °C for 1.5 h and then washed with water (2 × 150 mL) and saturated aqueous sodium chloride (2 × 150 mL), dried (Na_2SO_4), and filtered. The solvent was removed in vacuo to afford an oil that was purified by silica pad filtration, using a solvent gradient of 9:1 hexanes−EtOAc to 1:1 hexanes−EtOAc, to give 11.2 g (99%) of **8a** as a clear oil: $[\alpha]^{20}_D$ +21.12°. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.48−7.37 (m, 6H), 4.42−4.27 (m, 4H), 3.89−3.87 (m, 1H), 3.70−3.57 (m, 4H), 3.01 (s, 3H), 3.00 (s, 3H), 2.00−1.86 (m, 2H), 1.06 (s, 9H); MS (FD) *m*/*z* calcd for $C_{24}H_{36}O_8SiS_2$ 544, found 487 (544 − 57(*t*-Bu)). Anal. Calcd for $C_{24}H_{36}O_8SiS_2$: C, 52.92; H, 6.66. Found: C, 52.66; H, 6.46.

(*R*)-(1,1-Dimethylethyl)[4-iodo-2-(2-iodoethoxy)butoxy]diphenylsilane (8b). To a solution of bismesylate **8a** (11.2 g, 0.021 mol) in acetone (500 mL) were added sodium iodide (77.2 g, 0.515 mol) and sodium bicarbonate (0.17 g, 0.002 mol) and the reaction stirred at 55 °C for 18 h. As the reaction proceeded, a thick precipitate resulted. The acetone was removed in vacuo and the residue partioned between Et_2O (500 mL) and water (300 mL). The layers were separated, and the organic layer was washed with water (300 mL). The aqueous layers were re-extracted with Et_2O (200 mL) and the combined Et_2O extracts washed with a 10% aqueous solution of Na_2SO_2 (200 mL). The organic layers were washed with saturated aqueous sodium chloride (2 × 200 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to afford an oil that was purified by silica pad filtration, using 95:5 hexanes−EtOAc, to give 11.4 g (91%) of **8b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.48−7.37 (m, 6H), 3.90−3.82 (m, 1H), 3.73−3.51 (m, 4H), 3.39−3.30 (m, 2H), 3.19 (t, 2H, J = 6.6 Hz), 2.04−2.00 (m, 2H), 1.06 (s, 9H); MS (FD) *m*/*z* calcd for $C_{22}H_{30}I_2O_2Si$ 608, found 551 (608 − 57(*t*-Bu)). Anal. Calcd for $C_{22}H_{30}I_2O_2Si$: C, 43.43; H, 4.97. Found: C, 43.45; H, 4.93.

(*S*)-Tritylglycidol (17) from (*R*)-(+)-Glydicol (16). To a solution of trityl chloride (275.5 g, 1.0 mol) in CH_2Cl_2 (670 mL) at 0−5 °C was slowly added triethylamine (138 mL, 1.0 mol), followed by (*R*)-(+)-glycidol (**16**) (66.5 g, 0.9 mol, 89% ee), keeping the reaction temperature below 25 °C. The reaction was stirred at 20−25 °C for 24 h. On completion, the reaction was quenched by addition of saturated aqueous ammonium chloride (750 mL) and water (200 mL). The CH_2Cl_2 was removed in vacuo and the product isolated by solvent exchange into EtOH (800 mL). The EtOH was distilled to approximately 12 vol and the resulting solution cooled to 0 °C. The product, which precipitated out of solution, was isolated by filtration to afford 286.5 g (wet cake) of **17** as a white solid. Recrystallization from Pr^{i}OH (1065 mL) afforded, after drying in a vacuum oven at 55 °C overnight, 242.4 g (87%, 94% ee)[36] of **17** as a white crystalline solid: $[\alpha]^{20}_D$ −3.75° (*c* 0.99, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 6H, J = 7.8 Hz), 7.41−7.24 (m, 9H), 3.41 (d, 1H, J = 7.2 Hz), 3.21 (s, 1H), 3.20 (d, 1H, J = 7.2 Hz), 2.80 (t, 1H, J = 4.2 Hz), 2.66 (t, 1H, J = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.8, 128.0, 127.1, 86.7, 65.0, 51.3, 44.9; IR ($CHCl_3$) ν 3063, 3035, 3019, 3011, 2928, 1597, 1491, 1449, 1160, 1153, 1112, 1088,

1073, 1033, 1003, 918, 899, 856, 837 cm^{-1}; UV (EtOH) λ_{max} 260 nm (ϵ 857), 204.5 nm (ϵ 42 922); MS (FD) *m*/*z* calcd for $C_{22}H_{20}O_2$ 316, found 317 (M + 1, 100). Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37; O, 10.11. Found: C, 83.44; H, 6.37; O, 10.14.

(*S*)-Tritylglycidol (17) from (*R*)-1-Chloropropane-1,2-diol (21). To a solution of trityl chloride (1887 g, 6.7 mol) in CH_2Cl_2 (3.4 L) at room temperature was slowly added triethylamine (1.02 L, 7.30 mol). The reaction was then cooled to 0−5 °C, and (*R*)-1-chloro-2,3-propanediol (**21**) (680 g, 6.15 mol, 98% ee) in CH_2Cl_2 (3.4 L) was added over 15 min. The reaction was stirred at room temperature for 3 h and monitored by GC.[37] Upon complete formation of (*R*)-3-chloro-1-*O*-trityl-1,2-propanediol (**22**), the reaction was washed with 6.8 L of NH_4Cl (10%) and the resulting organic layer solvent exchanged into EtOH (3.4 L). To the ethanolic solution at room temperature was added KOH (608.6 g, 85%) in EtOH (3.4 L). The reaction was stirred at room temperature for 2 h, then cooled to 0 °C for 4 h. The mixture was filtered and the cake washed with cold EtOH (3.4 L). The isolated cake was slurried in water (6.8 L) at room temperature and filtered to afford (*S*)-trityl glycidol **17**. The material was then recrystallized from Pr^iOH (6.8 L, 13 vol) and after cooling to 0 °C filtered and dried in vacuo to afford 1.48 kg (77%, >98% ee) of (*S*)-trityl glycidol **17**.

(*S*)-1-(Triphenylmethoxy)-4-penten-2-ol (18). To a cooled (−30 °C) solution of vinylmagnesium bromide (475 mL, 0.474 mol, 1 M in THF) under N_2 was added CuI (3.1 g, 0.016 mol) and the resultant mixture stirred at −30 °C for 15 min. A solution of **17** (100.7 g, 0.316 mol) in THF (345 mL) was added dropwise over 30 min. The reaction was stirred −30 °C for 1 h and then quenched by slow addition of a saturated aqueous solution of ammonium chloride (820 mL) at −30 °C. The organic layer was washed with a 1:1 solution of NH_4OH-H_2O (420 mL) and saturated aqueous sodium chloride (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give 106 g (97%) of **18** as a clear oil: $[\alpha]^{20}_D$ −7.40° (*c* 0.97, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 6H, J = 7.8 Hz), 7.38−7.22 (m, 9H), 5.85−5.70 (m, 1H), 5.15−5.03 (m, 2H), 3.86 (t, OH), 3.76 (t, 1H), 3.22 (dd, 1H, J = 9.5 Hz, 4.8 Hz), 3.14 (dd, 1H, J = 10.2 Hz, 6.8 Hz), 2.31−2.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 134.5, 128.8, 128.0, 127.1, 117.8, 86.8, 70.4, 67.3, 38.4; IR ($CHCl_3$) ν 3602, 3064, 3026, 3013, 2978, 2931, 1641, 1599, 1491, 1449, 1392, 1184, 1153, 1074, 1033, 992, 923, 900 cm^{-1}; UV (EtOH) λ_{max} 260 nm (ϵ 787), 207 nm (ϵ 33 415); MS (FD) *m*/*z* calcd for $C_{24}H_{24}O_2$ 344, found 344 (100). Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02; O, 9.29. Found: 83.41; H, 7.01; O, 9.21. Two additional impurities were isolated from this reaction: **(*S*)-1-(Triphenylmethoxy)propan-2-ol (23):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.20 (m, 15 H), 4.70 (bs, 1H), 3.86−3.74 (m, 1H), 2.96 (dd, 1H, J = 5.9 Hz), 2.72 (dd, 1H, J = 5.7 Hz), 1.06 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 128.2, 127.7, 126.8, 85.6, 69.0, 65.2, 20.6; IR ($CHCl_3$) ν 3593, 3063, 2977, 2928, 2875, 1598, 1491, 1449, 1329, 1260, 1075, 983, 899 cm^{-1}; UV (EtOH) λ_{max} 260 nm (ϵ 775), 210 nm (ϵ 26 924); MS (FD) *m*/*z* calcd for $C_{22}H_{22}O_2$ 318, found 318 (100). Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96; O, 10.05. Found: C, 82.76; H, 7.19; O, 10.12. **(*S*)-1-Bromo-2-hydroxy-3-(triphenylmethoxy)propane (24):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.22 (m, 15 H), 4.03 (q, 1H, J = 5.7 Hz), 3.70 (dd, 1H, J = 5.5 Hz), 3.62 (dd, 1H, J = 5.2 Hz), 3.44 (dd, 1H, J = 5.7 Hz), 3.36 (dd, 1H, J = 5.2 Hz), 2.40 (d, 1H, J = 5.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 128.6, 127.9, 127.2, 86.9, 70.4, 64.9, 36.0; IR ($CHCl_3$) ν 3010, 1490, 1449, 1442, 1089, 1078 cm^{-1}; UV (EtOH) λ_{max} 260 nm (ϵ 909); MS (FD) *m*/*z* calcd for $C_{22}H_{21}O_2Br$ 396, found 396.

(*S*)-(Triphenylmethoxy)[[[2-(2-propenyloxy)-4-pentenyl]oxy]methyne] (19). To a solution of **18** (106 g, 0.308 mol) in THF (275 mL) was added $KOBu^t$ (296.8 g, 325 mL, 1.0 M in THF, 0.325 mol). The reaction was heated at 45 °C for 45 min to ensure complete formation of the alkoxide. The reaction was cooled to 21 °C, and allyl bromide (93.1 g, 67 mL, 0.77 mol) was slowly added. After being stirred at 21 °C for 1 h, the reaction was quenched by addition of 20% saturated aqueous ammonium chloride solution (295 mL) and extracted into EtOAc (450 mL). The organic layer was washed with deionized water (125 mL) and saturated aqueous sodium chloride (125 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford 118.5 g (99%) of **19** as a clear oil: $[\alpha]^{20}_D$ −10.07° (*c* 0.98, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 6H, J = 7.8 Hz), 7.38−7.23 (m, 9H), 6.06−5.92 (m, 1H), 5.89−5.74 (m, 1H), 5.40−5.26 (m, 2H), 5.26−5.01 (m, 2H), 4.21 (dd, 1H, J = 13.6 Hz, 5.4 Hz), 4.09 (dd, 1H, J = 12.2 Hz, 6.1 Hz), 3.63−3.54 (m, 1H), 3.28−3.16 (m, 2H), 2.45−2.37 (t, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 135.4, 135.0, 129.0, 128.0, 127.1, 117.1, 116.8, 86.7, 78.4, 71.3, 65.5, 36.9; IR ($CHCl_3$) ν 3693, 3064, 3036, 2926, 2874, 1961, 1711, 1643, 1598, 1491, 1450, 1347, 1184, 1154, 1076, 1034, 995, 922, 890 cm^{-1}; UV (EtOH) λ_{max} 260 nm (ϵ 721), 206 nm (ϵ 39 846); MS (FD) *m*/*z* calcd for $C_{27}H_{28}O_2$ 384, found 384 (100). Anal. Calcd for $C_{27}H_{28}O_2$: C, 84.34; H, 7.34; O, 8.32. Found: C, 84.60; H, 7.45; O, 8.22.

(*S*)-3-(2-Hydroxyethoxy)-4-(triphenylmethoxy)-1-butanol (20). To a solution of **19** (100 g, 0.26 mol, 90% purity) in MeOH−CH_2Cl_2 (600 mL, 1:1) was added Sudan red indicator (0.02 equiv, 0.1 wt %/wt solution in 3:1 CH_2Cl_2/EtOH) and the reaction cooled to −50 °C. Ozone was bubbled through the solution until the color changed from peach to light yellow. The reaction mixture was then transferred, over 45 min, to a solution of $NaBH_4$ (2.2 equiv) in 260 mL of 0.05 N NaOH that had been precooled to 0−5 °C. The temperature of the $NaBH_4$ solution was maintained at 15−20 °C during the addition. When the addition was complete, the reaction was allowed to warm to 25 °C and stirred for 12−16 h. After the pH of the solution was adjusted to 6.0−6.5 with 1 N HCl, the organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (250 mL). The combined organic layers were dried ($MgSO_4$), and solvent was removed in vacuo to afford 110−120 g (80−90%) of **20** as a clear yellow oil: $[\alpha]^{20}_D$ −10.06° (*c* 0.98, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 6H, J = 7.8 Hz), 7.25−7.09 (m, 9H), 3.76−3.47 (m, 7H), 3.16−3.02 (m, 2H), 1.65 (q, 2H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 128.8, 128.0, 127.1, 87.0, 78.6, 72.0, 66.4, 62.3, 60.1, 34.5; IR ($CHCl_3$) ν 3608, 3457, 3089, 3063, 3011, 2934, 2876, 1711, 1600, 1491, 1450, 1364, 1184, 1154, 1052, 1003, 986, 947, 900 cm^{-1}; UV (EtOH) λ_{max} 260 nm (ϵ 693), 206 nm (ϵ 37 474); MS (FD) *m*/*z* calcd for $C_{25}H_{28}O_4$ 392, found 392 (100%). Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19; O, 16.31. Found: C, 76.22; H, 7.31; O, 16.09.

(*S*)-3-[2-[(Methylsulfonyl)oxy]ethoxy]-4-(triphenylmethoxy)-1-butanol Methanesulfonate (8c). To a solution of **20** (500 g, 1.27 mol) in CH_2Cl_2 (4.8 L) at 0 °C was added triethylamine (386.4 g, 532 mL, 3.81 mol), followed by methanesulfonyl chloride (396.3 g, 268 mL, 3.46 mol), maintaining the temperature at <5 °C. The reaction was stirred at 0−5 °C for 1−2 h and then diluted with CH_2Cl_2 (500 mL) and washed twice with water (2 L) and saturated aqueous ammonium chloride (2 L). The aqueous layers were back-extracted with CH_2Cl_2 (1 L) and the combined organic layers dried ($MgSO_4$) and filtered. The solvent was removed in vacuo to give a solid that was recrystallized from 1:1 heptane−EtOAc to give 615 g (88%) of **8c** in three crops. Compound **8c** was unstable at room temperature and was stored at −5 °C until required. This instability prevented complete characterization of this compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, 6H, J = 7.8 Hz), 7.36−7.21 (m, 9H), 4.46−4.24 (m, 4H), 4.02−3.93 (m, 1H), 3.76−3.67 (m, 1H), 3.67−3.60 (m, 1H), 3.24−3.17 (m, 2H), 3.01 (s, 3H), 2.98 (s, 3H), 1.99−1.90 (m, 2H); ^{13}C NMR

(36) The enantiomeric excess of **17** was determined by chiral HPLC: A 10 mg sample placed in a 10 mL volumetric flask and diluted with 10 mL of hexanes. Column: Chiralcel OJ, 25 cm × 4.6 mm i.d., 5 μm. Wavelength: 220 nm. Flow rate: 1 mL/min. Injection volume: 20 μL. Isocratic mobile phase: 30% isopropyl alcohol in hexanes. (*R*)-isomer t_R = 6.5 min. (*S*)-isomer t_R = 8.0 min.

(37) The following GC conditions were employed to monitor the reaction: Column: DB-1701, 15 m × 0. 32 mm × 0.25 μm. Hold 35 °C, 2 min, ramp to 300 °C at 20 °C/min and hold for 10 min. (*R*)-1-Chloro-2,3-propanediol (**21**) t_R = 6.6 min, into (*R*)-3-chloro-1-*O*-trityl-1,2-propanediol (**22**) t_T = 15.8 min and (*S*)-trityl glycidol (**20**) t_R = 19.9 min.

(75 MHz, $CDCl_3$) δ 144.0, 128.9, 128.1, 127.4, 86.9, 76.1, 69.5, 68.6, 67.0, 65.8, 37.5, 37.9, 32.3.

(*S*)-4-(Triphenylmethoxy)-2-(2-bromoethoxy)-1-bromobutane (8d). A yellow solution of bromine (4.1 g, 25 mmol) in CH_2Cl_2 (50 mL) was cooled to −30 °C and titrated with triphenyl phosphite (7.9 g, 25 mmol) to a colorless solution. The $(PhO)_3PBr_2$ complex prepared at −30 °C was treated with pyridine (2.63 mL, 32 mmol) followed by diol **20** (4.0 g, 10.2 mmoL) in CH_2Cl_2 (30 mL) and allowed to warm to room temperature for 30 min. The reaction was diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), water (200 mL), and saturated aqueous sodium chloride (100 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo and the product dissolved in EtOH (20 mL). On cooling in an ice−water bath a solid crystallized out of solution; however, it was still contaminated with $(PhO)_3PO$. Therefore, it was reslurried twice in 4:1 EtOH:water at 0 °C. After isolation and drying, 3.6 g (67%) of bisbromide **8d** was obtained as a white crystalline powder: $[\alpha]^{20}_D$ −19.19° (*c* 1.04, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 6H, J = 7.8 Hz), 7.40−7.23 (m, 9H), 4.10−4.00 (m, 1H), 3.85−3.76 (m, 1H), 3.73−3.58 (m, 2H), 3.58−3.45 (m, 3H), 3.22 (d, 2H, J = 5.4 Hz), 2.22−1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.8, 128.0, 127.1, 87.0, 77.4, 70.7, 65.6, 35.5, 31.3, 30.5; IR (Kbr) 2915, 1487, 1447, 1110, 1087, 1026, 704; HRMS (EI) *m*/*z* exact mass calcd for $C_{25}H_{26}O_2Br_2$ 518.0102, found 518.0095. Anal. Calcd for $C_{25}H_{26}O_2Br_2$: C, 57.94; H, 5.06; Br, 30.84. Found: C, 58.19; H, 5.12; Br, 30.59.

(*S*)-4-(Triphenylmethoxy)-[2-(2-chlorethoxy)-1-chlorobutane (8e). A solution of tetrabutylammonium chloride·hydrate (23.3 g, 84 mmol) in toluene (500 mL) was heated to reflux and 200 mL of solvent azeotropically removed via a Dean−Stark trap to eliminate all water. The solution was cooled to room temperature, and bismesylate **8c** (11.5 g, 21 mmol) was added. The reaction was heated to reflux for 30 min and then concentrated to an oil that was extracted with EtOAc (500 mL), washed with water (500 mL) and saturated aqueous sodium chloride (100 mL), dried ($MgSO_4$), and filtered. The EtOAc was removed in vacuo to afford 11.4 g of an oil that was purified by column chromatography, using 2:1 hexanes:EtOAc as eluent, to afford 9.4 g (100%) of **8e**: $[\alpha]^{20}_D$ −23.57° (*c* 1.013, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, 6H, J = 7.8 Hz), 7.39−7.24 (m, 9H), 4.05−3.95 (m, 1H), 3.83−3.70 (m, 4H), 3.70−3.60 (m, 2H), 3.23 (d, 2H, J = 4.7 Hz), 2.12−1.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.8, 128.0, 127.2, 86.9, 86.5, 70.9, 66.0, 43.6, 41.9, 35.4; IR ($CHCl_3$) ν 3009, 1490, 1449, 1442, 1123, 1076, 1087 cm^{-1}; UV (EtOH) λ_{max} 259 nm (ϵ 659); MS (FD) *m*/*z* calcd for $C_{25}H_{26}O_2Cl_2$ 429, found 428 (100). Anal. Calcd for $C_{25}H_{26}O_2Cl_2$: C, 69.93; H, 6.10; O, 16.51. Found: C, 70.10; H, 6.18; O, 16.60.

(*S*)-4-(Triphenylmethoxy)-2-(2-iodoethoxy)-1-iodobutane (8f), A solution of bismesylate **8c** (3.7 g, 6.67 mmol) and tetrabutylammonium iodide (9.8 g, 26.7 mmol) in toluene (75 mL) was heated to reflux for 10 min. The toluene was then removed in vacuo to give an oil that was extracted with EtOAc (200 mL), washed with water (200 mL) and saturated aqueous sodium bisulfite (100 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 4.6 g of an oil that was purified by column chromatography, using 2:1 hexanes−EtOAc as eluent, to give 4.1 g (100%) of bisiodide **8f**. Compound **8f** was unstable at room temperature and was stored at −5 °C until required. This instability prevented complete characterization of this compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 6H, J = 7.8 Hz), 7.37−7.23 (m, 9H), 4.00−3.91 (m, 1H), 3.72−3.69 (m, 1H), 3.63−3.54 (m, 1H), 3.41−3.18 (m, 6H), 2.14−1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 129.0, 128.1, 127.3, 87.0, 78.9, 71.2, 65.6, 36.2, 6.7, 6.4. Anal. Calcd for $C_{25}H_{26}O_2I_2$: C, 49.04; H, 4.28; I, 41.45. Found: C, 48.98; H, 4.34; I, 41.47.

(1,1-Dimethylethyl)diphenyl[3-(2-propenyloxy)-4-(triphenylmethoxy)butoxy]silane (27). To a solution of **26** (36.0 g) in 200 mL CH_2Cl_2 was added triethylamine (12.7 g, 17.5 mL, 125.60 mmol) followed by trityl chloride (29.2 g, 104.64 mmol). The reaction was stirred at room temperature for 12 h and then quenched with saturated aqueous ammonium chloride and extracted into EtOAc. The organic layer was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 60.1 g (98%) (1,1-dimethylethyl)diphenyl[3-(2-hydroxy)-4-(triphenylmethoxy)butoxy]silane as an oil that was used directly in the allylation reaction.

To a solution of 1,1-dimethylethyl)diphenyl[3-(2-hydroxy)-4-(triphenylmethoxy)butoxy]silane (10.4 g, 17.73 mmol) in 100 mL of THF was added NaH (1.4 g, 35.46 mmol, 60% dispersion) and the reaction allowed to come to 45 °C for 1 h. Allyl bromide (3.8 mL, 5.36 g, 44.3 mmol) was added and the reaction then heated at 45 °C for 4 h. Analysis of the reaction indicated it had reached 50% completion. However, over the next 4 h the reaction was slow, and additional allyl bromide (3.8 mL) was added. The reaction was heated at 45 °C for 16 h, after which time TLC (9:1 hexanes:EtOAc) indicated that it had reached completion. The reaction was quenched with saturated aqueous ammonium chloride and extracted into EtOAc. The organic layer was washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give an oil that was purified by silica gel chromatography, using 9:1 hexanes−EtOAc, to afford 9.5 g (86%) of **27** as a clear oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65−7.15 (m, 25H), 5.93−5.80 (m, 1H), 5.25−5.00 (m, 2H), 4.04 (dd, 1H, J = 13.2 Hz, 5.3 Hz), 3.90 (dd, 1H, J = 13.2 Hz, 5.3 Hz), 3.75−3.55 (m, 3H), 3.02 (d, 2H, J = 4.5 Hz), 1.56−1.52 (m, 2H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.7, 143.6, 135.5, 135.3, 134.9, 133.1, 133.0, 129.7, 128.1, 127.8, 127.7, 126.9, 124.9, 115.8, 85.9, 74.5, 70.0, 65.2, 59.8, 54.8, 34.6, 26.7, 26.5, 18.6; IR (KBr) ν 3009, 2958, 2931, 2858, 1490, 1472, 1449, 1428, 1111, 1106, 1088, 997 cm^{-1}; UV (EtOH) λ_{max} 259 nm (ϵ 1423). Anal. Calcd for $C_{42}H_{46}O_3Si$: C, 80.47; H, 7.40. Found: C, 80.65; H, 7.55.

[1-[(Triphenylmethoxy)methy]-4-[[(1,1-dimethylethyl)-diphenylsilyl]oxy]butoxy]ethanol (28). To a solution of **27** (8.7 g, 13.92 mmol, 1.0 equiv) in MeOH−CH_2Cl_2 (100 mL, 1:1) was added Sudan red indicator (0.02 equiv, 0.1wt %/wt solution in 3:1 CH_2Cl_2−EtOH) and the reaction cooled to −50 °C. Ozone was bubbled through the solution until the color changed from peach to light yellow. The reaction mixture was then quenched at −50 °C with $NaBH_4$ (1.0 g, 27.84 mmol, 2.0 equiv), allowed to warm to 25 °C, and stirred for 12−16 h. After the pH of the solution was adjusted to 6.0−6.5 with 1 N HCl, the organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to afford an oil that was purified by chromatography, using 10:1 hexanes:EtOAc, as eluent to afford 6.2 g (70%) of **28** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.56 (m, 3H), 7.45−7.19 (m, 22H), 3.80−3.64 (m, 7H), 3.15 (d, 2H, J = 4.9 Hz), 2.32 (t, 1H, J = 6.0 Hz), 1.70−1.65 (m, 2H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 135.5, 129.6, 128.6, 127.7, 127.6, 127.5, 126.9, 86.7, 71.4, 66.3, 62.2, 60.2, 35.1, 31.5, 26.8, 22.6, 19.1, 14.1; IR (KBr) ν 3010, 2959, 2931, 2859, 2873, 1490, 1472, 1449, 1428, 1112, 1105, 1088, 1050, 823 cm^{-1}; UV (EtOH) λ_{max} 259 nm (ϵ 1322). Anal. Calcd for $C_{41}H_{46}O_4Si$: C, 78.05; H, 7.35. Found: C, 78.35; H, 7.47.

(1,1-Dimethylethyl)diphenyl[3-[2-(methanesulfonyloxy)ethoxy]-4-(triphenylmethoxy)butoxy]silane (11). To a solution of alcohol **28** (2.0 g, 3.17 mmol) in CH_2Cl_2 (20 mL) at 0−5 °C was added triethylamine (0.6 g, 6.32 mmol) followed by methanesulfonyl chloride (0.5 g, 4.80 mmol), and the reaction mixture was stirred for 30 min in an ice bath and followed to completion by TLC (CH_2Cl_2). The reaction was diluted with CH_2Cl_2 (50 mL), washed with a 10% aqueous ammonium chloride solution (100 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 2.1 g (91%) of **11** as an oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64−7.59 (m, 4H), 7.44−7.20 (m, 21H), 4.28 (t, 2H, J = 4.3 Hz), 3.92−3.88 (m, 1H), 3.75−3.61 (m, 4H), 3.15 (d, 2H, J = 4.9 Hz), 2.85 (s, 3H), 1.72−1.67 (m, 2H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.6, 135.8, 134.0, 130.6, 129.1, 128.7, 128.7, 127.9, 86.9, 76.7, 70.8, 68.4, 66.3, 60.8, 37.6, 35.4, 27.5, 19.6; IR (KBr) ν 3033, 2960, 2932, 2859, 1491, 1472, 1449, 1429,

1357, 1175, 1133, 1112, 1106, 1021, 998, 971, 924 cm^{-1}; UV (EtOH) λ_{max} 259 nm (ϵ 1370). Anal. Calcd for $C_{42}H_{48}O_6SiS$: C, 71.15; H, 6.82, S, 4.52. Found: C, 70.91; H, 6.59, S, 4.63.

(*S*)-6,7,10,11-Tetrahydro-19-methyl-9-[(triphenylmethoxy)methyl]-9*H*,18*H*,-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecine-18,20(19*H*)-dione (7). To a suspension of Cs_2CO_3 (13.3 g, 37.7 mmol) and **9** (5.9 g, 17.3 mmol) in DMF (425 mL) at 100 °C was added **8c** (12.4 g, 22.4 mmol) in DMF (175 mL) at 5 °C via syringe pump over 6 h. After **8c** had been added, the reaction was cooled to room temperature and stirred for 12 h. The reaction was then heated to 50 °C and 11 g of Hyflo added. After being stirred at 50 °C for 5 min, the mixture was filtered and the cake washed with DMF (2 × 25 mL). The DMF was removed in vacuo at 65 °C to 70 mL (11 volumes) and ACN (300 mL) added to the slurry over 30 min. The reaction volume was again reduced to 70 mL and additional ACN (70 mL) added. The reaction was then cooled to 0−5 °C and stirred for 3 h, and the solids that were collected were isolated by filtration and washed with ACN (20 mL) and water (20 mL). The product was dried at 50 °C to afford 6.6 g (54%) **7** as a red crystalline solid: $[\alpha]^{20}_D$ −9.95° (*c* 0.99, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (d, 1H, J = 8.1 Hz), 7.77 (d, 1H, J = 7.8 Hz), 7.28 (m, 23H), 4.12 (m, 4H), 3.68 (m, 1H), 3.52 (m, 1H), 3.28 (m, 2H), 3.07 (s, CH_3), 3.06 (m, 1H), 2.09−1.99 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.9, 143.5, 135.6, 131.5, 131.4, 131.0, 130.9, 128.1, 127.8, 127.0, 126.6, 126.5, 126.4, 121.5, 121.2, 120.0, 110.1, 110.0, 103.2, 86.3, 76.1, 66.7, 63.7, 45.8, 42.3, 31.4, 23.7; IR ($CHCl_3$) ν 2924, 1697, 1621, 1532, 1490, 1469, 1447, 1384, 1320, 1251, 1198, 1156, 1130, 1105, 1068, 1032, 1015, 985 cm^{-1}; UV (EtOH) λ_{max} 509 nm (ϵ 2500), 388 nm (ϵ 2604), 280 nm (ϵ 7584), 204 nm (ϵ 68 586); MS (FD) *m*/*z* calcd for $C_{46}H_{39}N_3O_4$ 697, found 697 (100). Anal. Calcd for $C_{46}H_{39}N_3O_4$: C, 79.17; H, 5.63; N, 6.02. Found: C, 79.03; H, 5.54; N, 6.28.

3-[1-[2-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-[(triphenylmethoxy)methyl]propoxy]ethyl]-1*H*-indol-3-yl]-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (30). To a solution of **9** (2.0 g, 5.77 mmol) and Cs_2CO_3 (0.9 g 2.89 mmol) in dry DMF (75 mL) at room temperature was added mesylate **11** (2.1 g, 2.98 mmol) in dry DMF (25 mL) and the reaction heated at 60 °C for 24 h under N_2. The reaction was cooled, diluted with EtOAc (200 mL), and washed with water (2 × 200 mL). The combined aqueous layers were re-extracted with EtOAc (100 mL) and the organic layers dried ($MgSO_4$) and filtered. The solvent was removed in vacuo to give 4.9 g of product that was purified by silica gel chromatography, using a gradient of 6:1 to 3:1 hexanes−EtOAc, to afford 1.4 g (49%) of **30** as a red foam. A sample 0.4 g (10%) of the dialkylated material **31** was also obtained and identified by mass spectrometry [MS (FAB$^+$) calcd for $C_{103}H_{103}O_8N_3Si_2$ 1566, found 1567]. Characterization of **30**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.72 (s, 1H) 7.66 (d, 1H, J = 2.7 Hz), 7.44 (d, 4H, J = 6.5 Hz), 7.13−7.04 (m, 23 H), 6.91 (t, 1H, J = 7.5 Hz), 6.84 (t, 1H, J = 7.5 Hz), 6.72 (d, 1H, J = 7.8 Hz), 6.69 (d, 1H, J = 7.8 Hz), 6.57 (t, 1H, J = 7.5 Hz), 6.46 (t, 1H, J = 7.5 Hz), 4.29−4.26 (m, 2H), 3.73−3.70 (m, 1H), 3.63−3.60 (m, 1H), 3.60−3.43 (m, 3H), 2.96 (s, 3H), 2.94−2.88 (m, 2H), 1.64−1.54 (m, 2H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 172.4, 144.6, 136.8, 135.8, 134.1, 133.4, 130.6, 129.9, 129.0, 128.6, 128.6, 127.8, 127.5, 126.7, 126.2, 122.5, 122.4, 122.1, 121.8, 120.4, 120.1, 112.6, 111.0, 106.6, 105.9, 86.9, 76.6, 69.1, 66.0, 60.8, 35.5, 32.2, 29.9, 29.6, 27.5, 24.7, 22.9, 19.5, 14.8; IR (KBr) ν 3400, 2953, 2927, 2855, 1757, 1696, 1531, 1457, 1448, 1427, 1384, 1194, 1112, 1104, 741, 704, 504 cm^{-1}; UV (EtOH) λ_{max} 482 nm (ϵ 7039), 479 nm (ϵ 7034), 470 nm (ϵ 6900), 465 nm (ϵ 6746); HRMS (EI) *m*/*z* exact mass calcd for $C_{62}H_{59}N_3O_5Si$ 953.4224, found 953.4234.

3-[1-[2-[3-Hydroxy-1-[(triphenylmethoxy)methyl]propoxy]ethyl]-1*H*-indol-3-yl]-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (32). A solution of **30** (1.3 g, 1.41 mmol) in dry THF (20 mL) at 0−5 °C was treated with a 1 M solution of tetrabutylammonium fluoride in THF (2.8 mL, 2.80 mmol) and the resultant purple solution warmed to room temperature for 1.5 h. The reaction was diluted with EtOAc (100 mL), washed with water (2 × 100 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 1.6 g of crude product that was purified over silica gel, using a gradient of 2:1 hexanes−EtOAc to 1:2 hexanes−EtOAc to give 0.9 g (89%) of **32** as a red foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.76 (s, 1H), 7.65 (d, 1H, J = 2.6 Hz), 7.42 (d, 1H, J = 8.3 Hz), 7.40−7.13 (m, 16H), 6.96 (t, 1H, J = 7.3 Hz), 6.91 (t, 1H, J = 7.3 Hz), 6.73 (d, 1H, J = 7.9 Hz), 6.71 (d, 1H, J = 7.9 Hz), 6.61 (t, 1H, J = 7.3 Hz), 6.53 (t, 1H, J = 7.3 Hz), 4.33−4.26 (m, 3H), 3.80−3.63 (m, 2H), 3.54−3.42 (m, 1H), 3.28−3.19 (m, 2H), 2.99 (s, 3H), 2.99−2.80 (m, 2H), 1.51−1.49 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 172.5, 144.7, 136.9, 136.8, 133.4, 129.9, 129.1, 128.8, 128.7, 127.8, 127.8, 127.5, 126.6, 126.3, 122.5, 122.1, 121.8, 120.4, 120.2, 112.6, 111.1, 106.6, 105.9, 86.8, 76.9, 69.1, 66.2, 58.0, 47.2, 35.9, 24.9; IR (KBr) ν 3394, 2928, 1695, 1531, 1490, 1448, 1442, 1384, 1339, 1195, 1125, 1099, 1068, 979, 764, 744, 707, 633 cm^{-1}; UV (EtOH) λ_{max} 483 nm (ϵ 6925), 481 nm (ϵ 6969), 468 nm (ϵ 6843), 416 nm (ϵ 3377); HRMS (EI) *m*/*z* exact mass calcd for $C_{46}H_{41}N_3O_5$ 715.3046, found 715.3051.

3-[1-[2-[3-[(Methylsulfonyl)oxy]-1-[(triphenylmethoxy)methyl]propoxy]ethyl]-1*H*-indol-3-yl]-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrolo-2,5-dione (10). A solution of alcohol **32** (0.8 g, 1.11 mmol) in CH_2Cl_2 (25 mL) at 0−5 °C under N_2 was treated with triethylamine (0.2 g, 2.22 mmol) followed by methanesulfonyl chloride (0.2 g, 1.67 mmol), and the reaction mixture was stirred 30 min at 0 °C. The reaction was diluted with CH_2Cl_2 (50 mL), washed with a 10% aqueous solution of NH_4Cl (2 × 50 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 0.9 g (100%) of mesylate **10** as a red foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.76 (s, 1H), 7.65 (d, 1H, J = 2.7 Hz), 7.42 (d, 1H, J = 8.3 Hz), 7.37−7.14 (m, 14H), 6.94 (t, 1H, J = 7.3 Hz), 6.88 (t, 1H, J = 7.3 Hz), 6.73 (d, 1H, J = 7.9 Hz), 6.70 (d, 1H, J = 7.9 Hz), 6.61 (t, 1H, J = 6.8 Hz), 6.50 (t, 1H, J = 6.8 Hz), 4.39−4.19 (m, 2H), 4.04 (t, 2H, J = 6.3 Hz), 3.75−3.58 (m, 2H), 2.99 (s, 3H), 2.92 (s, 3H), 2.89−2.84 (m, 3H), 1.80−1.72 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 172.5, 144.5, 136.9, 133.4, 129.9, 129.0, 128.7, 127.8, 127.5, 126.6, 126.3, 122.5, 122.1, 121.8, 120.4, 120.2, 112.6, 111.1, 106.5, 105.9, 86.9, 75.9, 69.2, 68.0, 65.8, 65.5, 55.8, 47.0, 39.9, 37.2, 32.3, 24.8; IR (KBr) ν 1757, 1697, 1533, 1448, 1384, 1353, 1174, 745, 707 cm^{-1}; UV (EtOH) λ_{max} 473 nm (ϵ 6722), 470 nm (ϵ 6745), 467 nm (ϵ 6706), 434 nm (ϵ 4832); HRMS (EI) *m*/*z* exact mass calcd for $C_{47}H_{43}N_3O_7S$ 793.2822, found 793.2827.

(*S*)-6,7,10,11-Tetrahydro-19-methyl-9-[(triphenylmethoxy)methyl]-9*H*,18*H*,-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecine-18,20(19*H*)-dione (7). To a suspension of Cs_2CO_3 (0.16 g, 0.490 mmol) in dry DMF (31 mL) at 100 °C under N_2 was added a solution of **10** (0.4 g, 0.49 mmol) in dry DMF (8 mL) over 6 h. The reaction was cooled to room temperature, diluted with EtOAc (50 mL), washed with 10% aqueous ammonium chloride (2 × 50 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to give 0.5 g of **7** that was purified over silica gel using CH_2Cl_2 as eluent to afford 0.26 g (78%) of macrocyclic bisindolylmaleimide **7**.

(*S*)-6,7,10,11-Tetrahydro-9-[(triphenylmethoxy)methyl]-5,21:12,17-dimetheno-9*H*-dibenzo[*e*,*k*]furo[3,4-*h*][1,4,13]-oxadiazacyclohexadecine-18,20-dione (33). A suspension of **7** (20.0 g, 0.03 mol) in EtOH (160 mL) and KOH (16.1 g, 0.3 mol) was heated to a gentle reflux (78 °C) for 19 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (200 mL), and washed with deionized water (100 mL) maintaining the temperature at 25 °C. The organic layer was removed, acidified with a 20% aqueous citric acid solution (100 mL), washed with water (100 mL), and diluted with EtOH (200 mL). After removal of 10 volumes of solvent the product crystallized out of solution. The slurry was cooled to 0−5 °C for 1 h, and the solids were collected by filtration and rinsed with EtOH (100 mL). The product was dried to afford 17.7 g (95%) **33**: $[\alpha]^{20}_D$ −27.06° (*c* 0.97, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, 1H, J = 7.0 Hz), 7.84 (d, 1H, J = 7.4 Hz), 7.63 (s, 2H), 7.53 (d, 1H, J = 8.1 Hz), 7.39 (d, 1H, J = 7.4 Hz), 7.38−7.11 (m, 19H),

4.35−4.03 (m, 4H), 3.76−3.66 (m, 1H), 3.60−3.50 (m, 1H), 3.42−3.31 (m, 1H), 3.09 (d, 2H, J = 4.4 Hz), 2.19−1.91 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.4, 143.5, 135.7, 132.5, 132.1, 132.0, 131.9, 131.8, 131.7, 131.4, 128.1, 127.9, 127.8, 127.7, 127.1, 127.0, 126.0, 125.9, 121.9, 121.4, 121.1, 120.7, 110.3, 102.2, 102.1, 86.3, 76.3, 66.0, 63.8, 45.8, 42.5, 31.5; IR ($CHCl_3$) ν 1752, 1527, 1490, 1471, 1449, 1393, 1360, 1321, 1264, 1195, 1159, 1103, 1067, 1019, 915, 738, 701, 631 cm^{-1}; UV (EtOH) λ_{max} 527 nm (ϵ 2059), 514 nm (ϵ 2091), 393 nm (ϵ 1906), 332 nm (ϵ 423), 288 nm (ϵ 4638), 229 (ϵ 18 963), 208 (ϵ 20 123); MS (FD) m/z alcd for $C_{45}H_{36}N_2O_5$ 684, found 684 (100). Anal. Calcd for $C_{45}H_{36}N_2O_5$: C, 78.93; H, 5.30; N, 4.09. Found: C, 78.67; H, 5.49; N, 4.25.

(*S*)-6,7,10,11-Tetrahydro-9-[(triphenylmethoxy)methyl]-9*H*,18*H*,-5,21:12,17-dimethenodibenzo[*e*,*k*]-pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecine-18,20(19*H*)-dione (34). To a solution of **33** (47.0 g, 0.07 mol) in DMF (470 mL) was added a premixed solution of HMDS (110.9 g, 0.69 mol, 145 mL) and MeOH (14 mL). The reaction was heated to 80 °C and monitored by HPLC for approximately 7 h. Upon completion, the reaction was cooled to room temperature and diluted with CH_2Cl_2 (470 mL). The solution was then cooled to 0−5 °C and quenched with 1 N HCl (470 mL), maintaining the temperature at 0−5 °C. The organic layer was removed and diluted with EtOH (470 mL). The solvent was removed until 10 volumes of the distillate remained, at which time the product crystallized out of solution. The reaction was cooled to 0−5 °C and stirred for 1 h. The solids were filtered and rinsed with cold EtOH (235 mL). The product was dried to a constant weight in a vacuum oven to afford 45.7 g (97%) of **34** as a purple solid: $[\alpha]^{20}_D$ −0.58° (c 0.98, MeOH): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.83 (d, 1H, J = 7.4 Hz), 7.75 (d, 1H, J = 7.7 Hz), 7.47 (d, 1H, J = 13.6 Hz), 7.41−7.06 (m, 22H), 4.25−3.96 (m, 4H), 3.73−3.63 (m, 1H), 3.57−3.46 (m, 1H), 3.31−3.21 (m, 1H), 3.08−2.95 (m, 2H), 2.16−1.91 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 143.5, 135.5, 132.2, 131.4, 131.3, 131.1, 131.0, 128.1, 127.8, 126.9, 126.6, 126.5, 121.6, 121.5, 121.2, 120.0, 110.0, 109.9, 103.3, 86.3, 76.0, 66.7, 63.7, 45.7, 42.2, 31.3; IR ($CHCl_3$) ν 1762, 1719, 1534, 1490, 1470, 1449, 1391, 1335, 1196, 1156, 1106, 1069, 1016, 988, 743, 706, 633 cm^{-1}; UV (EtOH) λ_{max} 494 nm (ϵ 4277), 382 nm (ϵ 4320), 281 nm (ϵ 11 034), 228 nm (ϵ 49 353), 208 nm (ϵ 70483); MS (FD) m/z calcd for $C_{45}H_{37}N_3O_4$ 683, found 683 (100). Anal. Calcd for $C_{45}H_{37}N_3O_4$: C, 79.04; H, 5.45; N, 6.14. Found: C, 78.99; H, 5.50; N, 6.26.

(*S*)-6,7,10,11-Tetrahydro-9-(hydroxymethyl)-9*H*,18*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]-oxadiazacyclohexadecine-18,20(19*H*)-dione (35). A suspension of **34** (40.6 g, 0.06 mol) in EtOH (400 mL) and 6 N HCl (400 mL) was heated at reflux for 2 h. The resulting slurry was cooled to room temperature, filtered, and rinsed with CH_2Cl_2 (80 mL). The isolated **35** was reslurried in CH_2Cl_2 (50 mL) at room temperature for 2 h to remove residual tritylated impurities. The solids were filtered and dried to afford 24.86 g (95%, >98% ee)[38] of **35** as a purple solid: $[\alpha]^{20}_D$ −11.26° (c 0.99, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.84 (d, 1H, J = 8.1 Hz), 7.80 (d, 1H, J = 8.1 Hz), 7.52 (d, 1H, J = 8.7 Hz), 7.51 (s, 1H), 7.45 (d, 1H, J = 8.7 Hz), 7.43 (s, 1H), 7.24−7.07 (m, 4H), 4.40−4.28 (m, 1H), 4.26−4.08 (m, 3H), 3.95−3.83 (m, 1H), 3.67−3.56 (m, 1H), 3.56−3.47 (dd, 1H, J = 11.4 Hz, J = 4.8 Hz), 3.44−3.36 (dd, 1H, J = 11.4 Hz, J = 3.6 Hz), 3.36−3.26 (m, 2H), 2.16−2.03 (m, 1H), 2.03−1.89 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 135.6, 135.5, 132.1, 131.5, 131.4, 131.4, 131.3, 131.2, 131.1, 126.5, 121.6, 121.5, 121.3, 120.0, 110.1, 109.9, 103.2, 103.0, 77.4, 66.1, 61.2, 49.5, 45.7, 42.6, 31.3; IR ($CHCl_3$) ν 3449, 1761, 1703, 1528, 1471, 1448, 1392, 1365, 1341, 1199, 1102, 1033, 801, 749, 744 cm^{-1}; UV (EtOH) λ_{max} 500 nm (ϵ 4826), 377 nm (ϵ 4586), 281 nm (ϵ 11 567), 233 nm (ϵ 45 031), 205 nm (ϵ 47 341); MS (FD) m/z calcd for $C_{26}H_{23}N_3O_4$ 441, found 441 (100). Anal. Calcd for $C_{26}H_{23}N_3O_4$; C, 70.74; H, 5.25; N, 9.52. Found: C, 70.91; H, 5.38; N, 9.81.

(*S*)-6,7,10,11-Tetrahydro-9-[[(methylsulfonyl)oxy]methyl]-9*H*,18*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecine-18, 20(19*H*)-dione (39). To a suspension of **35** (329.5 g, 0.74 mol, 1.0 equiv) in THF (6.6 L) was added pyridine (177 mL, 2.24 mol) and methanesulfonic anhydride (268 g, 1.49 mol). The reaction was heated at reflux for 1 h and then cooled to room temperature and diluted with THF (3 L). To the reaction solution was added 1 N HCl (3.3 L) and the mixture stirred for 15−20 min. The layers were separated and the aqueous layer re-extracted with EtOAc (2 L). The combined organic layers were concentrated in vacuo until mainly water was distilling. The product **39**, which crystallized from solution, was filtered and rinsed with deionized water. The solids were dried to afford 391 g (100%) of **39** as a purple solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.84 (d, 1H, J = 7.7 Hz), 7.69 (d, 1H, J = 7.5 Hz), 7.50 (m, 4H), 7.20 (t, 2H, J = 6.99 Hz, J = 8.1 Hz), 7.12 (t, 2H, J = 7.7 Hz), 4.41−4.37 (m, 2H), 4.28−4.11 (m, 4H), 3.95−3.86 (m, 1H), 3.68−3.57 (m, 2H), 3.17 (s, 3H), 2.19−1.92 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 135.6, 135.5, 132.2, 131.3, 126.6, 126.5, 121.6, 121.5, 121.3, 120.2, 120.1, 110.1, 109.9, 103.3, 103.2, 74.8, 69.1, 66.5, 45.5, 42.5, 36.4, 31.1; IR ($CHCl_3$) ν 3869, 3610, 3441, 3026, 2978, 1765, 1723, 1624, 1603, 1538, 1523, 1472, 1393, 1365, 1340, 1220, 1197, 1177, 1111, 1071, 1094, 994, 963 cm^{-1}; UV (EtOH) λ_{max} 495 nm (ϵ 4228), 380 nm (ϵ 4096), 281 nm (ϵ 10 598), 232 nm (ϵ 40 337), 206 nm (ϵ 41 098); MS (FD) m/z calcd for $C_{27}H_{25}N_3O_6S_1$ 519, found 519 (100). Anal. Calcd for $C_{27}H_{25}N_3O_6S_1$ C, 62.42; H, 4.85; N, 8.09. Found C, 62.26; H 4.88; N, 7.96. $[\alpha]^{20}_D$ −22.40° (c 1.0, MeOH).

(*S*)-6,7,10,11-Tetrahydro-9-[(dimethylamino)methyl]-9*H*,18*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*]-[1,4,13]oxadiazacyclohexadecine-18,20(19*H*)-dione (1). A 10 gal stainless steel reactor was charged with **39** (770 g, 1.48 mol) and 18.7 L of a 2 M solution of dimethylamine (37 mol, 25 equiv) in DMF. The reactor was sealed and heated at 65 °C for 17 h. The reaction was then cooled to room temperature and the DMF removed in vacuo to 5−7 volumes. MeOH (40 volumes) was added at 60 °C and the mixture stirred at 60 °C for 45 min, during which time **1** crystallized out of solution as a red solid. The reaction was allowed to cool to room temperature and stir overnight. The slurry was then cooled to 0−5 °C for an additional 4 h and filtered. The product was rinsed with 4 × 1 L of cold MeOH and dried to afford 585 g (84%) of **1**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.82 (d, 1H, J = 4.8 Hz), 7.78 (d, 1H, J = 4.8 Hz), 7.46−7.41 (m, 4H), 7.24−7.06 (m, 4H), 4.38−4.05 (m, 4H), 3.93−3.82 (m, 1H), 3.47−3.40 (m, 1H), 3.37 (t, 2H, J = 7.2 Hz), 3.24 (t, 2H, J = 6.9 Hz), 2.47−2.32 (m, 1H), 2.23−2.09 (m, 1H), 2.00−1.88 (m, 2H), 1,0.84b (q, 2H, J = 6.6 Hz), 1.76 (q, 2H, J = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 136.0, 135.7, 132.0, 131.9, 131.0, 130.9, 126.6, 126.3, 121.7, 121.6, 121.5, 121.4, 120.2, 120.1, 110.0, 103.6, 74.1, 67.3, 57.3, 45.5, 43.3, 43.0, 41.7, 31.5; IR ($CHCl_3$) ν 3440, 2976, 2947, 2870, 2827, 2776, 1763, 1720, 1536, 1521, 1470, 1391, 1364, 1337, 1098, 1045, 1016, 986 cm^{-1}; UV (EtOH) λ_{max} 493 nm (ϵ 3944), 382 nm (ϵ 3796), 282 nm (ϵ 9946), 232 nm (ϵ 38 382), 204 nm (ϵ 43 887); MS (FD) m/z calcd for $C_{28}H_{28}N_4O_3$ 468, found 468 (100). Anal. Calcd for $C_{28}H_{28}N_4O_3$: C, 71.78; H, 6.02; N, 11.96. Found: C, 71.53; H, 6.19; N, 11.72.

(*S*)-6,7,10,11-Tetrahydro-9-(pyrrolidinomethyl)-9*H*,-18*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]-oxadiazacyclohexadecine-18,20(19*H*)-dione (2). To a solution of **39** (1.5 g, 2.89 mmol) in 30 mL of *N*,*N*-dimethylacetamide was added pyrrolidine (6.02 mL, 72.20 mmol, 25 equiv) and the reaction heated at 65 °C for 17 h and then cooled to room temperature. To the red slurry was added 12 N NaOH (0.24 mL) and the mixture stirred for 30 min. The reaction was then extracted into CH_2Cl_2 (125 mL) and washed with 10% aqueous ammonium chloride (125 mL) and 5% aqueous LiCl solution (125 mL). The CH_2Cl_2 was removed in vacuo and the

(38) The enantiomeric excess of **35** was determined by chiral HPLC: A 2 mg sample was placed in a 5 mL volumetric flask and diluted with 5 mL of MeOH. Column: SS Whelk 01 (Regis Chemical Co.). Wavelength: 233 nm. Flow rate: 0.5 mL/min. Injection volume: 20 μL. Isocratic mobile phase: MeOH. (*R*)-isomer t_R = 21.1 min. (*S*)-isomer t_R = 22.7 min.

residue triturated with EtOH (30 mL) to afford, after drying, 1.2 g (83%) of **2** as a red solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.82 (d, 1H, J = 4.8 Hz), 7.78 (d, 1H, J = 4.8 Hz), 7.46−7.41 (m, 4H), 7.24−7.06 (m, 4H), 4.38−4.05 (m, 4H), 3.93−3.82 (m, 1H), 3.63−3.51 (m, 1H), 3.47−3.40 (m, 1H), 3.37 (t, 2H, J = 7.2 Hz), 3.24 (t, 2H, J = 6.9 Hz), 2.47−2.32 (m, 1H), 2.23−2.09 (m, 1H), 2.00−1.88 (m, 2H), 1.84 (q, 2H, J = 6.6 Hz), 1.76 (q, 2H, J = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 135.7, 135.7, 132.2, 131.7, 131.5, 130.5, 126.6, 121.6, 121.4, 120.0, 110.1, 109.9, 103.4, 103.2, 76.9, 72.1, 66.8, 57.5, 54.1, 48.7, 46.2, 42.6, 32.8, 26.8, 23.1; IR (KBr) υ 1714, 1532, 1467, 1390, 1336, 1197, 739, 747 cm^{-1}; UV (EtOH) λ_{max} 281 nm (ϵ 10 056); 232 nm (ϵ 39 032); HRMS (EI) exact mass calcd for $C_{30}H_{30}N_4O_3$ M^+ 494.2318, found 494.2328.

(*S*)-6,7,10,11-Tetrahydro-9-[(benzylamino)methyl]-9*H*,-18*H*,5,21:12,17-dimethenodibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]-oxadiazacyclohexadecine-18,20(19*H*)-dione (3). To a solution of **39** (1.5 g, 2.89 mmol) in 30 mL of *N*,*N*-dimethylacetamide was added benzylamine (7.9 mL, 72.2 mmol, 25 equiv) and the reaction heated at 65 °C for 30 h in a sealed vessel. The reaction was cooled to room temperature, triethylamine (0.40 mL, 2.89 mmol, 1.0 equiv) was added, and the reaction was stirred for 30 min. The reaction was then extracted into EtOAc (100 mL) and washed with water (100 mL) and saturated aqueous sodium chloride (100 mL). The aqueous layers were re-extracted with EtOAc (25 mL) and the combined organic layers concentrated in vacuo. To the residue was added EtOH (30 mL), and the solid that precipitated out was isolated by filtration and dried to afford 1.5 g (95%) **3** as a red solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.86 (bs, 1H), 7.83 (d, 1H, J = 7.8 Hz), 7.79 (d, 1H, J = 7.8 Hz), 7.54−7.37 (m, 4H), 7.34−7.06 (m, 9H), 4.38−4.25 (m, 1H), 4.25−3.98 (m, 4H), 3.81−3.71 (m, 1H), 3.63 (s, 2H), 3.58−3.46 (m, 2H), 2.63−2.47 (m, 2H), 2.22−2.07 (m, 1H), 2.07−1.93 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 140.7, 135.6, 132.1, 131.5, 131.3, 131.2, 128.0, 127.8, 126.5, 126.4, 121.6, 121.5, 121.3, 120.0, 119.9, 110.0, 109.9, 103.3, 103.1, 76.8, 66.1, 53.2, 49.7, 45.8, 42.7, 32.4; IR (KBr) υ 3694, 3439, 3010, 2939, 2869, 1764, 1721, 1624, 1536, 1521, 1470, 1391, 1363, 1338, 1196, 1157, 1108, 1015, 988, 834 cm^{-1}; UV (EtOH) λ_{max} 505 nm (ϵ 2203), 379 nm (ϵ 2141), 282 nm (ϵ 5648), 233 nm (ϵ 21 287), 204 nm (ϵ 27 990); MS (FD) m/z calcd for $C_{33}H_{30}N_4O_3$ 530, found 530 (M^+, 100). Anal. Calcd for $C_{33}H_{30}N_4O_3$: C, 74.70; H, 5.70; N, 10.56. Found: C, 74.40; H, 5.76; N, 10.37.

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