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Synthetic Studies toward Ecteinascidin 743

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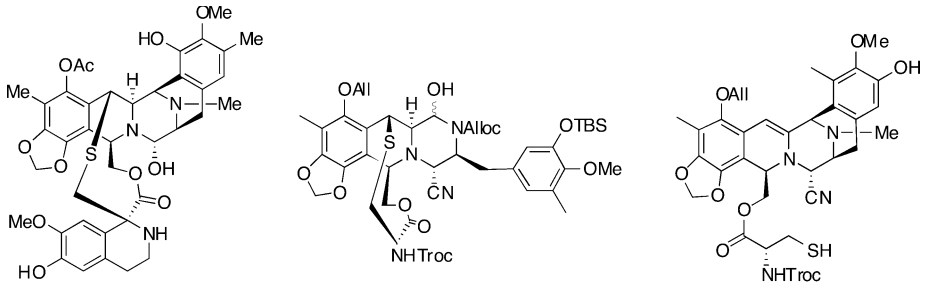

An efficient synthesis of a fully functionalized tetracycle (A-B-C-H) **7** containing a 1,4-bridged 10-membered lactone was developed. Phenolic aldol condensation between 2-methylsesamol (**15**) and Garner's aldehyde provided the protected amino diol **16**, which was converted to free amine **11** in excellent yield. A Pictet−Spengler reaction between **11** and ethyl glyoxylate under carefully controlled conditions (LiCl, toluene, 1,1,1,3,3,3-hexafluoro-2-propanol, room temperature) provided the acid-sensitive tetrahydroisoquinoline (**18**) in high yield, which was converted to the amino alcohol **9**. Enantioselective alkylation of a glycine template in the presence of a catalytic amount of chiral cinchonidium salt was the key step for the access of enantiomerically pure amino aldehyde **10**. Union of the two fragments **9** and **10** via oxazolidine intermediate afforded amino nitrile **39**, which upon esterification of the primary alcohol with (*R*)-*N*-(*S*-4,4′,4″-trimethoxyltrityl) Cys (**42**) afforded **43**. Cyclization of **43** (1% trifluoroacetic acid in trifluoroethanol) provided compound **44** by a domino process involving (a) unmasking of the *S*-trimethoxytrityl group, (b) fragmentation of dioxane assisted by an electron-rich aromatic ring, and (c) formation of a 1,4-bridged 10-membered lactone via formation of a sulfide linkage. Treatment of **7**, obtained in two steps from **44b**, under acidic conditions (0.5% methyl sulfonic acid in acetonitrile) afforded the pentacyclic compound **51** via fragmentation of the 10-membered cyclic sulfide followed by an intramolecular Pictet−Spengler reaction.

Introduction

The ecteinascidins, a family of tetrahydroisoquinoline alkaloids isolated from the Caribbean tunicate *Ecteinascidia turbinate*,[1] possess potent cytotoxic activity against a variety of tumor cell lines in vitro and against several rodent tumors and human tumor xenografts in vivo.[2] One of its members, ecteinascidin 743 (Et 743, **1a**, Figure 1) is currently in phase II/III clinical trials in Europe and the United States for ovarian, endometrial, and breast cancer and several types of sarcoma. It showed particularly high activity in cases of advanced sarcoma that had relapsed or were resistant to conventional therapy. The antiproliferative activity of Et 743 is greater than that of taxol, camptothecin, adriamycin, mitomycin C, cisplatin, bleomycin, or etopside by 1−3 orders of magnitude. Et 743 binds to the minor groove of the DNA by way of three hydrogen bond contacts between the A- and E-ring of Et 743 and the three base pairs recognition sequence, the most critical being the interaction of the E-subunit

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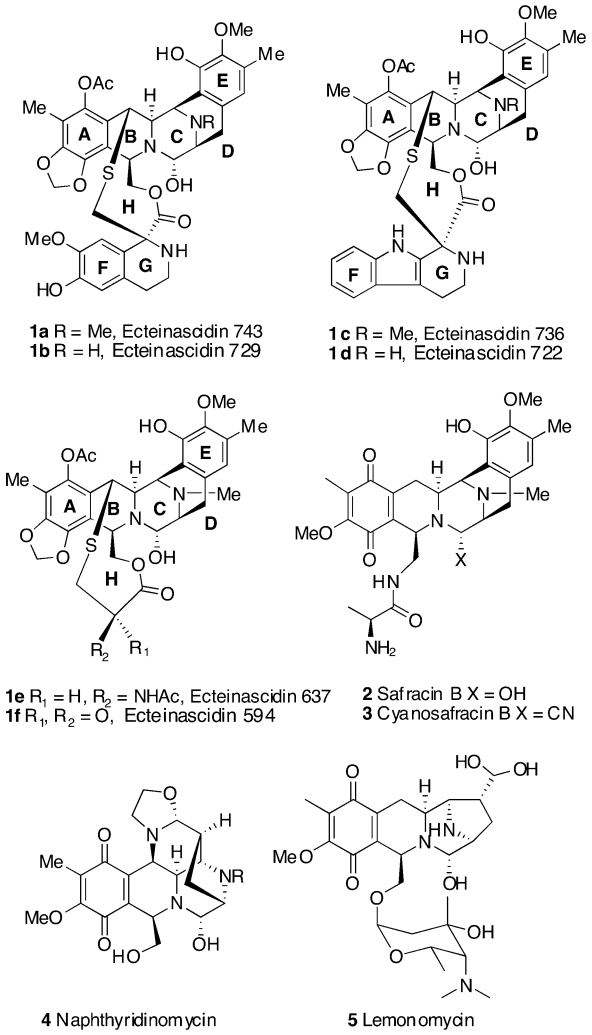

FIGURE 1. Structures of ecteinascidin 743 and related natural products.

with the base located 3′ to the modification site. In addition, through intramolecular acid-catalyzed dehydration of the carbinolamine moiety, Et 743 forms a covalent bond with the exocyclic 2-amino group of guanine.[3] It was demonstrated that the formation of Et 743/DNA complex is reversible under nondenaturing conditions and that Et 743 can migrate from the nonfavored bonding sequence (e.g., 5′-AGT) to the favored DNA target site (e.g., 5′-AGC), leading to the observed site-specificity.[4] In the Et 743/DNA adduct, the double helix bends toward the major groove and the third domain (ring F-G) of Et 743 positions itself outside the complex, making it available to interact with proteins and at the same time disrupting DNA-protein binding.[5−7] Although the F-G subunit has little contact with the minor groove of DNA, its presence is of utmost importance for the antitumor activity of Et 743. Indeed, it has been shown that modifying the F-G subunit changes the drug's ability to inhibit cell division. For example, Et 736 (**1c**) with a tetrahydro-β-carboline residue instead of a tetrahydroisoquinoline at the F-G part has a different bioactivity profile relative to Et 743. It is only slightly active against M5076 ovarian sarcoma and an MX-1 human mammary carcinoma xenograft but shows a higher level of activity in vivo in mice against P388 leukemia.[1d,8] Et 637 (**1e**) and Et 594 (**1f**), lacking the F-G subunit, are generally 10−50 times less active than Et 743 against MEL 28 and CV-A cell lines.[1e]

Structurally, Et 743 is composed of three tetrahydroisoquinoline systems interconnected via two bridged ring systems. Specifically, ring A-B and ring D-E are fused together, producing an additional six-membered ring (ring C) and a labile carbinolamine functional group that serves to alkylate the DNA. In addition, ring A-B is linked to the third tetrahydroisoquinoline (F-G) by a 10-membered lactone having a 1,4-bridged benzylic sulfide linkage. Overall seven stereocenters and eight rings are found in Et 743. Et 743 is structurally related to the saframycin class of antibiotics,[9] the noticeable difference being the higher oxidation state of the C-4 carbon in Et 743 compared to that in saframycin (**2**, **3**). The same difference can be recognized in two other structurally related natural products, naphthyridinomycin (**4**)[10] and lemonomycin (**5**, Figure 1).[11]

The restricted natural availability of ecteinascidins (1 g from 1 ton of tunicate) in conjunction with their potent antiproliferative activities and complex molecular architecture has made them attractive synthetic targets.[12] To date, two total syntheses have been accomplished by Corey[13] and Fukuyama,[14] respectively. A semisynthesis from cyanosafracin B (**3**)[15] has been developed by Cuevas, Manzanares, and co-workers at PharmaMar. In addition, other synthetic approaches have been reported from a number of research groups, including those of Kubo,[16] Danishefsky,[17] Williams,[18]

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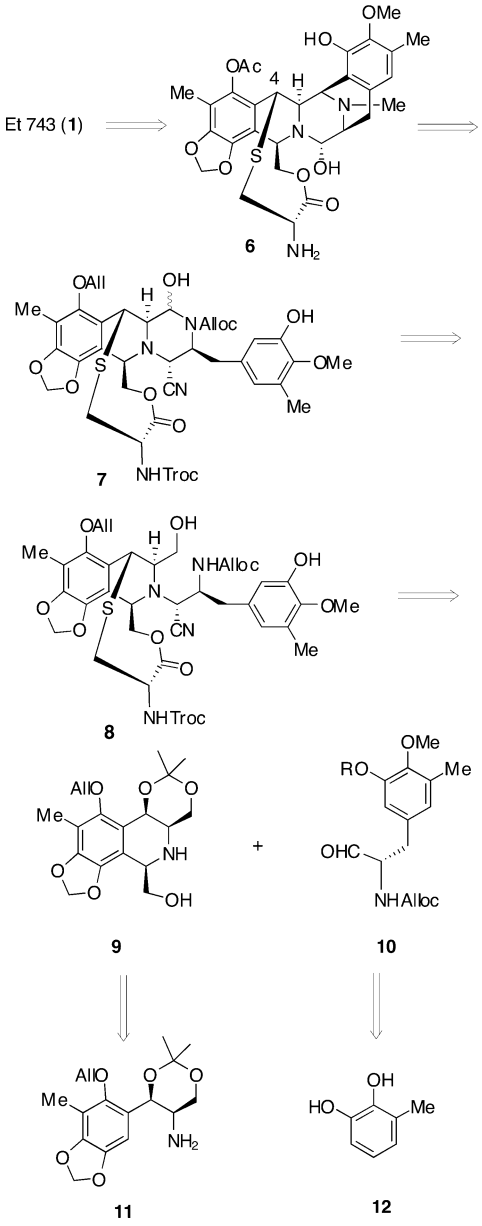
Magnus,[19] and Liu et al.[20] A simpler synthetic analogue of Et 743 named phthalascidin (Pt-650) that displayed virtually the same biological activities as the natural product has been discovered by Corey and Schreiber.[21] We have been investigating an alternative synthetic approach that is retrosynthetically depicted in Scheme 1. It was anticipated that cyclization of suitably protected carbinolamine **7**, which embodies all of the requisite functionalities to Et 743, would afford the desired hexacyclic compound **6** whose conversion to the natural product is known. Compound **7** could be traced back to the amino alcohol **8**, which in turn could be prepared by assemblage of fully functionalized tetrahydroisoqunoline **9** and amino aldehyde **10**. The C-4 hydroxy group was strategically positioned in **9** to facilitate the formation of the 10-membered lactone via an intramolecular carbon−sulfur bond forming process. One concern associated with this approach is the compatibility of the benzyl sulfide bond with the acidic conditions that would be required for the subsequent transformations. Moreover, the steric hindrance imposed by the pre-existing 10-membered macrolactone may potentially hamper the nucleophilic attack of the aromatic ring (E) onto the incipient iminium intermediate from the same side (β-face) defined by the macrolactone. Nevertheless, the overall approach is attractive for its convergency. We detail herein the successful synthesis of compound **7** and results of its subsequent cyclization reaction.[22]

SCHEME 1. Retrosynthetic Analysis of Et 743



Results and Discussion

Synthesis of Highly Functionalized Tetrahydroisoquinoline 9 and Macrolactone 27. The synthesis of tetrahydroisoquinoline **18** is shown in Scheme 2. Protection of sesamol (**13**) as the MOM ether followed by regioselective *ortho*-lithiation and methylation gave **14**,[23] which was cleanly unmasked (TMSCl, NaI in MeCN) to provide free phenol **15**. Phenolic aldol condensation between **15** and Garner's aldehyde[24] according to Casiraghi[25] provided, after column chromatography, the *syn* amino diol **16** in 98% yield as the only diastereomer. Compound **16** was converted into the 1,3-dioxane **17** in a three-step sequence involving (a) selective allylation of phenol, (b) selective hydrolysis of oxazolidine, and (c) selective ketalization of 1,3-diol. Finally, selective deprotection of *N-tert*-butyloxy carbamate following Ohfune's procedure proceeded smoothly to provide the free amine **11** in 90% yield.[26]

The benzylic hydroxy group in compound **11** is particularly vulnerable under acidic conditions as a result of the presence of an electron-rich aromatic ring. This acid-sensitivity posed a significant challenge in the realization of the subsequent Pictet−Spengler (P−S) reaction for the synthesis of tetrahydroisoquinolines.[27] Indeed, condensation between **11** and ethyl glyoxalate

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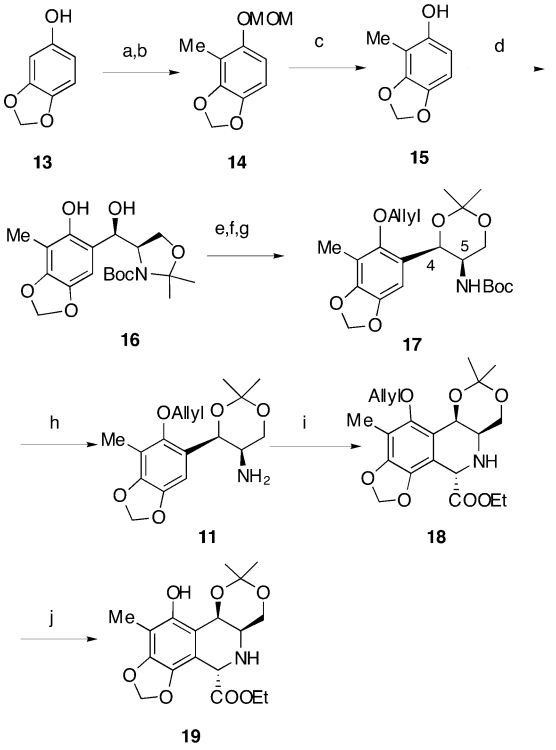
SCHEME 2. Synthesis of Highly Oxygenated Acid-sensitive Tetrahydroisoquinoline 18[a]



[a] Reaction conditions: (a) NaH, MOMCl, Et_2O−DMF, 0 °C, 90%; (b) BuLi, TMEDA, hexane, 0 °C, then MeI, Et_2O, −78 °C to rt, 93%; (c) TMSCl (1.2 equiv), NaI (5 equiv), MeCN, 0.05 M, −30 °C, then KOH, 85−90%; (d) MeMgCl, in THF, then Garner's aldehyde, CH_2Cl_2, 98%; (e) Cs_2CO_3, NaI, DMF, AllylBr; (f) pTsOH (0.1 equiv), MeOH, 0 °C; (g) dimethoxypropane, pTsOH (0.05 equiv), 70% for three steps; (h) TBDMSOTf, lutidine, −60 to 0 °C, then MeOH, KF, rt, 90%; (i) Table 1; (j) $Pd(PPh_3)_4$, Bu_3SnH, CH_2Cl_2, 90%.

led either to the decomposition of reactants under a variety of acidic conditions or to the recovery of starting materials under mild neutral conditions. Consequently, Lewis acid promoted Pictet−Spengler cyclization was next examined. After a survey of reaction conditions varying the Lewis acids [$Yb(OTf)_3$, $Sc(OTf)_3$, LiBr, $Ti(O^i\text{-}Pr)_4$],[28] the solvents (CH_2Cl_2, DMF, toluene, ethanol, dimethoxyethane), the temperatures, and the additives (base for lanthanide triflate, Na_2SO_4, molecular sieves), we found that the reaction performed in toluene in the presence of LiBr provided the desired tetrahydroisoquinoline (**18**) as a single diastereomer in about 40% yield. The stereochemistry of **18** was determined to be 1,3-*trans*-3,4-*cis* by the X-ray analysis of phenol **19** (cf. Supporting Information), obtained by deallylation of the former under Guibé's conditions [$Pd(PPh_3)_4$, Bu_3SnH, CH_2Cl_2, 90%].[29,30]

The promising results obtained with LiBr in toluene prompted us to further optimize the reaction conditions, and the results are summarized in Table 1. It was found that solvents dramatically influenced the reaction outcome. Whereas the Pictet−Spengler (P−S) reaction did not occur in EtOAc, THF, and DME, addition of trifluoroethanol (TFE, $pK_a = 12.4$)[31] as cosolvent of toluene changed the reaction selectivity to give predominantly the desired *cis* isomer (*trans*/*cis* = 1/2, entry 6). Interestingly, employing 1,1,1,3,3,3-hexafluoro-2-propanol ($pK_a = 9.3$)[31] allowed the reaction to be performed at room temperature, although the conversion remained low (entry 7, reaction time 24 h). Under these conditions, the *trans* isomer again became the major product (*trans*/*cis* = 6/1). Heating the reaction mixture to 40 °C improved the conversion but also inevitably caused the decomposition of the desired product. It was observed that in the course of this reaction, the color of the reaction mixture gradually changed from colorless to brown, probably due to the generation of bromine and/or related species. Since we speculated that these species would be responsible for the degradation of starting materials as well as P−S product, we switched the lithium bromide to lithium chloride and found the change highly rewarding (entries 9−14). As a weaker Lewis acid than LiBr, LiCl did not promote the P−S reaction in toluene (entry 1 vs 9). Nevertheless, the cooperative effect between LiCl and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) allowed the P−S reaction of **11** and ethyl glyoxylate to proceed cleanly at room temperature (entry 13). While adding molecular sieves can further increase the reaction efficiency (entry

TABLE 1. Synthesis of Tetrahydroisoquinoline 18 by Pictet−Spengler Reaction of 1 with ethyl glyoxylate

entry	promoter[a]	solvent	temp	yield[b]
1	LiBr	Tol	80 °C	40−50%[c]
2	LiBr	Tol	60 °C	40%[c]
3	LiBr	THF	60 °C	0%[d]
4	LiBr	DME	80 °C	0%[d]
5	LiBr	EtOAc	70 °C	0%[d]
6	LiBr	Tol/TFE (4/1)	80 °C	40−50%[e]
7	LiBr	Tol/HFIP (4/1)	rt	25%[f]
8	LiBr	Tol/HFIP (4/1)	40 °C	38%[f]
9	LiCl	Tol	80 °C	0%[d]
10	LiCl	Tol/HFIP (4/1)	80 °C	10%
11	LiCl	Tol/HFIP (8/1)	40 °C	60%[c]
12	LiCl	Tol/HFIP (16/1)	40 °C	58%[c]
13	LiCl	Tol/HFIP (4/1)	rt	65%[c]
14	**LiCl**	**Tol/HFIP (4/1)[g]**	**rt**	**85%[c]**
15	LiCl	Tol/EtOH (4/1)	rt	0%
16		Tol/HFIP (4/1)	rt	0%
17		Tol/HFIP (4/1)	85 °C	50%
18	phenol[h]	$ClCH_2CH_2Cl$	85 °C	50%[f]
19	AcOH	toluene	rt	0%
20		TFE	80 °C	0%[d]

[a] Three equivalents were used except for entry 18. [b] Isolated yield after flash chromatography. [c] *trans* isomer only. [d] The corresponding imine was formed. [e] *trans*/*cis* = 1/2. [f] *trans*/*cis* = 6/1. [g] Molecular sieves were added, reaction time was 48 h. [h] 2,6-Di-*tert*-butyl-4-methyl phenol, 0.1 equiv. Abbreviations: TFE = trifluoroethanol; HFIP = hexafluoroisopropanol; rt = room temperature.

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(30) **Crystal data for 19:** colorless crystal (0.075 × 0.20 × 0.80 mm^3). $C_{18}H_{23}NO_7$, M_w = 365.37. Orthorombic system, space group $P2_12_12_1$, $Z = 4$, $a = 5.513(6)$, $b = 12.528(14)$, $c = 26.192(23)$ Å; V =1809 $Å^3$, $D_c = 1.342$ g·cm^{-3}, $F(000) = 776$, l (Mo Kα) = 0.71073 Å, $m = 0.104$ mm^{-1}; 6899 data measured (q range 1.55−31.4°) on Nomius Kappa-CCD area-detector diffractometer. Refinement with SHELXL93. $R_1(F) = 0.0457$ for the 2135 observed reflections and $wR_2(F^2) = 0.1441$ for all the 2554 unique data. GOF S =1.072. Residual electrons density between −0.13 and 0.12 e $Å^3$. The detailed X-ray date has been deposited at The Cambridge Crystallographic Data Centre (CCDC 217803).
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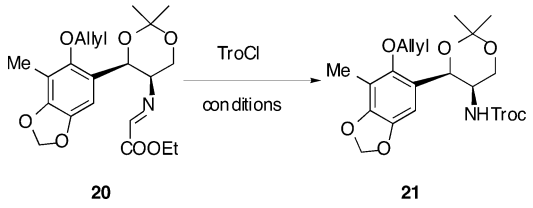
14), increasing the reaction temperature was detrimental due most probably to product decomposition (entries 10−12). Although the exact role of HFIP was unclear, its weak Brønsted acidity (pK_a = 9.3), strong ionizing power,[32] and hydrogen bond donor ability[33] may be relevant to its unique role in this transformation. Indeed, no reaction occurred when the same reaction was performed using ethanol as cosolvent under otherwise identical conditions (entry 15). Furthermore, the action of both Lewis acid (LiCl) and Brønsted acid (HFIP) might be synergistic, since in the absence of LiCl no reaction occurred at room temperature under otherwise identical conditions (entry 16). Nevertheless, it is worthy of noting that by heating the reaction mixture to 85 °C, the Pictet−Spengler reaction took place in a mixture of solvents (toluene/HFIP = 1/4) in the absence of Lewis acid (entry 17). Apparently, at this temperature, the acidity of HFIP is enough to promote the P−S reaction.[34] Parallel to this observation, it was found that 2,6-di-*tert*-butyl-4-methyl phenol (0.1 equiv) was also capable of catalyzing the reaction to provide the *trans* isomer (**9**) in 50% yield (entry 18). On the other hand, acetic acid is too strong an acid and led only to the degradation of the materials (entry 19). Overall, under the optimized conditions (LiCl, toluene/HFIP = 4/1, room temperature, molecular sieves 4 Å, 48 h, entry 14), the desired Pictet−Spengler reaction took place smoothly to provide exclusively the *trans* isomer (**18**) in 85% yield. This protocol is highly reliable and can be performed on a multigram scale without erosion of the yield and diastereoselectivity.

Conversion of imine to the corresponding iminium by acylation is often an efficient way to increase its electrophilicity. Since the imino ester (**20**) resulting from the condensation of **11** and ethyl glyoxylate is isolable, we briefly examined its reaction with a chloroformate with the hope to obtain directly the *N*-acylated tetrahydroisoquinoline.[35] However under a set of conditions varying the solvents (toluene, dichloromethane, acetonitrile), the additives (NaI, DMAP, $AgNO_3$), and the temperatures (−40 °C to room temperature), only the simple *N*-Troc derivative **21** (*N*-2,2,2-trichloroethyloxycarbonyl), probably resulting from a sequence of acylation-hydrolysis, was isolated (Scheme 3).

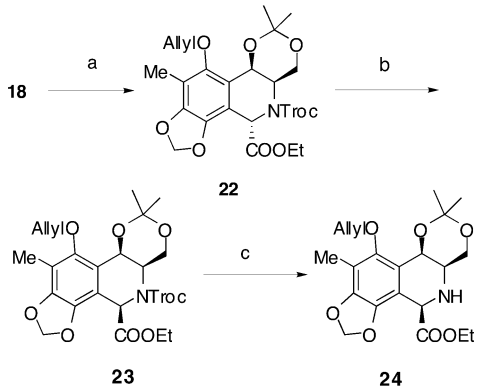
With compound **18** in hand, epimerization of the C-1 center was next examined.[18a] All attempts with this substrate being uniformly unsuccessful, a three-step sequence was developed (Scheme 4). Thus *N*-acylation of **18** with trichloroethyl chloroformate under Schotten−

SCHEME 3



20 **21**

SCHEME 4. Epimerization of 1,3-trans Tetrahydroisoquinoline 18 to 1,3-cis Isomer 24[a]



[a] Reaction conditions: (a) TrocCl, CH_2Cl_2, aq $NaHCO_3$; (b) DBU, THF; (c) Zn, AcOH−Et_2O (1/10), rt, 90%.

Baumann conditions provided **22**. Gratifyingly, stirring a THF solution of **22** in the presence of DBU for 12 h provided exclusively the *cis* isomer **23**. Reductive removal of the *N*-Troc function was initially problematic because of the epimerization of the C-1 center. After careful examination of the reaction parameters, it was ultimately found that by decreasing the quantity of acetic acid, the *cis* isomer **24** was produced exclusively. Under these optimized conditions, purification of intermediate **22** and **23** was not required and the *cis* isomer **24** was obtained from the *trans* isomer **18** in 90% yield for this three-step sequence.

Taking into consideration the X-ray structure of **19**, the epimerization via *N*-acylated intermediate **22** can be rationalized as shown in Scheme 5. The compound **22** can exist in two conformations. The conformer **22b** wherein the *N*-acyl residue is positioned in a pseudo-equatorial position should be more stable than **22a**, the latter being destabilized by severe steric repulsions. Enolization of the ester (**22b**) followed by protonation from the side opposite to the C-3 substituent would give the desired *cis* isomer **23**, which upon reductive removal of *N*-Troc function provided the all-*cis* compound **24**.

With an efficient synthesis of **24** being developed, the construction of the 1,4-bridged macrolactone was next envisaged (Scheme 6). Reduction of amino ester **24** with LAH afforded the amino alcohol **9**, which was chemoselectively *O*-acylated with (*R*)-*N*-Troc-(*S*-trityl) cysteine (**25**, EDCI, DMAP) to give ester **26** in 83% yield. The C-4 hydroxy group in tetrahydroisoquinoline (**24**) was strategically introduced with the aim to facilitate the formation of the benzylic sulfide bond, Indeed, parallel to the present studies, we have demonstrated that reaction of alcohol **16** with thiol in the presence of TFA gave the

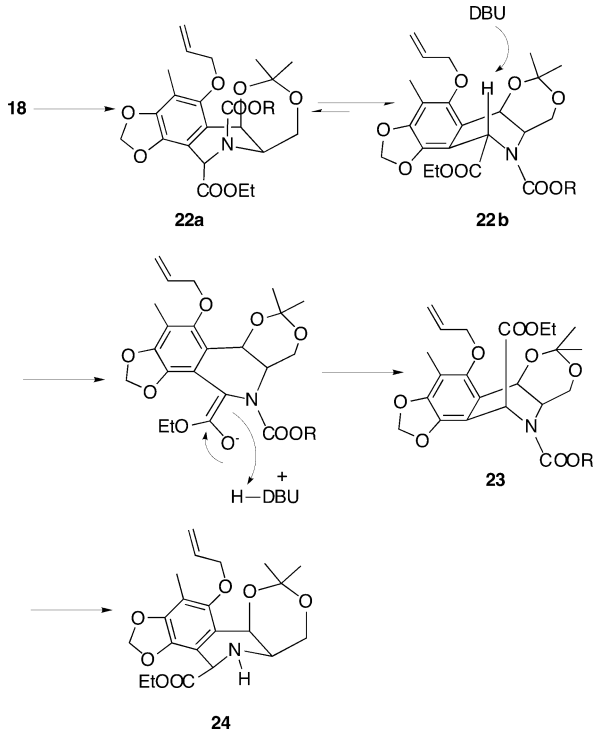
(32) Schadt, F. L.; Bentley, T. W.; Schleyer, P. V. R. *J. Am. Chem. Soc*. **1976**, *98*, 7667−7674.

(33) Eberson, L.; Hartshorn, M. P.; Persson, O.; Radner, F. *J. Chem. Soc. Chem. Commun*. **1996**, 2105−2112.

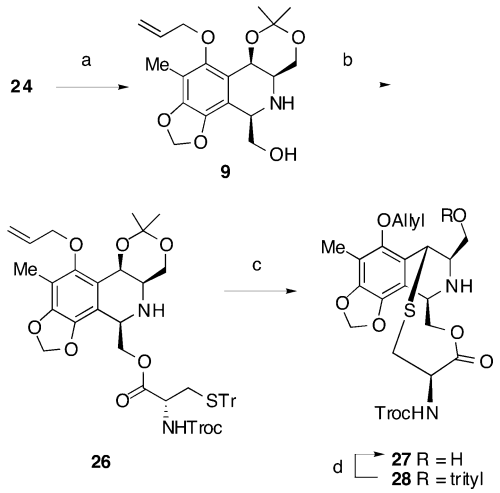
(34) Selected recent leading references on HFIP-assisted transformations. (a) Diels−Alder reaction: Cativirla, C.; García, J. I.; Majoral, J. A.; Salvatella, L. *Can. J. Chem*. **1994**, *72*, 308−311. (b) Ring opening of epoxides: Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett*. **2000**, *41*, 2895−2898. Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem*. **2000**, *65*, 6749−6751. Rodrigues, I.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem*. **2001**, *66*, 2098−2103. Magueur, G.; Crousse, B.; Ourévitch, M.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem*. **2003**, *68*, 9763−9766. (c) Epoxidation and Baeyer−Villiger reaction: Neimann, K.; Neumann, R. *Org. Lett*. **2000**, *2*, 2861−2863. (d) Guanidinylation: Snider, B. B.; O'Hare, S. M. *Tetrahedron Lett*. **2001**, *42*, 2455−2458. (e) Ring opening of cyclic sulfate: Johnston, B. D.; Ghavami, A.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2002**, *124*, 8245−8250. (f) Oxidative amidation of phenol: Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett*. **2005**, *7*, 175−177.

(35) Wang, H.; Ganesan, A. *Tetrahedron Lett*. **1997**, *38*, 4327−4328.

SCHEME 5. Conformation Analysis on the Based-catalyzed Epimerization of 22



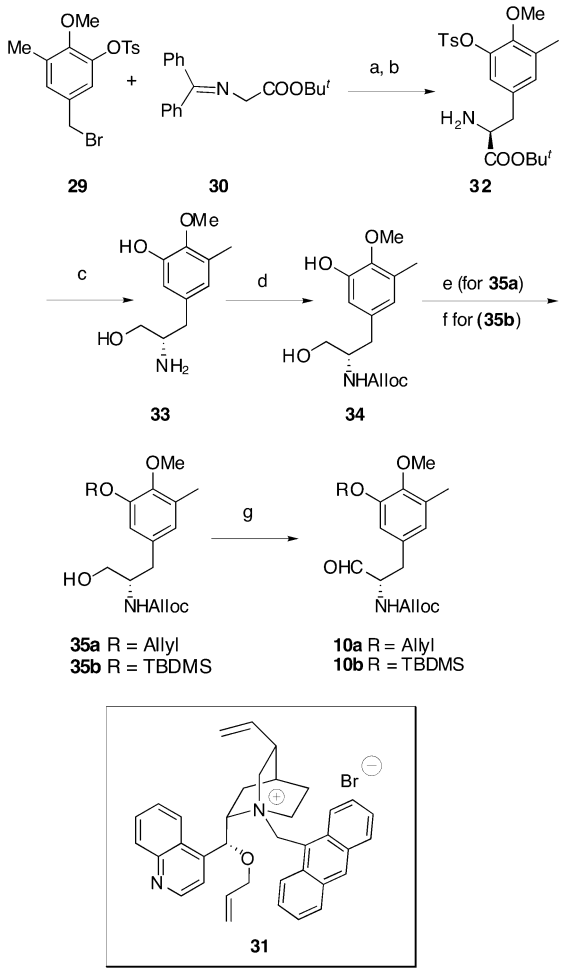
SCHEME 6. Construction of 10-membered Macrolactone[a]



[a] Reagents and conditions: (a) LAH, THF, −20 to 0 °C, 85%; (b) (*R*)-*N*-Troc-(*S*-trityl)cysteine (**25**), EDCI, DMAP, CH_2Cl_2, 83%; (c) TFA/toluene 1/1, 0 °C, 70%; (d) HCOOH, Et_3SiH, CH_2Cl_2, 92%.

corresponding sulfide in excellent yield.[36] Indeed, by simply dissolving **26** in toluene in the presence of TFA (v/v = 1/1) at 0 °C, we were able to isolate the macrocycle **27** in 70% yield, together with small amount of its *O*-tritylated derivative **28**. In this experimentally simple procedure, a sequence of domino processes involving initial sulfide deprotection, fragmentation of dioxane, C−S bond formation with the concurrent macrocyclization, and *O*-tritylation occurred at the expense of other competitive processes. Only one stereoisomer (1,4-*cis*) was

SCHEME 7. Enantioselective Synthesis of Amino Aldehyde 10[a]



[a] Reagents and conditions (a) **31** (0.1 equiv), $CsOH·H_2O$ (0.1 equiv), CH_2Cl_2, −78 °C; (b) THF/H_2O/AcOH (1:1:1), 87% for two steps; (c) $LiBH_4$, MeOH, Et_2O, rt, then aq 2 N NaOH, EtOH, 80 °C; (d) AllocCl, aq $NaHCO_3/CH_2Cl_2$ (1:1); 78% from **32**; (e) AllylBr, $NaHCO_3$, acetone, 92%; (f) TBSCl, imidazole, DMF, then 2 N HCl, 91% overall yield from **34**; (g) Swern oxidation, 92%.

produced as a result of the inherent higher ring strain of the *trans* counterpart. Compound **28** was transformed into **27** in high yield under reductive conditions (HCOOH, Et_3SiH). Parallel to this work, a similar strategy has been independently developed by the group of Danishefsky.[17c]

Synthesis of Amino Aldehyde 10. The protected L-3-hydroxy-4-methoxy-5-methyl phenylalanal (**10**) was prepared featuring a key enantioselective alkylation step (Scheme 7).[37−41] Following Corey's procedure, alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester **30** by 3-tosyloxy-4-methoxy-5-methyl benzyl bromide **29** in the presence of a catalytic amount of *O*-(9)-allyl-*N*-(9′-anthracenylmethyl)cinchonidium bromide **31** (0.1 equiv)

(36) De Paolis, M.; Blankenstein, J.; Bois-Choussy, M.; Zhu, J. *Org. Lett*. **2002**, *4*, 1235−1238.

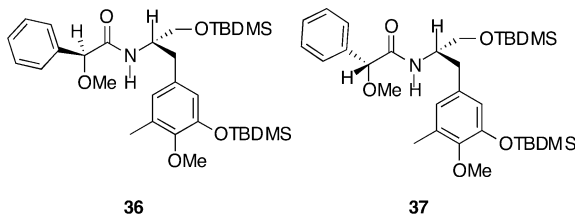
(37) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415.

(38) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res*. **2004**, *37*, 518−525.

(39) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc*. **1999**, *121*, 6519−6520. (b) Ooi, T.; Maruoka, K. *Acc. Chem. Res*. **2004**, *37*, 526−533.

(40) (a) O'Donnell, M. J. *Acc. Chem. Res*. **2004**, *37*, 505−517.

(41) For an alternative synthesis of this amino acid, see ref 18b.



36 **37**

FIGURE 2. Assignment of absolute configuration of amino alcohol **35b**.

afforded, after chemoselective hydrolysis of the imine function (THF−H_2O−AcOH), the amino ester **32** in 87% overall yield. Reduction of ester to alcohol followed by detosylation under basic conditions gave the amino alcohol **33**. Selective *N*-acylation with allyl chloroformate afforded *N*-Alloc derivative **34**. Masking of phenol as allyl ether followed by oxidation of the primary alcohol provided amino aldehyde **10a** in 64% overall yield from **32**. Alternatively, simultaneous protection of the phenol and the primary hydroxy group as TBDMS ethers followed by selective removal of the TBDMS group from the primary alcohol gave the amino alcohol **35b**, which was oxidized (Swern oxidation) to provide the expected amino aldehyde **10b**.

The (*S*) configuration of amino ester **32** was assigned, taking for granted the Corey−Lygo empirical model. To confirm this assignment, both (*S*)- and (*R*)-*O*-methyl mandelic amides **36** and **37** were synthesized (Figure 2). The calculated chemical shift differences ($\Delta\delta_{ArCH_2}$(**36**−**37**) = −0.08 ppm; $\Delta\delta_{TBDMSOCH_2}$ (**36**−**37**) = 0.09 ppm) are in accord with the *S* configuration of the amino alcohol and hence that of the amino ester **32**.[42] In addition, analysis of ^{1}H NMR spectra of compounds **36** and **37** indicated that the de of **36** and **37**, and hence the ee of their precursor **32**, is higher than 90%.

Assemblage of Two Fragments and Cyclization Studies. Our initial efforts focused on the union of lactone **27** and amino aldehyde **10a** by way of a Strecker reaction. This would represent the most convergent approach following our projected synthetic scheme. Unfortunately, all attempts under a variety of conditions[43] failed to provide the desired amino nitrile, probably because of the steric hindrance around the secondary amine. We then turned our attention to the condensation between **9** and **10**. The acid-lability of **9** was a primary concern at the outset since the Strecker reaction is usually performed under acidic conditions. Indeed, initial efforts on the reaction of **9**, **10**, and cyanide (KCN or TMSCN) in the presence of either Lewis acids or Brønsted acids were uniformly unsuccessful. After much experimentation, a two-step sequence was developed. Thus, mixing of **9** and **10a** (or **10b**) in toluene in the presence of 3 Å molecular sieves gave the oxazolidine **38** as a mixture of two diastereomers (Scheme 8). After filtration and evaporation of the filtrate, the crude residue was treated with TMSCN in the presence of BF_3·OEt_2 at −30 °C to afford aminonitrile (**39**) in 80% overall yield as two separable diastereoisomers in a ratio of 3/1. The reaction temperature of the second step should be carefully controlled (below −20 °C) in order to avoid the competitive ring-opening of the dioxane. Indeed, when the same reaction was performed at 0 °C, the dicyanide **40** was isolated in about 30% yield as a mixture of four diastereomers whose structure was deduced from ^{1}H NMR and mass spectroscopic data.

The major isomer of the amino nitrile **39** (vide infra for configuration assignment) was engaged in the subsequent transformation. Coupling of (*R*)-*N*-Troc (*S*-trityl) Cys **25** with **39a** provide ester **41** in 80% yield. Treatment of **41** under a variety of conditions led only to degradation and failed to produce even trace amounts of the desired macrocycle. This is in sharp contrast to the cyclization of compound **26** where an excellent yield of **27** was obtained. We reasoned that in the case of **41**, the fragmentation of the dioxane function preceded deprotection of the *S*-trityl function, leading to the unstable *ortho* quinone methide intermediate that degraded in the absence of an appropriate nucleophile. To ensure the occurrence of the desired domino process, the timing of *S*-trityl deprotection and dioxane fragmentation needed to be carefully readjusted. While switching the protective group into a base-sensitive function and proceeding via the same transformation in two separable steps, i.e., *S*-deprotection and cyclization, is an obvious choice, we nevertheless preferred an acid-sensitive protecting group since this option would allow us to realize the deprotection-cyclization in one step. From experimental results, it is evident that a protective group that is even more acid-labile than trityl would be required in order to maximize the chance of success. Toward this end, a trimethoxytrityl group was envisaged.[44] Coupling of **39a** or **39b** with (*R*)-*N*-Troc-(*S*-4,4′,4″-trimethoxyltrityl) Cys (**42**)[45] under standard conditions afforded the compound **43a** or **43b** in 75−80% yield, respectively. Gratifyingly, by simply dissolving **43a** in TFE containing 1% TFA, the desired domino sequence took place smoothly to afford the bridged macrocycle **44a** in 55−65% yield. By the same sequence, compound **43b** was converted into **44b** under identical conditions in 65% yield. The TBS ether survived under such mild acidic conditions. The formation of *S*-trimethoxytrityl derivative **45** was observed and identified. However, its isolation was not necessary since unmasking the *O*-trimethoxytrityl function proceeded smoothly under the cyclization conditions upon prolonging the reaction time. It was known that for each methoxy group introduced, acid-lability of the trityl group increased by about 1 order of magnitude.[46] We thus suspected that under mild acidic conditions, deprotection of the *S*-4,4′,4″-trimethoxyltrityl group would lead to **46** and the stabilized carbenium cation **47**. The fragmenta-

(42) (a) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202−4205. (b) Helmchen, G.; Sauber, K. *Tetrahedron Lett.* **1972**, 3873−3878.

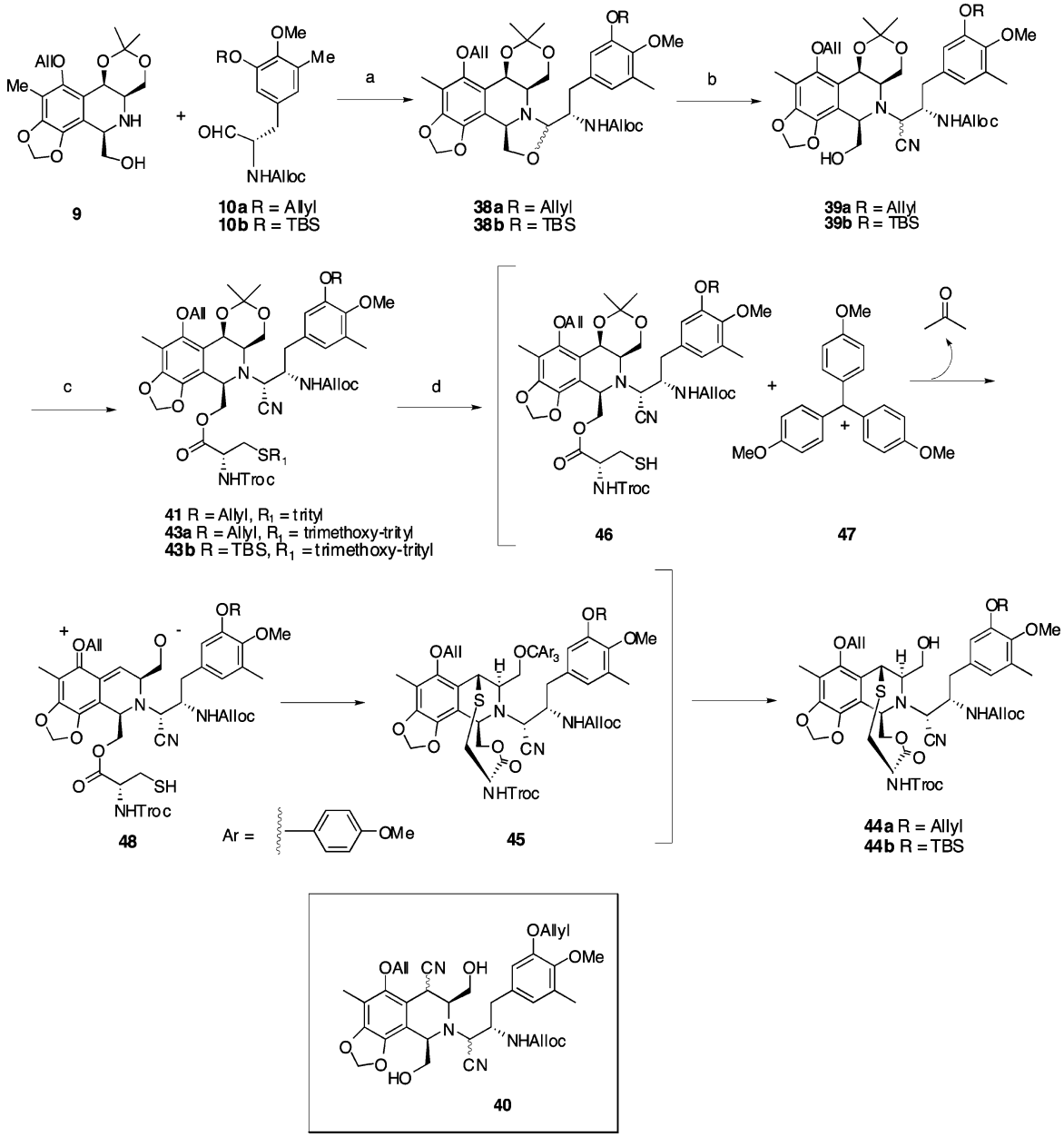
(43) The following conditions have been tested: (a) AcOH, KCN, (b) KCN, MeCN, H_2O, (c) TMSCN, MeOH, CH_2Cl_2, ZnI_2 (0.1 equiv), (d) TMSCN, MeOH, CH_2Cl_2, (e) TMSCN, MeOH, Et_2O, $LiClO_4$, (f) LiBr, KCN, toluene, trifluoroethanol, and (g) $Yb(OTf)_3$, TMSCN, CH_2Cl_2, However, none of them provided the desired amino nitrile. In most cases, starting materials were recovered or decomposed under forcing conditions (longer reaction time, higher reaction temperature).

(44) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1992**, *114*, 5859−5860.

(45) Synthesized from commercial available (*R*)-*N*-(*S*-4,4′,4″-trimethoxyltrityl) Cys (**25**) in three steps: (a) TrocCl, $NaHCO_3$, H_2O/1,4-dioxane, 45 °C; (b) Et_3SiH, TFA, CH_2Cl_2; (c) (*p*-4-MeOPh)$_3$CCl, CH_2Cl_2; 76% overall yield for three steps.

(46) (a) Smith, M.; Rammler, D. H.; Goldberg, I. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 430−440. (b) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003**, *32*, 170−180.

SCHEME 8. Assemblage and Construction of Macrolactone[a]



[a] Reagents and conditions: (a) toluene, 3Å molecular sieves, 40 °C; (b) TMSCN, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −30 °C, 70−80% for two steps (dr = 3:1); (c) EDCI, DMAP, CH_2Cl_2, (*R*)-*N*-Troc(trityl) Cys (**25**), 78% or (*R*)-*N*-Troc-(trimethoxy trityl) Cys (**42**), 74%; (d) 1% TFA in TFE, 0 °C to rt, 65%.

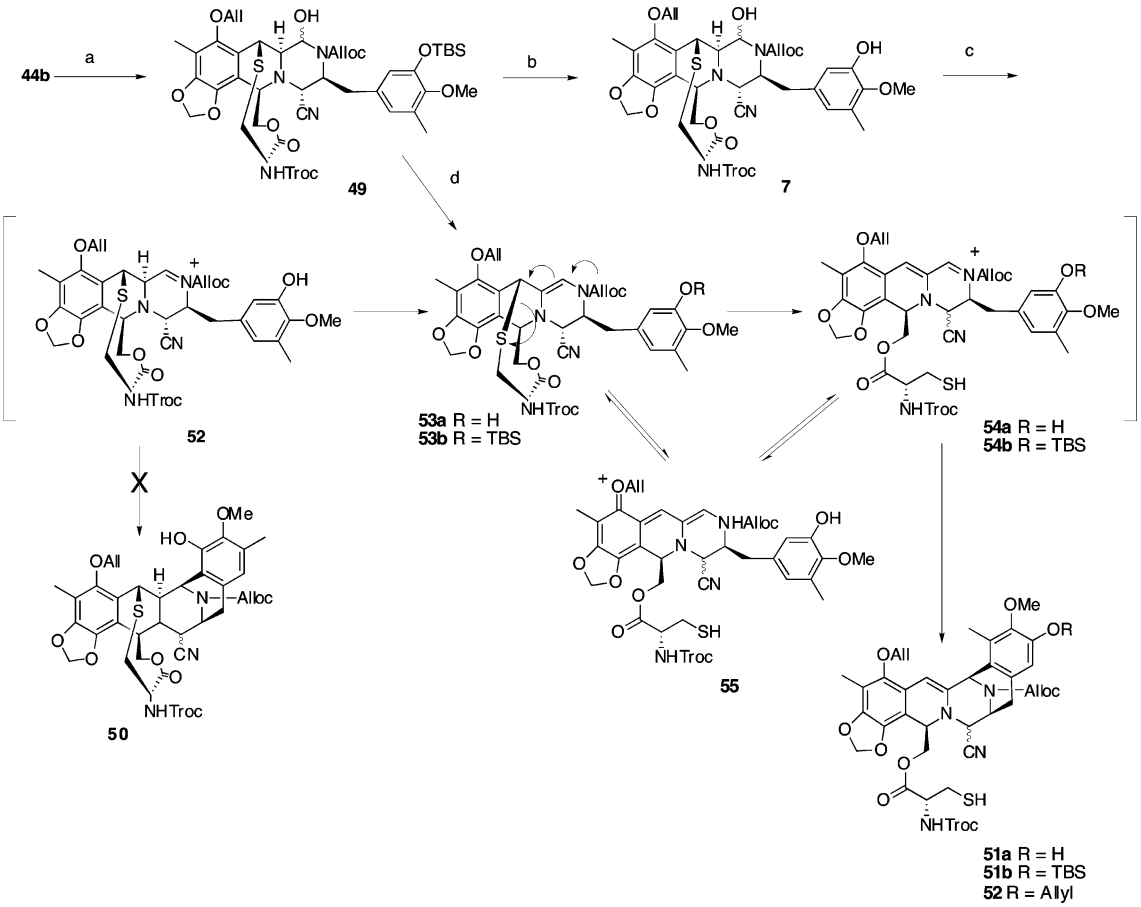
tion of dioxane assisted by the electron-rich aromatic ring would produce the *ortho* quinone methide intermediate **48**, which would suffer the intramolecular nucleophilic addition of thiol to produce the 1,4-bridged 10-membered ring.[47,48] The primary alcohol revealed upon fragmentation of the dioxane would be partially tritylated, leading to **45** that may ultimately be converted to compound **44**.

Compound **44b** has all of the requisite functionalities for construction of the missing C and D rings. Our final efforts toward this goal are summarized in Scheme 9. Swern oxidation of **44b** provided the aldehyde that was intercepted directly by the tethering carbamate function to provide the stable aminal **49** in 74% yield. Removal of TBS ether under carefully controlled conditions afforded the phenol **7** that was ready for the pivatol cyclization step.[49] After much experimentation, a clean transformation was observed when a MeCN solution of **7** was treated

(47) For the quinone methide initiated cyclization for the synthesis of five- and six-membered rings, see: (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136−1138. (b) Angle, S. R.; Rainier, J. D. *J. Org. Chem.* **1992**, *57*, 6883−6890. (c) Angle, S. R.; Arnaiz, D. O.; Boyce, J. P.; Frutos, R. P.; Louie, M. S.; Mattson-Arnaiz, H. L.; Rainier, J. D.; Turnbull, K. D.; Yang, W. *J. Org. Chem.* **1994**, *59*, 6322−6337.

(48) For recent examples of formation/trapping of *o*-quinone methide, see: (a) Van de Water, R. W.; Magdziak, D. J.; Chau, J. N. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502−6503. (b) Lindsley, C. W.; Chan, L. K.; Goess, B. C.; Joseph, R.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 422−423. (c) Pande, P.; Shearer, J.; Yang, J.; Greenberg, W. A.; Rokita, S. E. *J. Am. Chem. Soc.* **1999**, *121*, 6773−6779. (d) Angle, S. R.; Rainier, J. D.; Woytowicz, C. *J. Org. Chem.* **1997**, *62*, 5884−5892. (e) Taing, M.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 329−340

SCHEME 9. Construction of Pentacyclic Ring System[a]



[a] Reagents and conditions: (a) Swern oxidation, 74%; (b) KF, AcOH, MeOH, 89%; (c) 0.5% CF_3SO_3H in CH_3CN, 0 °C, 78%; (d) MsCl, CH_2Cl_2, Et_3N, 40 °C.

with trifluoromethanesulfonic acid (0.5 vol %), providing the one single compound **51a**. The ^1H NMR spectrum of **51a** displayed only one aromatic proton at δ 6.68 ppm. High-resolution mass spectrometry indicated a molecular formula of $C_{38}H_{39}Cl_3N_4O_{11}S$ ($M + Na^+$, calcd for $C_{38}H_{39}Cl_3N_4O_{11}SNa$ 887.1299 and 889.1270, found 887.1311 and 889.1298) corresponding to a dehydration product of **7**. The analysis of ^1H NMR spectra recorded at room temperature was complicated as a result of the presence of interchangeable conformers within the NMR time scale. However, by recording the spectra at 253 K, two well distinguishable sets of peaks appeared in the ^1H NMR and ^{13}C spectra. From detailed NMR studies (COSY, HMBC, HMQC, NOESY), the structure **51a** was proposed as shown in Scheme 9. The presence of long-distance C−H correlation between H-4 signals (at δ 6.26 and 6.23 ppm for two rotamers) and the ^{13}C signals of C-11, C-10, C-9, C-3, C-8, and C-5 is indicative of the presence of a benzylic proton, whereas $^1H-^{13}C$ correlations observed between H-15 and C-16, between 18-Me protons and C-19, and between H-11 and C-19 indicated that the nucleophilic addition to acyliminium intermediate occurred at C-19 rather than the expected C-15 (Figure 3). Interestingly, the regioselectivity observed is opposite to that observed by Williams in a related

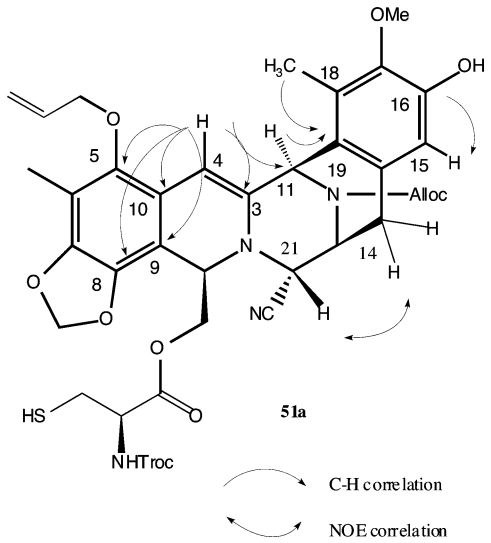


FIGURE 3. Structure determination of pentacyclic compound **51a**.

system.[18c] The observation of NOE correlation between H_{21} and H_{14} indicated the *R*-configuration of C-21, which corresponded to the configuration of the natural product. Compound **44a** was similarly converted to pentacyclic compound **52** following the same synthetic sequence as detailed for **44b**.

(49) Veerman, J. J. N.; Bon, R. S.; Hue, B. T. B.; Girones, D.; Rutjes, F. P. J. T.; Van Maaresveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2003**, *68*, 4486-4494.

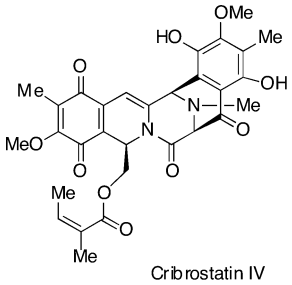


FIGURE 4. Structure of cribrostatin IV.

The formation of compound **51a** could be rationalized as follows. Dehydration of aminal under acidic conditions would produce the acyliminium interemediate **52**. The nucleophilic addition of phenol onto this electrophilic species would produce the expected product **50**. However, the fact that the nucleophile must approach the iminium from the same face as that occupied by the adjacent macrocycle might significantly retard this process. Therefore, an alternative iminium-enamine tautomerization would take place to produce enamine **53a**. Cleavage of the C−S bond assisted by the lone pair electron of nitrogen would then produce the conjugated acyliminium **54a**.[50] Alternatively, ring opening of the macrolactone could also be assisted by the electron-rich aromatic ring, leading to oxonium **55**, which would tautomerize to the acyl iminium **54a**. Whatever the mechanism of fragmentation, the β-face of the acyliminium is now sterically more accessible, and nucleophilic addition of phenol could take place to provide the observed compound **51a**. Interestingly, the thiol function was quite stable and did not dimerize upon flash column chromatography. Alternatively, the enamine **53b** was prepared by treatment of **49** with MsCl under basic conditions (MsCl, Et_3N, CH_2Cl_2, 40 °C).[51] However, when it was submitted to acidic conditions (CF_3SO_3H, MeCN), the same sequence of fragmentation-cyclization occurred, leading to **51b** in 87% yield.

The pentacyclic compound **51** with a double bond at C-3 and C-4 positions possesses the correct oxidation level for the formation the 10-membered cycle. Furthermore, we thought that chemistry developed herein would be useful for the development of a short synthesis of cribrostatin IV (Figure 4), another member of the tetrahydroisoquinoline class of natural products.[52] An elegant total synthesis of this alkaloid has very recently been accomplished by Danishefsky.[53]

In summary, a strategy has been developed for the access of tetracycle **7** that embodies all of the requisite functionalities en route to the natural product Et 743. The synthesis is highly convergent and has been carried out on a multigram scale featuring the following key steps: (a) union of two fragments **9** and **10** via an oxazolidine intermediate, and (b) acid-promoted macrocyclization via formation of the carbon−sulfur bond with concomitant formation of the 10-membered ring. Although compound **7** was responsive to the intramolecular Pictet−Spengler reaction, a destructive ring opening of the 1,4-bridged lactone also occurred, leading to the formation of a pentacyclic compound, **51**. In the course of this study, it was discovered that a combination of a mild Lewis acid (LiCl) and a mild Brønsted acid (HFIP) constituted excellent reagents for performing the Pictet−Spengler reaction of a highly acid-sensitive substrate. We are currently investigating the potential application of these conditions to other reactions, as well as an alternative strategy for the total synthesis of Et 743.

Experimental Section

Compound 16. To a solution of phenol **15** (1.8 g, 11.8 mmol) in anhydrous THF (20 mL) was added CH_3MgCl in THF (22 wt %, 4.2 mL, 12.6 mmol) at room temperature. After 5 min of stirring, a solution of Garner's aldehyde (3.0 g, 13.0 mmol, in 25 mL CH_2Cl_2) was introduced dropwise and the resulting reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4 and the volatile was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford **16** (4.5 g, 11.6 mmol, 98%) as a colorless oil. $[\alpha]_D^{23} = -10$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) ν 3242, 1651, 1468, 1406 cm^{-1}; ^1H NMR (250 MHz $CDCl_3$, 293 K) δ 8.39 (br·s, 1H), 6.62 (br·s, 1H), 6.31 (s, 1H), 5.86 (d, J = 1.0 Hz, 1H), 5.84 (d, J = 1.0 Hz, 1H), 4.66 (d, J = 8.4 Hz, 1H), 4.32 (m, 1H), 3.64 (m, 2H), 2.08 (s, 3H), 1.57 (s, 3H), 1.51 (s, 9H), 1.47 (s, 3H); ^{13}C NMR (62.5 MHz $CDCl_3$, 293 K) δ 155.8, 149.8, 146.6, 139.6, 114.8, 109.3, 105.4, 100.8, 94.7, 82.2, 80.2, 65.1, 62.4, 28.3 (×3), 27.0, 24.4, 8.6; LRMS (ESI^-) *m/z* 379.9 (M − H).

Tetrahydroisoquinoline 18. A suspension of amine **11** (1.0 g, 3.1 mmol), LiCl (410.0 mg, 9.4 mmol), molecular sieves 4 Å (200.0 mg), and ethyl glyoxalate (350.0 mg, 3.4 mmol) in toluene/HFIP (4:1, v/v, 10 mL) was stirred at room temperature for 48 h. The reaction mixture was then diluted with CH_2Cl_2 and filtered through a short pad of Celite. The filtrate was evaporated to dryness and the residue was purified by flash column chromatography to afford **18** (1.07 g, 2.6 mmol, 85%) as a colorless oil. Mp 122 °C; $[\alpha]_D^{23} = +24°$ (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) ν 2985, 1746, 1475, 1157, 1092 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$, 293 K) δ 6.08 (ddt, J = 17.3, 10.8, 5.5 Hz, 1H), 5.95 (d, J = 1.3 Hz,1H), 5.90 (d, J = 1.3 Hz, 1H), 5.46 (dq, J = 17.5, 2.8 Hz, 1H), 5.28 (dq, J = 10.9, 1.3 Hz, 1H), 5.06 (d, J = 1.4 Hz, 1H), 4.79 (s, 1H), 4.52 (ddt, J = 12.4, 5.2, 1.4 Hz, 1H), 4.29−4.22 (m, 4H), 3.93 (dd, J = 12.4, 1.3 Hz, 1H), 2.93 (m, 1H), 2.15 (s, 3H), 1.60 (s, 3H), 1.39 (s, 3H), 1.27 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 171.3, 151.2, 146.2, 139.8, 133.8, 120.5, 116.4, 113.2, 112.6, 101.4, 98.8, 75.0, 64.5, 61.0, 60.0, 54.5, 46.3, 29.8, 18.7, 13.9, 9.3; LRMS (ESI^+) *m/z* 405.9 $(M + H)^+$, 428.0 $(M + Na)^+$; HRMS (ESI^+) *m/z* calcd for $C_{21}H_{27}NO_7Na$ $(M + Na)^+$ 428.1685, found 428.1651.

***N*-Troc-1,3-*trans*-Tetrahydroisoquinoline 22.** To a biphasic solution of amine **18** (220.0 mg, 0.54 mmol) in CH_2Cl_2 (5.0 mL) and saturated aqueous $NaHCO_3$ (5.0 mL) was added TrocCl (0.083 mL, 0.6 mmol) at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford **22** (311.0 mg, 98%) as a colorless oil. $[\alpha]_D^{23} = +40°$ (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν 2955, 2934, 1742, 1461, 1385, 1167, 1037, 939 cm^{-1};

(50) For a related example, see: Rikimaru, K.; Mori, K.; Kan, T.; Fukuyama, T. *J. Chem. Soc., Chem. Commun*. **2005**, 394−396.
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^{1}H NMR (300 MHz $CDCl_3$, 293 K) δ 6.13 (ddt, J = 17.3, 10.8, 5.7 Hz, 1H), 6.06 (s, 1H), 6.03 (d, J = 1.1 Hz, 1H), 5.95 (d, J = 1.1 Hz, 1H), 5.44 (dq, J = 17.6, 2.8 Hz, 1H), 5.28 (dq, J = 10.8, 1.5 Hz, 1H), 5.12 (d, J = 3.1 Hz, 1H), 4.83 (d, J = 12.1 Hz, 1H), 4.80 (d, J = 12.1 Hz, 1H), 4.48 (ddt, J = 13.2, 5.4, 0.9 Hz, 1H), 4.36 (dd, J = 13.3, 3.8 Hz, 1H), 4.26 (ddt, J = 13.2, 5.4, 1.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 3H), 3.78 (m, 1H), 2.15 (s, 3H), 1.60 (s, 3H), 1.39 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz $CDCl_3$, 293 K) δ 171.1, 169.5, 151.3, 147.2, 140.0, 133.7, 118.1, 116.9, 114.2, 110.1, 101.6, 99.9, 95.1, 75.4, 74.9, 63.1, 62.0, 61.5, 55.3, 52.2, 27.7, 20.9, 14.1, 9.5; LRMS (ESI$^+$) *m/z* 602.0, 604.0 (M + Na)$^+$; HRMS (ESI$^+$) *m/z* calcd for $C_{24}H_{28}NO_9NaCl_3$ (M + Na)$^+$ 602.0727 and 604.0698, found 602.0728 and 604.0701.

1,3-*cis*-Tetrahydroisoquinoline 24. To a solution of *N*-Troc amine **22** (326.0 mg, 0.56 mmol) in dry THF (3.0 mL) was added DBU (0.134 mL, 1.13 mmol) dropwise. After being stirred at room temperature for 14 h, the reaction mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used directly for next step. To a solution of crude 1,3-*cis*-*N*-Troc amine **23** in Et_2O/AcOH (10:1, v/v, 6.0 mL) was added Zn powder (2.7 g, 42.0 mmol). After being stirred at room temperature for 1 h, the reaction mixture was diluted with diethyl ether (100 mL) and filtered with a short pad of Celite. The filtrate was washed with saturate aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford amine **24** (205.0 mg, 0.51 mmol, 90%) as a colorless oil. $[\alpha]_D^{23}$ = −2° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) ν 3018, 1738, 1458, 1382, 1223, 1103 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$, 293 K) δ 6.11 (ddt, J = 16.9, 10.3, 5.5 Hz, 1H), 5.94 (d, J = 1.2 Hz, 1H), 5.91 (d, J = 1.2 Hz, 1H), 5.43 (dq, J = 17.1, 2.8 Hz, 1H), 5.27 (dq, J = 10.9, 1.3 Hz, 1H), 5.09 (d, J = 1.0 Hz, 1H), 4.71 (s, 1H), 4.56 (ddt, J = 12.5, 5.3, 1.7 Hz, 1H), 4.32−4.28 (m, 3H), 4.24 (m, 1H), 3.94 (dd, J = 11.4, 1.1 Hz, 1H), 2.53 (m, 1H), 2.15 (s, 3H), 1.66 (s, 3H), 1.44 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz $CDCl_3$, 293 K) δ 171.2, 151.2, 146.4, 139.3, 133.9, 120.9, 116.3, 113.1, 112.8, 101.2, 98.8, 75.2, 64.6, 61.4, 60.1, 57.5, 49.3, 29.6, 18.7, 13.9, 9.1; HRMS (ESI$^+$) *m/z* calcd for $C_{21}H_{27}NO_7Na$ (M + Na)$^+$ 428.1685, found 428.1714.

Amino Ester 32. To a solution of imine **30** (3.4 g, 11.2 mmol) and *O*(9)-allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide **31** (0.6 g, 1.1 mmol) in CH_2Cl_2 (12 mL) were added $CsOH{\cdot}H_2O$ (18.8 g, 111.7 mmol) and a CH_2Cl_2 (8 mL) solution of bromide **29** (4.3 g, 11.2 mmol) dropwise at −78 °C. After being stirred vigorously at −78 °C for 30 h, the suspension was diluted with ether, washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was dissolved in HOAc/THF/H_2O (1:1:1, 57 mL) and the resulting solution was stirred at room temperature for 2 h. The solution was then made basic by addition of solid $NaHCO_3$ and water. The aqueous phase was extracted with AcOEt. The combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration and column chromatography, the amino ester **32** (4.3 g, 87%) was isolated as a colorless oil. $[\alpha]_D^{23}$ = +13° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν 3382, 3034, 2981, 2938, 1725, 1598, 1495, 1370, 1293, 1218, 1178 cm^{-1}; ^{1}H NMR (250 MHz $CDCl_3$, 293 K) δ 7.78 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 6.90 (s, 1H), 6.79 (s, 1H), 3.67 (s, 3H), 3.51−3.45 (dd, J = 7.3, 5.5 Hz, 1H), 2.92−2.84 (dd, J = 13.7, 5.5 Hz, 1H), 2.71−2.63 (dd, J = 13.7, 7.7 Hz, 1H), 2.44 (s, 3H), 2.19 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 174.0, 149.3, 145.1, 142.2, 133.2, 133.1, 132.8, 130.4, 129.5 (×2), 128.4 (×2), 121.8, 81.2, 60.5, 56.0, 40.2, 27.9 (×3), 21.6, 15.9; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{30}NO_6S$ + H (M + H)$^+$ 436.1795, found 436.1789.

Aminonitrile 39a. To a solution of amino alcohol **9** (85 mg, 0.23 mmol) and aldehyde **10a** (117.0 mg, 0.35 mmol) in toluene (1.2 mL) was added 3 Å molecular sieves (260.0 mg). After being stirred at 40 °C overnight, the mixture was diluted with AcOEt and filtered. The combined filtrate was concentrated in vacuo to furnish the crude oxazolidine **38a**. To the solution of the crude **38a** in CH_2Cl_2 (2.4 mL), cooled to −30 °C, were added TMSCN (93.0 mg, 126.0 μL, 0.94 mmol) and $BF_3.OEt_2$ (33.0 μL, 0.26 mmol), successively. After being stirred at −30 °C for 1.5 h, the reaction was quenched with saturated $NaHCO_3$ and extracted with AcOEt. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography to afford the aminonitrile **39a** as two separable diastereomers. The major isomer (96.0 mg, 0.14 mmol, 60% for two steps): $[\alpha]_D^{23}$ = −24° (*c* 0.47 $CHCl_3$); IR ($CHCl_3$) ν 3447, 3019, 2959, 2929, 2401, 1719, 1511, 1232 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$, 293 K) δ 6.68 (s, 1H), 6.66 (s, 1H), 6.11 (m, 2H), 6.06 (d, J = 1.3 Hz, 1H), 5.98 (d, J = 1.3 Hz, 1H), 5.90 (m, 1H), 5.47 (br.d, 1H), 5.41−5.23 (m, 6H), 5.02 (d, J = 7.9 Hz, 1H), 4.55 (m, 5H), 4.45 (m, 1H), 4.39 (ddt, J = 12.1, 5.1, 1.2 Hz, 1H), 4.31 (ddt, J = 12.1, 4.9, 1.0 Hz, 1H), 4.12 (m, 2H), 3.95 (m, 1H), 3.85 (m, 5H), 3.32 (dd, J = 13.9, 3.1 Hz, 1H), 3.11 (m, 1H), 2.97 (dd, J = 13.5, 10.2 Hz, 1H), 2.54 (m, 1H), 2.24 (s, 3H), 2.16 (s, 3H), 1.60 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 155.8, 151.5, 150.1, 147.1, 146.4, 139.7, 133.6, 133.4, 132.6, 132.5, 132.0, 123.8, 118.8, 117.7, 117.4, 117.1, 116.9, 114.0, 112.9, 112.6, 101.7, 99.3, 75.7, 69.3, 66.3, 65.8, 63.0, 62.5, 61.4, 60.1, 55.8, 55.4, 54.2, 35.8, 29.3, 19.2, 15.9, 9.3; HRMS (ESI$^+$) *m/z* calcd for $C_{38}H_{47}N_3O_{10}Na$ (M + Na)$^+$ 728.3159, found 728.3167. The minor isomer (36.0 mg, 0.05 mmol, 22% for two steps): $[\alpha]_D^{23}$ = −2° (*c* 0.51 $CHCl_3$); IR ($CHCl_3$) ν 3434, 3013, 2929, 2399, 1715, 1496, 1232 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$, 293 K) δ 6.64 (s, 1H), 6.63 (s, 1H), 6.11 (m, 2H), 6.02 (d, J = 1.5 Hz, 1H), 6.00 (d, J = 1.5 Hz, 1H), 5.90 (m, 1H), 5.63 (d, J = 5.9 Hz, 1H), 5.46 (dd, J = 16.9, 2.2 Hz, 2H), 5.33 (d, J = 2.9 Hz, 1H), 5.35−5.20 (m, 4H), 4.58 (m, 4H), 4.39 (ddt, J = 12.5, 5.1, 1.5 Hz, 2H), 4.31 (ddt, J = 12.5, 5.9, 1.5 Hz, 1H), 4.07−4.01 (m, 2H), 3.87 (m, 1H), 3.85 (s, 3H), 3.70 (br.d, J = 12.5 Hz, 1H), 3.58 (m, 1H), 3.17 (dd, J = 14.0, 4.4 Hz, 1H), 3.10 (dd, J = 14.0, 8.8 Hz, 1H), 2.51 (m, 1H), 2.26 (s, 3H), 2.16 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$, 293K) δ 156.0, 151.4, 150.1, 147.0, 146.6, 139.5, 133.6, 133.3, 132.6, 132.1, 131.9, 124.0, 118.9, 117.6, 117.4, 117.2, 117.1, 113.9, 113.0, 112.9, 101.6, 99.2, 75.7, 69.4, 65.9, 65.7, 62.9, 62.5, 60.1, 58.7, 55.8, 55.7, 54.6, 29.7, 29.1, 19.2, 15.9, 9.3; HRMS (ESI$^+$) *m/z* calcd for $C_{38}H_{47}N_3O_{10}Na$ (M + Na)$^+$ 728.3159, found 728.3132.

Aminonitrile 39b. In a manner similar to that used in the preparation of **39a**, treatment of **10b** (824.0 mg, 2.02 mmol) and **9** (490.0 mg, 1.35 mmol) gave **39b** (590.0 mg, 0.75 mmol, 56% for the major isomer) as a colorless oil. $[\alpha]_D^{23}$ = −29° (*c* 1.0 $CHCl_3$); IR ($CHCl_3$) ν 3447, 3016, 2930, 2229, 1719 (forte), 1585, 1490, 1384, 1200, 1113 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$, 293 K) δ 6.66 (s, 1H), 6.58 (s, 1H), 6.07 (m, 1H), 5.99 (d, J = 1.2 Hz, 1H), 5.95 (d, J = 1.2 Hz, 1H), 5.85 (m, 1H), 5.17−5.45 (m, 4H), 5.37 (d, J = 2.6 Hz, 1H), 5.03 (d, J = 6.8 Hz, 1H), 4.54 (m, 2H), 4.43 (m, 1H), 4.39 (m, 1H), 4.25 (ddt, J = 12.1, 5.1, 1.0 Hz, 1H), 3.96−4.16 (m, 3H), 3.73−3.92 (m, 3H), 3.73 (s, 3H), 3.29 (dd, J = 13.6, 3.1 Hz, 1H), 3.11 (m, 1H), 2.93 (dd, J = 13.5, 10.2 Hz, 1H), 2.51 (br.s, 1H), 2.22 (s, 3H), 2.14 (s, 3H), 1.58 (s, 3H), 1.42 (s, 3H), 0.97 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 156.5, 150.9, 149.5, 149.3, 147.9, 140.5, 134.5, 134.4, 133.4, 133.2, 125.2, 120.7, 119.6, 118.6, 118.0, 117.7, 114.8, 113.7, 102.5, 100.1, 76.6, 67.1, 66.6, 63.8, 63.4, 62.1, 60.6, 56.7, 56.3, 55.1, 36.2, 30.1, 26.5 (×3), 20.0, 19.1, 16.8, 10.1, −4.2 (×2); LRMS (ESI$^+$) *m/z* 802.4 (M + Na)$^+$; HRMS (ESI$^+$) *m/z* calcd for $C_{41}H_{57}N_3O_{10}SiNa$ (M + Na)$^+$ 802.3711, found 802.3704.

Macrolactone 44a. To a solution of the ester **43a** (55.0 mg, 0.42 mmol) in TFE (5.0 mL) at 0 °C was added a solution of TFA (60.0 μL) in TFE (1.0 mL) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated

under reduced pressure. The residue was purified by flash column chromatography to afford the macrocycle **44a** (25.0 mg, 0.027 mmol, 65%) as a colorless oil. $[\alpha]_D^{23} = +10°$ (*c* 0.86 $CHCl_3$); IR ($CHCl_3$) ν 3524, 3422, 3016, 2928, 2362, 1732, 1506, 1101 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$, 293 K) δ 6.78 (s, 1H), 6.74 (s, 1H), 6.09 (s, 1H), 6.05 (m, 2H), 5.99 (s, 1H), 5.93 (d, J = 6.6 Hz, 1H), 5.92 (m, 1H), 5.51−5.20 (m, 6H), 4.95 (d, J = 9.6 Hz, 1H), 4.82 (d, J = 2.2 Hz, 1H), 4.69 (s, 2H), 4.57−4.50 (m, 8H), 4.43 (m, 1H), 4.25 (ddt, J = 11.0, 6.6, 1.5 Hz, 1H), 4.08 (br.d, J = 8.8 Hz, 1H), 3.89 (dd, J = 12.5, 3.7 Hz, 1H), 3.82 (m, 4H), 3.45 (br.d, J = 11.0 Hz, 1H), 3.10 (dd, J = 14.7, 2.2 Hz, 1H), 3.03 (m, 1H), 2.90 (dd, J = 13.2, 8.8 Hz, 1H), 2.41 (dd, J = 14.7, 2.9 Hz, 1H), 2.21 (s, 3H), 2.18 (s, 3H), 1.61 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 169.0, 155.7, 153.7, 151.6, 150.5, 147.0, 146.7, 138.8, 133.4, 133.3, 133.1, 132.4, 132.2, 131.8, 123.9, 117.8, 117.6, 117.3, 116.7, 113.3, 113.0, 112.9, 101.9, 95.1, 74.7, 74.0, 69.4, 66.6, 66.0, 65.5, 62.0, 60.4, 60.1, 57.7, 55.4, 55.3, 52.3, 43.3, 29.7, 16.1, 9.9; LRMS (ESI$^+$) *m/z* $(M + Na)^+$ 947.3, 949.3.

Macrolactone 44b. In a manner similar to that used for the preparation of **44a**, treatment of **43b** (180.0 mg, 0.13 mmol) gave **44b** (82.0 mg, 0.081 mmol, 63%) as a colorless oil. $[\alpha]_D^{23} = +40°$ (*c* 1.0 $CHCl_3$); IR ($CHCl_3$) ν 3420, 3019, 2931, 2857, 1735, 1505, 1257, 1107 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$, 293 K) δ 6.74 (s, 1H), 6.69 (s, 1H), 6.08 (s, 1H), 5.97 (s, 1H), 6.1−5.8 (m, 3H), 5.5−5.1 (m, 5H), 4.93 (d, J = 8.8 Hz, 1H), 4.83 (d, J = 2.4 Hz, 1H), 4.67 (s, 2H), 4.6−4.4 (m, 6H), 4.4−4.0 (m, 2H), 3.85 (br.d, J = 14.5,Hz, 1H), 3.73 (m, 4H), 3.50 (br.d, J = 13.8 Hz, 1H), 3.11 (dd, J = 14.9, 1.7 Hz, 1H), 3.04 (m, 1H), 2.81 (dd, J = 13.6, 8.7 Hz, 1H), 2.37 (dd, J = 15.1, 3.0 Hz, 1H), 2.23 (s, 3H), 2.19 (s, 3H), 0.99 (s, 9H), 0.18 (s, 3H), 0.17 (s,1H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 169.3, 158.6, 156.0, 154.1, 150.9, 149.1, 147.4, 139.2, 137.1, 133.7, 132.8, 130.9, 124.8, 120.4, 119.0, 118.1, 118.0, 117.1, 113.7, 113.3, 102.3, 95.5, 75.1, 74.4, 67.1, 66.4, 65.8, 62.3, 60.2, 58.0, 55.7, 55.6, 52.7, 43.6, 33.2, 33.2, 25.7 (×3), 18.4, 16.1, 9.8, −4.2 (×2); LRMS (ESI$^+$) *m/z* 1021.3, 1023.3 $(M + Na)^+$; HRMS (ESI$^+$) *m/z* calcd for $C_{44}H_{57}N_4O_{12}Si\ NaSCl_3$ $(M + Na)^+$ 1021.2426, 1023.2449, found 1021.2441, 1023.2443.

***N,O*-Hemiacetal 49.** To a stirred solution of oxalyl chloride (7.0 μL, 0.079 mmol) in CH_2Cl_2 (0.15 mL) cooled to −78 °C was added a solution of DMSO (14.0 μL, 0.20 mmol) in CH_2Cl_2 (0.15 mL). After 5 min of stirring at −78 °C, a solution of alcohol **44b** (66.0 mg, 0.066 mmol) in CH_2Cl_2 (0.50 mL) was added and the mixture was stirred at the same temperature for 1 h. TEA (46.0 μL, 0.33 mmol) was added, the reaction was then allowed to warm to 0 °C, and stirring was continued for another 30 min. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. After concentration and column chromatography, the hemiacetal **49** (49.0 mg, 0.049 mmol, 74%) was isolated as a colorless oil. $[\alpha]_D^{23} = -28°$ (*c* 1.0 $CHCl_3$); IR ($CHCl_3$) ν 3421, 2958, 1735, 1684, 1462, 1303, 1099 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$, 293 K) δ 6.73 (d, J = 1.1 Hz, 1H), 6.69 (s, 1H), 6.11 (d, J = Hz,-1H), 6.09 (m, 1H), 5.99 (d, J = 1.1 Hz, 1H), 5.92 (d, J = 6.7 Hz, 1H), 5.68 (m, 1H), 5.67 (d, J = 11.3 Hz, 1H), 5.49 (dd, J = 8.2, 1.5 Hz, 1H), 5.47 (dd, J = 16.9, 2.1 Hz, 1H), 5.30 (dd, J = 10.9, 2.1 Hz, 1H), 5.24−5.14 (m, 1H), 5.11 (d, J = 1.8 Hz, 1H), 4.70 (s, 2H), 4.58 (m, 3H), 4.27 (m, 3H), 4.16 (dd, J = 11.5, 2.0 Hz, 1H), 3.94 (d, J = 2.4 Hz, 1H), 3.80 (m, 1H), 3.73 (s, 3H), 3.3−3.1 (m, 3H), 2.53 (dd, J = 8.2, 2.3 Hz, 1H), 2.46 (dd, J = 14.8, 3.0 Hz, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 1.03 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 168.7, 157.0, 154.0, 151.0, 148.8, 148.6, 147.1, 139.0, 133.5, 132.4, 132.3, 131.8, 125.2, 120.6, 119.0, 118.6, 118.1, 117.1, 113.5, 113.3, 102.1, 95.3, 77.0, 74.9, 74.4, 66.7, 65.6, 60.5, 59.9, 58.0, 56.9, 55.3, 55.3, 39.5, 34.8, 32.7, 25.9 (×3), 18.5, 16.2, 10.0, −4.2, −4.4; LRMS (MALDI) *m/z* 1035.24, 1037.25; HRMS (MALDI) *m/z* calculated $C_{44}H_{55}N_4O_{12}SiKSCl_3$ $(M + K)^+$ 1035.2009 and 1037.1979, found 1035.2009, 1037.1953.

Phenol 7. To a solution of hemiacetal **49** (74.0 mg, 0.074 mmol) in MeOH (4.0 mL) was added a solution of $KF{\cdot}2H_2O$ (21.0 mg, 0.22 mmol) in MeOH (4.0 mL), AcOH (4.5 μL, 0.076 mmol), and H_2O (0.2 mL). After being stirred at room temperature for 4 h, the mixture was partitioned between AcOEt and saturated NaCl/H_2O/saturated $NaHCO_3$ (1:1:0.2). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to afford phenol **7** (58.0 mg, 0.066 mmol, 89%) as a pale yellow powder. $[\alpha]_D^{23} = -21°$ (*c* 1.0 $CHCl_3$); IR ($CHCl_3$) ν 3533, 3421, 3013, 2929, 1735, 1683, 1502, 1432, 1099 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$, 293 K) δ 6.78 (d, J = 1.4 Hz, 1H), 6.67 (s, 1H), 6.11 (s, 1H), 6.09 (m, 1H), 5.99 (s, 1H), 5.98 (d, J = 6.6 Hz, 1H), 5.67 (d, J = 11.3 Hz, 1H), 5.66 (m, 1H), 5.49 (dd, J = 8.1, 1.6 Hz, 1H), 5.47 (dd, J = 17.1, 2.0 Hz, 1H), 5.30 (dd, J = 10.9, 2.1 Hz, 1H), 5.18 (m, 2H), 5.10 (d, J = 1.4 Hz, 1H), 4.71 (d, J = 1.3 Hz, 2H), 4.56 (m, 3H), 4.26 (m, 3H), 4.15 (dd, J = 11.4, 2.0 Hz, 1H), 3.94 (d, J = 2.4 Hz, 1H), 3.79 (m, 1H), 3.77 (s, 3H), 3.21 (m, 3H), 2.51 (dd, J = 2.4, 8.1 Hz, 1H), 2.47 (dd, J = 14.7, 3.0 Hz, 1H), 2.29 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 166.9, 155.2, 152.2, 149.1, 147.1, 145.3, 142.7, 137.2, 131.9, 131.7, 129.9, 129.2, 122.5, 117.4, 116.8, 116.4, 115.3, 112.9, 111.8, 111.5, 100.3, 93.6, 75.5, 73.1, 72.6, 65.0, 65.0, 63.8, 59.0, 58.8, 56.3, 55.2, 53.5, 37.1, 33.3, 30.8, 14.3, 8.3; LRMS (MALDI) *m/z* 905.2, 907.2 $(M + Na)^+$; HRMS (MALDI) *m/z* calcd for $C_{38}H_{41}N_4O_{12}NaSCl_3$ $(M + Na)^+$ 905.1405, 907.1375, found 905.1415, 907.1364.

Thiol 51a. To a solution of **7** (20.0 mg, 0.023 mmol) in MeCN (3.0 mL) was added a solution of trifluoromethanesulfonic acid (25.0 μL) in MeCN (2.0 mL) at 0 °C, and the mixture was stirred at 0 °C for 40 min. The reaction was quenched by addition of saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to afford **51a** (16.0 mg, 0.019 mmol, 84%) as a colorless oil: $[\alpha]_D^{23} = +77°$ (*c* 1.0 $CHCl_3$); IR ($CHCl_3$) ν 3530, 3419, 2928, 1733, 1702, 1683, 1420, 1251, 1100 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$, 293 K) two rotamers δ 6.69 & 6.67 (s, 1H), 6.29 & 6.23 (br.s, 1H), 6.10 (m, 1H), 6.01 (s, 1H), 5.90 (m, 1H), 5.88 (s, 1H), 5.81 (d, J = 7.2 Hz, 1H), 5.62 & 5.54 (br.s, 1H), 5.45 (dd, J = 17.0, 1.4 Hz, 1H), 5.32 (br.d, J = 10.0 Hz, 1H), 5.3−5.2 (m, 2H), 4.95−4.80 (m, 3H), 4.73−4.52 (m, 4H), 4.51 (d, J = 3.7 Hz, 1H), 4.35−4.25 (m, 2H), 3.72 (s, 3H), 3.70 (m, 1H), 3.46 (dd, J = 4.2, 10.9 Hz, 1H), 3.36 (br.d, 1H), 3.02(m, 2H), 2.28 (br.s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$, 293 K) δ 168.7, 154.1, 153.7 & 153.3, 148.2, 147.5, 146.2, 144.2, 139.4, 134.9 & 134.8, 133.6, 132.2, 128.9 & 128.6, 127.9 &127.5, 126.1 & 125.8, 118.6, 118.0, 117.9, 117.1, 116.3, 114.0, 112.8 & 112.5, 104.2, 102.9 & 102.4, 101.6, 95.2, 75.2, 75.1, 66.8, 64.2, 61.0, 56.7 & 56.4, 55.5, 53.1 & 52.2, 52.7, 49.8 & 48.8, 29.4 & 29.1, 11.3, 9.4; LRMS (ESI$^+$) *m/z* 887.1, 889.2; HRMS (ESI$^+$) *m/z* calcd for $C_{38}H_{39}N_4O_{11}NaSCl_3$ $(M + Na)^+$ 887.1299, 889.1270, found 887.1311, 889.1298.

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Supporting Information Available: Experimental procedure and spectroscopic data of compounds **9**, **10a,b**, **11**, **15**, **17**, **19**, **26**−**28**, **34**, **35a,b**, **36**, **37**, **41**, **43a,b**, **51b**, and **53b**; synthesis of bromide **29** from methyl catechol; and X-ray data for compound **19** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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