Intramolecular Pictet-Spengler Reaction of *N*-Alkoxytryptamines. 3.[1] Stereoselective Synthesis of (-)-Debromoeudistomin L and (-)-*O*-Methyldebromoeudistomin E and Their Stereoisomers[2]

Pedro H. H. Hermkens,[†] Jan H. v. Maarseveen,[†] Harry C. J. Ottenheijm,[†] Chris G. Kruse,[‡] and Hans W. Scheeren*[,†]

Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands, and Duphar Research Laboratories, P.O.B. 2, 1380 AA Weesp, The Netherlands

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The *N*-hydroxytryptamines **10** and **11** were converted into the *N*-alkoxy derivatives **32-34** (overall yield 57-72%) by successive protection with [2-(trimethylsilyl)ethyl]chloroformate providing **27** and **28**, reaction with functionalized chloromethyl sulfides, and deprotection with a "naked" fluoride. Intramolecular cyclization succeeded with **33** and **34** by reduction of the methyl ester with DIBAL and treatment with TFA to give diastereomeric pairs with a slight selectivity for the trans isomer (53-81%, cis/trans ≈ 35/65). Removal of the BOC group gave debromoeudistomin L ((-)-**1e**), its three stereomers (**42a,b** and (+)-**1e**), *O*-methyldebromoeudistomin E ((-)-**1f**), and its stereomer **43**.

The increased research on secondary metabolites with interesting pharmacological activities has led to the discovery of the class of indole alkaloids containing a tetrahydro-β-carboline fragment annulated with a oxathiazepine unit. These compounds, the eudistomins (**1a-d**) (Scheme I), were isolated by Rinehart and Kobayashi from the colonial tunicate *Eudistoma olivaceum*.[3] More recently, Munro isolated the sulfoxide of eudistomin K (**1b**) and the unsubstituted eudistomin **1e** from *Ritterella sigillinoides*.[4] These compounds display potent antitumor activity and antiviral activity against *Herpes simplex* Type 1 (HSV-1) and *Polio* vaccine Type I viruses.[3,4] Because of its unique structure and its biological activity, this class of compounds constitutes a major challenge for total synthesis. Common in the approaches reported so far[5] is the construction of the C ring of the β-carboline **2** as the first step by an intermolecular Pictet-Spengler reaction of **3** and a cysteinal derivative **4** (route A, Scheme I). However, subsequent ringclosure **2** → **1** to form the oxathiazepine ring appeared a difficult task, and only recently two total syntheses of eudistomin L employing this approach were reported.[6] Recently, we reported[1] the synthesis of corynanthe analogs with an 1,2-oxazine as D ring by an intramolecular Pictet-Spengler ringclosure of *N*-alkoxytryptamine derivatives. The feature of this approach is that ring C and D are formed simultaneously. By making use of the driving force of the Pictet-Spengler reaction this methodology was subsequently employed for construction of the 7-membered oxathiazepine ring of eudistomin derivatives in reasonable yield.[7] It was shown that intramolecular Pictet-Spengler reaction of *N*-alkoxytryptamine derivative **5** (Y = COOMe or $CH(OMe)_2$, R_1-R_4 = H), derived from **3** and **4** (X = CH_2Cl), give (±)-deaminodebromoeudistomin L (**1g**) (route B, Scheme I).

Here we report the total synthesis of (-)-debromoeudistomin L (**1e**) and (-)-*O*-methyldebromoeudistomin E (**1f**) and their stereoisomers, by intramolecular Pictet-Spengler reaction of *N*-alkoxytryptamine derivatives (**5**), derived from *N*-hydroxytryptamine (**3**) and a derivative of chloromethylcysteine (**4**, X = CH_2Cl, R_4 = HNBOC, Y = COOMe) (route B, Schem I).

Synthesis of the *N*-Hydroxytryptamine Derivatives. Compound **10** was prepared via a known procedure,[8] viz. nucleophilic displacement of the quaternarized amino function of gramine **6** with the anion of nitromethane gave **8** of which the nitro group was reduced (Scheme II). 5-Methoxy-*N*-hydroxytryptamine (**11**) was prepared in an analogous fashion. Reaction of 5-methoxygramine (**7**) with nitromethane in the presence of dimethyl sulfate and sodium methoxide gave the nitro compound **9** (98%). Reduction of the nitro group by Al(Hg) in ethyl acetate saturated with water gave compound **11** (93%).

***S*-(Chloromethyl)cysteine Derivatives.** From the synthesis of model compound **1g** we learned that compound **4** should contain the fragments X = CH_2Cl and Y = $CH(OMe)_2$ or COOMe. Thus, to obtain the correct stereochemistry at C(1) of the target molecules a chloromethyl sulfide derivative of D-cysteinal or D-cysteine methyl ester should be employed. Because of the tendency of cystinal derivatives[9] to racemization and the high costs of D-cysteine derivatives, we decided to approach these compounds from D-serine methyl ester. In order to explore the feasibility of our approach we initially started with the more readily available L-serine methyl ester.

For the cysteinal derivatives (Y = $CH(OMe)_2$) we started with *N*-[(*tert*-butyloxy)carbonyl]-*O*-[(*tert*-butyl)dimethylsilyl]-L-serine methyl ester[10] (**12**) which was reduced

[†] University of Nijmegen.
[‡] Duphar Research Laboratories.

(1) Intramolecular Pictet-Spengler reaction of *N*-alkoxytryptamines. 2. See: Hermkens, P. H. H.; Maarseveen, J. H. v.; Berens, H. C.; Smits, J. M. M.; Kruse, C. G.; Scheeren, J. W. *J. Org. Chem.* **1990**, *55*, 2200.

(2) Part of the work described herein was presented on the 31th NOS, Ithaca (USA), abstract B15, June 20, 1989, and the 12th ICHC, Jerusalem (Israel), abstract A18, August 14, 1989.

(3) (a) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524. (b) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Larfargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378.

(4) (a) Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1987**, *28*, 1825. (b) Lake, R. J.; Brennan, M. M.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *Tetrahedron Lett.* **1988**, *29*, 2255. (c) Lake, R. J.; Blunt, J. W.; Munro, M. H. G. *Aust. J. Chem.* **1989**, *42*, 1201.

(5) (a) Han, S. Y.; Lakshmikantham, M. V.; Cava, M. P. *Heterocycles* **1985**, *23*, 1671. (b) Nakagawa, M.; Liu, J. J.; Ogata, K.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 6087. (c) Plate, R.; Hout, v. R. H. M.; Behm, H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 555. (d) Nakagawa, M.; Liu, J. J.; Ogata, K.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1988**, 463.

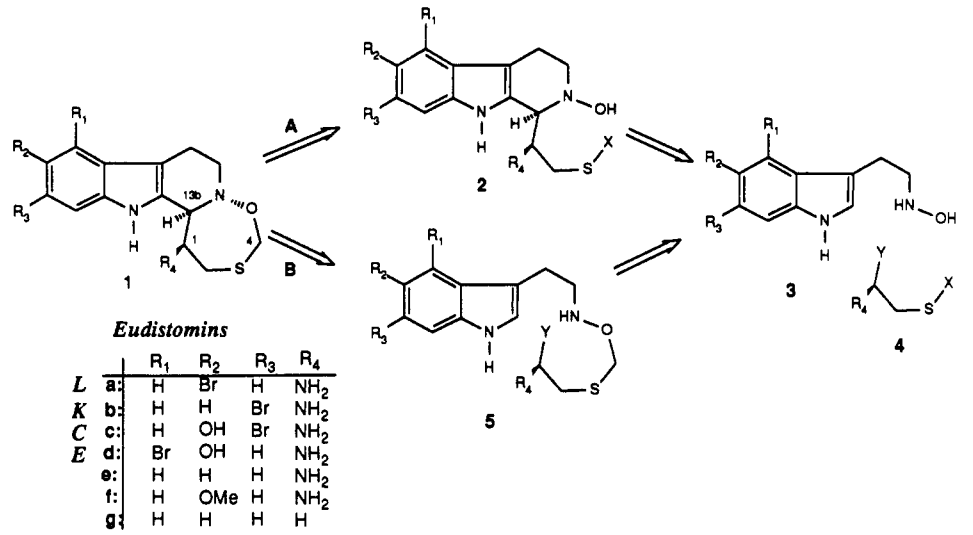
(6) (a) Still, I. W. J.; Strautmanis, J. R. *Tetrahedron Lett.* **1989**, *30*, 1041. (b) Nakagawa, M.; Liu, J. J.; Hino, T. *J. Am. Chem. Soc.* **1989**, *111*, 2721.

(7) Hermkens, P. H. H.; Maarseveen, J. H. v.; Kruse, C. G.; Scheeren, J. W. *Tetrahedron Lett.* **1989**, *30*, 5009.

(8) Cohen, A.; Heath-Brown, B. *J. Chem. Soc.* **1965**, 7179. By modification of the reaction conditions, we were able to synthesize the *N*-hydroxy compounds in high yields.

(9) (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081.

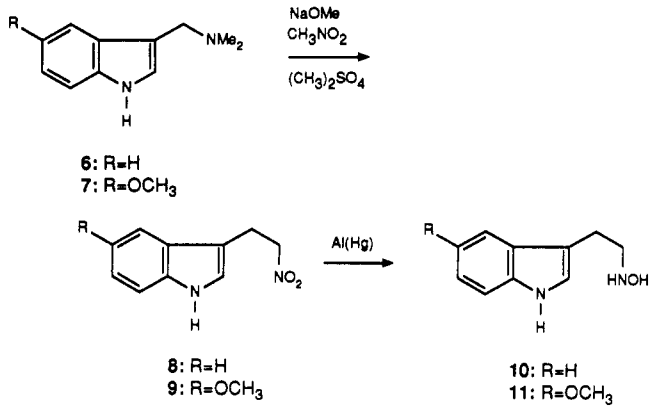
Scheme I



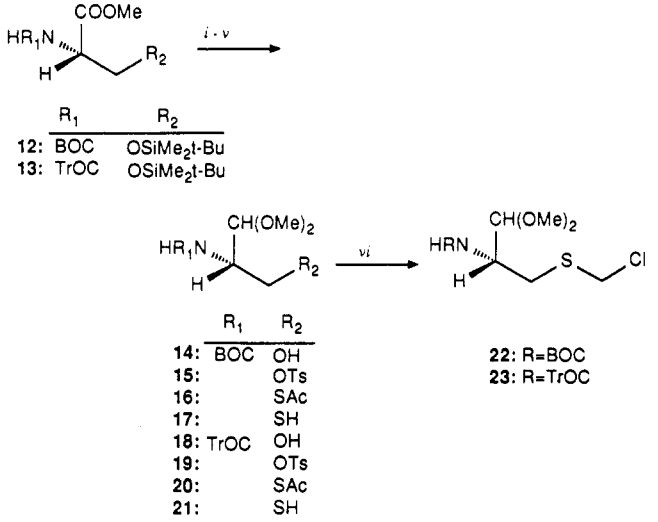
Eudistomins

		R_1	R_2	R_3	R_4
L	a:	H	Br	H	NH_2
K	b:	H	H	Br	NH_2
C	c:	H	OH	Br	NH_2
E	d:	Br	OH	H	NH_2
	e:	H	H	H	NH_2
	f:	H	OMe	H	NH_2
	g:	H	H	H	H

Scheme II

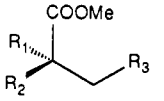


Scheme III[a]



[a] (i) DIBAL/toluene, −70 °C; (ii) $HC(OMe)_3$/MeOH/TFA; (iii) TsCl/pyridine; (iv) $CsCO_3/CH_3COSH$/DMF; (v) NaOMe; (vi) $BrCH_2Cl$/KOH/TEBAC.

Chart I



	R_1	R_2	R_3
24a(L)	HNBOC	H	OTs
24b(D)	H	HNBOC	OTs
25a(L)	HNBOC	H	SAc
25b(D)	H	HNBOC	SAc
26a(L)	HNBOC	H	SCH_2Cl
26b(D)	H	HNBOC	SCH_2Cl

with DIBAL in toluene at −70 °C to the corresponding serinal derivative (Scheme III). The aldehyde was not isolated as such but immediately treated with trimethyl orthoformate in methanol and trifluoroacetic acid (TFA), whereby the silyl protective group was removed and the dimethyl acetal was formed in one step, giving **14** in 46% yield in an ee of 94% (vide infra).

The next step is the introduction of the sulfur atom. Recently, a method for the conversion of alcohols into thiols via reaction of the corresponding mesylate with cesium thiocarboxylates was published.[11] This method proved to be successful for our purpose also. The alcohol **14** was transformed into the corresponding tosylate **15**. Subsequent treatment with cesium thioacetate in DMF yielded the thioacetate **16** in 67% yield based on the alcohol **14**. This compound was converted quantitatively with sodium methoxide into the thiol **17**, which immediately was alkylated by a phase-transfer reaction with bromochloromethane using powdered KOH and triethylbenzylammonium chloride (TEBAC) to give the chloromethyl sulfide **22** in nearly quantitative yield.[12] Thus, the overall yield **12** → **22** is 31%.

In an analogous fashion, i.e. **13** → **18** → **19** → **20** → **21** → **23**, the [(2,2,2-trichloroethyl)oxy]carbonyl (TrOC) protected compound **23** was prepared in an overall yield of 14% (Scheme III). In contrast with their free aldehyde congeners,[9] the dimethyl acetal derivatives **16** and **20** did not undergo racemization during storage.

To obtain the cysteine methyl ester derivatives (Y = COOMe) the hydroxyl function of BOC-L-Ser-OMe and BOC-D-Ser-OMe was converted by the same procedure to the corresponding chloromethylsulfides (→ **24a** → **25a** →

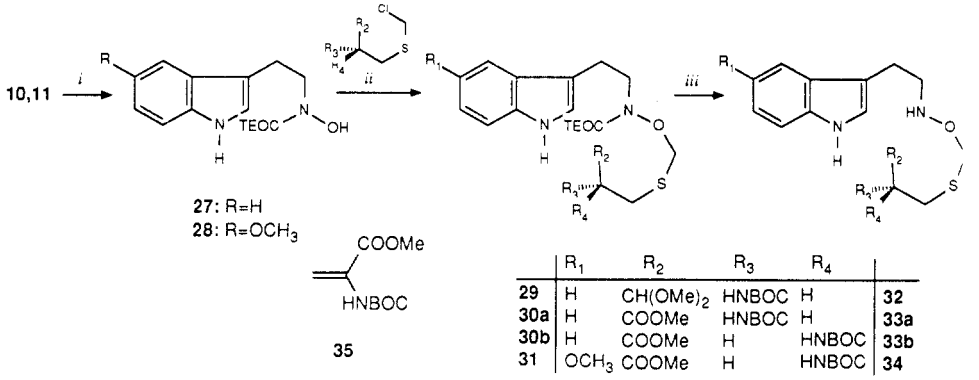
(10) We were aware that serine-derived aldehydes have been prepared starting from other serine derivatives, but felt that they would not be suitable for our purposes. (a) Pht-Ser(Ac)-al: Newman, H. *J. Am. Chem. Soc.* **1973**, *95*, 4098. (b) BOC-Ser(Bzl)-al: Stanfield, C. F.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* **1981**, *46*, 4797. (c) Cbz-Ser(Bzl)-al: Garner, P. *Tetrahedron Lett.* **1984**, 5855.

(11) Strijtveen, B.; Kellog, R. M. *J. Org. Chem.* **1986**, *51*, 3664.

(12) Treatment of the thiol **17** with paraformaldehyde and HCl—the traditional method for preparation of chloromethyl sulfides (see ref 13)—gave poor yields (5–10%).

(13) (a) Bohme, H. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1612. (b) Walter, L. A.; Goodson, L. H.; Fosbinder, R. J. *J. Am. Chem. Soc.* **1945**, *67*, 655.

Scheme IV[a]



	R_1	R_2	R_3	R_4	
29	H	$CH(OMe)_2$	HNBOC	H	32
30a	H	COOMe	HNBOC	H	33a
30b	H	COOMe	H	HNBOC	33b
31	OCH_3	COOMe	H	HNBOC	34

[a] (i) CH_2Cl_2/dioxane, $Me_3SiCH_2CH_2OCOCl$; (ii) NaH/DME, NaI; (iii) F^-.

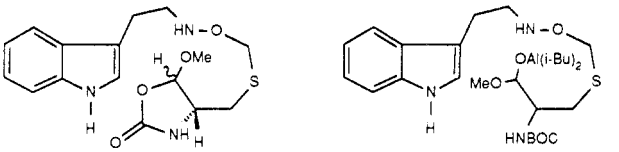
26a; 71%) and (→ **24b** → **25b** → **26b**; 77%) (Chart I). The subsequent conversion of the OH into the SH group occurred without loss of enantiomeric purity.[14]

Coupling. Selective O-alkylation of the *N*-hydroxytryptamines **10**–**11** was not possible. However, we have demonstrated[1] that in a one-pot synthesis the [[2-(trimethylsilyl)ethyl]oxy]carbonyl (TEOC) protected *N*-hydroxytryptamine **27** can be O-alkylated by alkylhalogenides, to give after deprotection *N*-alkoxytryptamines in good yields. The *N*-hydroxyurethane **27** was prepared as reported earlier.[1] In an analogous manner **11** was treated with 2-(trimethylsilyl)ethyl chloroformate[15] in dichloromethane/dioxane to give **28** in 76% yield (Scheme IV).

An efficient method for coupling of the chloromethyl sulfides **22**, **23**, **26a**, and **26b** with **27** was only found after several unsuccessful attempts (Scheme IV). Application of the alkaline systems DMSO/KOtBu, DMSO/K_2CO_3, DME/KOtBu, or benzene/$AgNO_3$/Et_3N[16] gave no reaction or unindentified products. The conditions of choice were analogous to those used in the preparation of (methylthio)methyl esters.[17] Compound **27** was treated with sodium hydride in dimethoxyethane (DME) and subsequently coupled with the iodomethyl sulfide formed in situ from **22** and sodium iodide in DME. The alkylated product **29** was not isolated but deprotected immediately by adding tetrabutylammonium fluoride (TBAF) to give the *N*-alkoxyamine **32** in an overall yield of 75%. The coupling failed, however, when the TrOC-protected chloromethyl sulfide **23** was used. Starting material **27** was recovered quantitatively. This failure is due to decomposition of **23** under the basic alkylation conditions used.[18]

Following the same procedure employing now the methyl ester **26a** the dehydro amino acid derivative **35** (35%) (Scheme IV) and the desired thiomethyl ether **30a** (34%) were isolated together with recovered starting material **27** (59%). This β-elimination reaction could be prevented by adding the anion of **27** very slowly to the in situ prepared iodomethyl sulfide of **26a**. The thiomethyl ether **30a** was now isolated in 85% yield. Deprotection with TBAF without isolation of **30a** gave **33a** in a moderate yield (48%). Likewise, deprotection of *isolated* **30a** with TBAF gave **33a** in only 61% yield. An alternative deprotection method[19] with a "naked" fluoride generated by tetrabutylammonium chloride and potassium fluoride dihydrate in acetonitril at 60 °C gave **33a** in high yield (85%). We do not have an explanation for the lower ability of TBAF to remove the TEOC group of **30a** as compared to **29**.

Chart II



36 **37**

In a similar manner the D-cysteine derivative **26b** was coupled with **27** and **28** to give **30b** (84%) and **31** (88%), respectively. Deprotection of these compounds with the above-mentioned fluoride reagent gave **33b** (86%) and **34** (81%), respectively.

The conversions **26a** → **30a** and **26b** → **30b**/**31** deserve further comment. Despite the application of basic conditions in the coupling step we observed only minor losses of enantiomeric purity in the end products (−)-**1e** and (−)-**1f** (vide infra). However, we found noticeable racemization when a slight excess of sodium hydride was used in the generation of the alkoxide anion.

Cyclization. The intramolecular Pictet–Spengler reaction of the dimethyl acetal **32** did not proceed as smoothly as the one we observed earlier[1,7] for *N*-alkoxytryptamine derivatives with a dimethyl acetal function at the end of the alkoxy chain. Treatment of **32** with TFA gave the two stereoisomers of the cyclic urethane **36** as the main products (Chart II). Apparently, the in situ formed alkoxycarbenium ion is quenched intramolecularly by the BOC group.[20] Unfortunately, the cyclic urethane compounds decomposed on further treatment with acid.

We described earlier[1,7] that compound **5** (Y = COOMe, R_1–R_4 = H) cyclized immediately after reduction of the methyl ester with DIBAL at −70 °C and subsequent addition of TFA. The difference in reactivity of the inter-

(14) The optical purity of the products **25a** and **25b** was determined by successive removal of the acetyl group of **25a** and **25b** and oxidation of the resulting thiol with I_2 to give the L-BOC-cystine and D-BOC cystine derivatives. The observed specific rotations $[\alpha]^{22}_D$ −97.3° and $[\alpha]^{22}_D$ +94.8° are in accordance with data earlier observed by Ottenheijm et al. for the D-BOC cystine derivative $[\alpha]^{22}_D$ +92.9°. Ottenheijm, H. C. J.; Liskamp, R. M. J.; Nispen, S. P. J. M. v.; Boots, H. A.; Tijhuis, M. W. *J. Org. Chem.* **1981**, *46*, 3273.

(15) (a) Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358. (b) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

(16) Suzuki, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1979**, 1277.

(17) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269.

(18) The TrOC group is base-labile, see: Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; pp 226 and 324.

(19) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

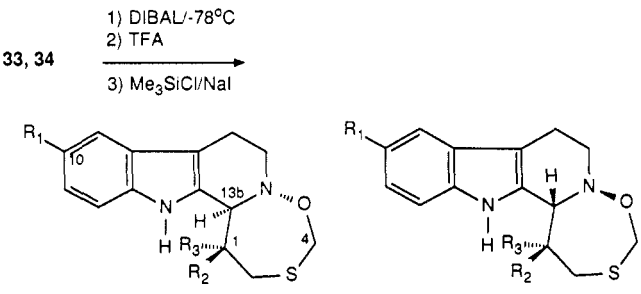
(20) We have tried to prevent this undesired reaction by using the less acid sensitive protective group TrOC. However, as a result of the basic conditions required during the coupling of **27** with **23**, the latter decomposed.

Table I. Cyclization of the *N*-Alkoxytryptamines 33 and 34

entry	compound	solvent	cyclization condition	TFA (equiv)	yield[a] (%)	cis/trans[b]
1	**33a**	toluene	−70 °C/3 h	5	52	29/71
2		toluene	RT/1 h	5	41	39/61
3		DME	−70 °C/3 h	5	70	13/87
4		CH_2Cl_2	−70 °C/3 h	5	52	31/69
5		CH_2Cl_2	−90 °C/0.5 h	15	58	41/59
6	**33b**	CH_2Cl_2	−90 °C/0.5 h	15	53	34/66
7	**34**	CH_2Cl_2	−90 °C/0.5 h	15	81	30/70

[a] These yields are based on starting material and refer to isolated compounds. [b] Ratios are based on isolated compounds. These are in agreement with the product ratios determined by HPLC.

Scheme V



	R_1	R_2	R_3	
38a	H	H	HNBOC	**39a**
39b	H	HNBOC	H	**38b**
40	OCH_3	HNBOC	H	**41**
42a	H	H	NH_2	(+)-**1e**
(-)-**1e**	H	NH_2	H	**42b**
(-)-**1f**	OCH_3	NH_2	H	**43**

mediate obtained after the DIBAL reduction with that of the dimethyl acetal derivatives was enormous, indicating a different mechanism in the Pictet–Spengler reaction to follow. Consequently we reasoned that the undesired reaction we observed with the dimethyl acetal **32** may be avoided by using the methyl ester derivatives **33** and **34**. Indeed, reduction of **33a** with DIBAL at −70 °C in toluene followed by addition of TFA gave the cyclized products **38a** and **39a** in 52% yield (ratio **38a**/**39a** = 71/29) (Scheme V and Table I, entry 1). Presumably, cyclization under acidic conditions occurs either via the activated mixed acetal **37** (Chart II) or via the corresponding free aldehyde. The observed stereochemistry seems to be the result of a kinetically controlled reaction. Prolonged treatment of either the cis isomer **38a** or the trans isomer **39a**, respectively, under the reaction conditions caused no formation of the other isomer.

The ^{1}H NMR data of compound **39a** show a great resemblance with those reported by Nakagawa[21] for the compound with a cis relationship between the protons of C(1) and C(13b). The characteristic differences between the spectra of **38a** and **39a** are (i) the downfield shift of the indole NH proton δ 9.98 (**39a**: 8.52) probably participating in a H-bridge with the nitrogen of the HNBOC group on C(1)[22] and (ii) the AB spectrum of the OCH_2S protons at δ 5.26 (**39a**: 4.98) and δ 4.77 (**39a**: 4.83) with ^2J = 11.4 Hz (**39a**: 9.1Hz). Therefore, the relative stereochemistry at the C(1) and C(13b) centers was tentatively assigned as trans in **38a**[23] and cis in **39a**.

Although the *inter*molecular Pictet–Spengler reaction of **10** with cysteinals proceeds with high diastereoselectivity yielding predominantly the cis isomer,[6b] the corresponding *intra*molecular cyclization shows a low diastereoselectivity toward the trans isomer. The complexity of the cyclization mechanism[24] makes it difficult to give a rational explanation for this reversal in the stereochemical outcome of the reactions.

We studied the cyclization by varying the solvent, the cyclization temperature and the amount of TFA used (Table I, entries 1–5). The ratio **38a**(trans)/**39a**(cis) depends slightly on the solvent used. Whereas for all the solvents used the major product has a trans relationship between the C(1) and C(13b) protons, it was observed that toluene and dichloromethane give a higher ratio with respect to the cis compound than dimethoxyethane does (entries 1, 3–4). Raising the temperature to room temperature gave a slight improvement of the ratio with respect to the cis isomer; the yield dropped, however (entry 2). The best result was obtained when 15 equiv of TFA was added at once to a cooled solution (−90 °C) of the reactant in dichloromethane (entry 5). Therefore, the compounds **33b** and **34** were cyclized under these conditions to give **38b** and **39b** in 53% yield (ratio **38b**/**39b** = 66/34) and **40** and **41** in 81% yield (ratio **41**/**40** = 30/70), respectively (Scheme V, Table I, entries 6–7). The stereochemistry of **38b**, **39b**, **40**, and **41** was assigned by comparing their ^{1}H NMR spectra with those of **38a** and **39a**.

The specific rotations of **39a** and **39b** are nearly identical with those reported by Nakagawa,[6b] who established the optical purity of these eudistomin derivatives by NMR techniques.

Deprotection. The most widely used procedure for removal of the BOC group involves treatment with TFA at 0 °C.[25] However, we found that under these conditions **39b** gave the desired amine (−)-**1e** in low yield only due to decomposition of the latter. The method of choice appeared to be a mild deblocking method reported by Stammer;[26a] it consists of cleavage of the the carbamate by trimethylsilyl iodide (TMSI) at room temperature in acetonitrile. Compound **39b** was treated for 2 h with the in situ generated TMSI (2 equiv of TMSCl and NaI)[26b] at room temperature in CH_3CN to give debromoeudistomin L ((−)-**1e**) in 94% yield (Scheme V). The deprotections **38a** → **42a**, **38b** → **42b**, **39a** → (+)-**1e**, **40** → (−)-**1f**, and **41** → **43** proceeded in an analogous fashion in yields of 95%, 89%, 98%, 95%, and 78%, respectively.[27] The

(21) Nakagawa, M., personal communication.
(22) CPK models show that this N–H–N bridge can only be incorporated in a six-membered ring for this diastereomer.
(23) Later on we were able to confirm this assignment by single-crystal X-ray analysis of the trans derivative **43**, see ref 28.

(24) Bailey, P. D. *Tetrahedron Lett.* **1987**, *28*, 5181 and references cited therein.
(25) Lundt, B. F.; Johansen, N. L.; Vølund, A. *Int. J. Pept. Protein Res.* **1978**, *12*, 258.
(26) (a) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495. (b) Olah, G. A.; Narang, S. C.; Gupta, B. G. D.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
(27) We determined the enantiomeric excess of the compounds (−)-**1e** and (−)-**1f** by HPLC using the chiral column Cyclobond I (250 by 4.6 mm, eluens 0.5% Et_3N in CH_3CN/TFA, pH = 3.5, flow = 1 mL/min, λ = 254 nm). The HPLC profile of the compound (−)-**1e** (K = 2.16) showed the presence of (+)-**1e** (K = 1.93) in a ratio of (−)-**1e**/(+)-**1e** = 94.5/5.5 so that its ee is 89%. Under identical conditions we found for (−)-**1f** an ee of 86%.

structure of **43** is verified by a single-crystal X-ray analysis.[28] Deprotection of the cis isomers hardly affected their ^{1}H NMR spectra, whereas in case of the trans isomers **42a**, **42b**, and **43** the ^{1}H NMR spectra changed drastically. The differences that attract attention are peak-broadening, a single peak for OCH_2S at δ 4.94, and the upfield shift of C(13b)H. However, the ^{1}NMR spectrum of **42a** at −31 °C showed peak sharpening and clearly two conformations in a ratio of 82/18.[29] Significant differences between the conformers are the indole NH shifts (δ 10.34 versus 9.78) and the AB spectrum of OCH_2S (δ 4.99 and 4.97, ^2J = 9.5 Hz, versus δ 5.37 and 4.88, ^2J = 11.1 Hz). The downfield shift of the indole NH proton of the trans compounds is probably a result of a H-bridge with the nitrogen of the amino group on C(1).

Conclusion

In conclusion, we have shown that *N*-alkoxytryptamines with a methyl ester at the end of the alkoxy chain (**33a**, **33b**, and **34**) undergo—after reduction with DIBAL and subsequent treatment with TFA—an intramolecular Pictet–Spengler reaction to give eudistomin derivatives in reasonable yields. Cyclization occurs with a slight diastereoselective preference for the trans isomer. Removal of the BOC group yields (−)-debromoeudistomin L ((−)-**1e**), its enantiomer (+)-**1e**, and the two diasteromers **42a** and **42b** or (−)-*O*-methyldebromoeudistomin E ((−)-**1f**) and its diastereomer **43**.

We are currently investigating the biological activity of these compounds. Further work on the total synthesis of other derivatives by this method is in progress, as well as a study of the cyclization mechanism.

Experimental Section

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model Lambda 5. Proton magnetic resonance spectra were measured on a Bruker WH-90 or on a Bruker AM 400 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, or Cl_2–TDM.[31] For column chromatography Merck silica gel (type 60H) was used.

5-Methoxy-3-(2-nitroethyl)indole (9). This synthesis is a modification of Cohen's procedure.[8] Sodium methoxide, which was freshly made from 1.22 g (53 mmol) of sodium in dry methanol (50 mL), was added to a stirred solution of 5-methoxygramine (**7**) (9.8 g, 48 mmol) and dimethyl sulfate (12.1 g, 96 mmol) in nitromethane/methanol, 2/1, v/v (250 mL). After completion of the reaction (24 h) as was monitored by TLC ($CHCl_3$/MeOH, 99/1, v/v) most of the solvent was removed by evaporation in vacuo at room temperature. The residue was dissolved in dichloromethane and subsequently washed with 5% NH_4OH, 1 N HCl, and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$/MeOH, 99/1, v/v) to yield 10.34 g (98%) of **9**: EIMS (70 eV) *m/z* (relative intensity) 220 (M^+, 60), 174 ($[M - NO_2]^+$, 69), 173 ($[M - HNO_2]^+$, 100), 130 (57); ^{1}H NMR δ 8.00 (br s, 1 H, NH), 7.30 (dd, 1 H, J = 8.7 Hz, C(7)H), 7.04–6.81 (m, 3 H, C(2)H and C(4)H and C(6)H), 4.67 (t, 2 H, CH_2NO_2), 3.89 (s, 3 H, OCH_3), 3.47 (t, 2 H, indole C(3)-CH_2).

5-Methoxy-3-[2-(hydroxyamino)ethyl]indole (11). To a stirred solution of **9** (9 g, 41 mmol) in EtOAc (saturated with water) was added freshly prepared Al(Hg) (Fieser and Fieser, vol. 1, p 20) portionwise. After completion of the reaction (5 h) as was monitored by TLC ($CHCl_3$/MeOH, 93/7, v/v), the reaction mixture was filtered, the residue was dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was crystallized from EtOAc/*n*-hexane to give 7.83 g (93%) of **11**: R_f 0.17 ($CHCl_3$/MeOH, 93/7, v/v); EIMS (70 eV) *m/z* (relative intensity) 206 (M^+, 21), 160 ($[C_{10}H_{10}NO]^+$, 100); ^{1}H NMR δ 7.94 (br s, 1 H, NH), 7.25 (d, 1 H, J = 9.0 Hz, C(7)H), 7.04–6.74 (m, 3 H, C(2), C(4), and C(6)H), 5.73 (br s, 2 H, HNOH), 3.84 (s, 3 H, OCH_3), 3.34–2.90 (m, 4 H, C(3)CH_2CH_2N). Anal. Calcd for $C_{11}H_{14}N_2O_4$ (MW 206.246): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.30; H, 6.94; N, 13.36.

***N*-[(*tert*-Butyloxy)carbonyl]-*O*-(*tert*-butyldimethylsilyl)-L-serine Methyl Ester (12).** To a stirred solution of L-BOC-Ser-OMe (20.9 g, 95.4 mmol) and imidazole (16.2 g, 240 mmol) in DMF (200 mL) was added dropwise *tert*-butyldimethylsilyl chloride (15.9 g, 105 mmol). The reaction was stirred at 50 °C for 5 days after which the solvent was removed in vacuo. The residue was dissolved in dichloromethane and successively washed with a 1 N HCl solution and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give crude **12**. The crude reaction product was subjected to column chromatography ($CHCl_3$) to give 28.15 g (89%) of **12**: oil; R_f 0.61 ($CHCl_3$); $[\alpha]^{22}_D$ +7.5° (*c* = 3.2, methanol); CIMS (100 eV) *m/z* (relative intensity) 334 ($[M + 1]^+$, 12), 278 (28), 260 ($[M - OC_4H_9]^+$, 13), 234 (49), 220 (43), 49 (100); ^{1}H NMR δ 5.32 (br d, 1 H, NH), 4.33 (m, 1 H, CHN), 3.95 and 3.76 (AB part ABX spectrum, 2 H, ^2J = 11.4 Hz, J = 2.7 Hz, J = 8.0 Hz, CH_2OSi), 3.71 (s, 3 H, OCH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.00 (s, 6 H, $Si(CH_3)_2$).

***N*-[(2,2,2-Trichloroethoxy)carbonyl]-*O*-(*tert*-butyldimethylsilyl)-L-serine Methyl Ester (13).** The same procedure was followed as described for **12**. L-TrOC-Ser-OMe (4.15 g, 14.1 mmol), imidazole (2.1 g, 31 mmol), and *tert*-butyldimethylsilyl chloride (2.54 g, 16.9 mmol) in DMF (25 mL) gave after column chromatography ($CHCl_3$) 5.35 g (92%) of **13**: R_f 0.79 ($CHCl_3$/MeOH, 97/3, v/v); ^{1}H NMR δ 5.73 (br d, 1 H, NH), 4.70 (s, 2 H, CH_2CCl_3), 4.37 (m, 1 H, $CHCH_2O$), 3.92 (m, 2 H, $CHCH_2O$), 3.71 (s, 3 H, OCH_3), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.00 (s, 6 H, $Si(CH_3)_2$).

***N*-[(*tert*-Butyloxy)carbonyl]-L-serinal Dimethyl Acetal (14).** To a stirred solution of **12** (28 g, 84 mmol) in dry toluene (250 mL) was added a solution of DIBAL in toluene (1.2 equiv) in an argon atmosphere at such a rate that the temperature did not raise above −70 °C. After stirring for 2 h a 10% HCl/EtOH solution was added carefully. The reaction mixture was poured into 300 mL of 10% aqueous HCl solution. The organic layer was separated and washed with brine. The organic layer was dried ($MgSO_4$), and the solvent was evaporated in vacuo to give 25 g of crude serinal derivative. Without further purification the crude reaction product (25 g, 83 mmol) was dissolved in methanol (250 mL) and trimethyl orthoformate (75 mL) and trifluoroacetic acid (1 mL) were added. After completion of the reaction (24 h) most of the solvent was removed by evaporation in vacuo. The residue was dissolved in dichloromethane and successively washed with an aqueous 1 N $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$/MeOH, 99/1, v/v) to give 9 g (46%) of **14** as a colourless oil. The yield is based on the ester **12**: R_f 0.31 ($CHCl_3$/MeOH, 97/3, v/v); $[\alpha]^{22}_D$ −20.2° (*c* = 3.4, methanol); CIMS (100 eV) *m/z* (relative intensity) 236 ($[M + 1]^+$, 29), 204 ($[M - CH_3O]^+$, 11), 180 (20), 162 ($[M - C_4H_9O]^+$, 26), 148 (100); ^{1}H NMR δ 5.16 (br s, 1 H, NH), 4.42 (d, 1 H, $CH(OMe)_2$), 4.00–3.50 (m, 3 H, $NCHCH_2$), 3.46 (s, 6 H, 2 OCH_3), 2.61 (br s, 1 H, OH), 1.46 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{10}H_{21}NO_5$ (MW 235.283): C, 51.05; H, 9.00; N, 5.95. Found: C, 50.99; H, 8.89; N, 5.88.

The enantiomeric excess of compound **14** was established by coupling it with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl

(28) Bosman, W. P.; Smits, J. M. M.; Beurskens, P. T.; Hermkens, P. H. H.; Maarseveen, J. H. v. *J. Crystallogr. Spectrosc. Res.*, submitted.

(29) For hydroxylamine derivatives it has been described that the presence of the O atom adjacent to N atom slows down the rate of nitrogen inversion to such an extent that at low temperatures the different conformations can be separated, see ref 30. We currently investigate whether the two conformations observed for compound **43a** at −31 °C are a result of such a nitrogen inversion process.

(30) Ridell, F. G. *Tetrahedron* **1981**, *37*, 849 and references cited therein.

(31) Arx, E. v.; Faupel, M.; Bruggen, M. *J. Chromatogr.* **1976**, *120*, 224.

chloride according to the literature.[32] The obtained MTPA ester [$[\alpha]^{22}_D$ −45.3° (c = 2.65, methanol); ^{1}H NMR δ 7.51 (m, 2 H, $C_6H_2H_3$), 7.40 (m, 3 H, $C_6H_3H_2$), 4.74 (br d, 1 H, NH), 4.42 (d, 2 H, OCH_2), 4.25 (d, 1 H, $CH(OMe)_2$), 4.10 (br s, 1 H, OCH_2CH), 3.53 (q, 3 H, CF_3COCH_3), 3.37 and 3.35 (2 s, 6 H, 2 OCH_3), 1.42 (s, 9 H, $C(CH_3)_3$)] showed in the NMR spectrum two signals for ^{19}F at 0.0912 and −0.0012 ppm in a ratio of 3/97, respectively. Therefore the enantiomeric excess of compound **14** is 94%. A racemic mixture of **14** showed clearly two signals at 0.0896 and −0.001 03 ppm in ratio of 1/1.

***N*-[(2,2,2-Trichloroethoxy)carbonyl]-L-serinal Dimethyl Acetal (18).** The same procedure was followed as described for **14**. From **13** (2.85 g, 7 mmol) and DIBAL (8.5 mmol) in toluene (25 mL) the serinal derivative was obtained which was converted without further purification with trimethyl orthoformate (7.5 mL), methanol (25 mL), and TFA (0.1 mL) to give after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 1.20 g (39%) of **18**: R_f 0.11 ($CHCl_3$/MeOH, 99/1, v/v); ^{1}H NMR δ 5.83 (br s, 1 H, NH), 4.73 (s, 2 H, CH_2CCl_3), 4.45 (d, 1 H, $CH(OMe)_2$), 4.03–3.63 (m, 3 H, $NCHCH_2$), 3.47 (s, 6 H, 2 OCH_3), 2.92 (br s, 1 H, OH).

General Procedure for the Preparation of the Thioacetates. *N*-[(*tert*-Butyloxy)carbonyl]-*S*-acetyl-L-cysteinal Dimethyl Acetal (16). To a solution of the alcohol **14** (8.7 g, 37 mmol) in dry pyridine (60 mL) was added tosyl chloride (7.75 g, 40.7 mmol) at −10 °C. The reaction mixture was stirred at 4 °C overnight. After completion of the reaction as was monitored by TLC ($CHCl_3$/MeOH, 99/1, v/v), most of the pyridine was removed by evaporation in vacuo at room temperature. The residue was dissolved in dichloromethane and subsequently washed two times with a 2 N $KHSO_4$ solution to remove the pyridine and then with water. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give 13.3 g (90%) of crude **15**.

To a suspension of $CsCO_3$ (7.06 g, 21.7 mmol) in dry DMF (85 mL) was added freshly distilled thioacetic acid (3.3 g, 43.3 mmol). As the $CsCO_3$ was dissolved, the crude tosylate **15** (13.3 g, 34.2 mmol) dissolved in 40 mL of dry DMF was added. The reaction mixture was stirred in the dark overnight and was kept under an argon atmosphere. After completion of the reaction the solvent was evaporated in vacuo. The residue was dissolved in dichloromethane (200 mL) and washed with water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude reaction product was subjected to column chromatography (EtOAc/*n*-hexane, 20/80, v/v) to give **16** (67%, based on the alcohol **14**): R_f 0.42 (EtOAc/*n*-hexane, 40/60, v/v); $[\alpha]^{22}_D$ −70.4° (c = 3.55, MeOH); CIMS (100 eV) *m/z* (relative intensity) 294 ($[M + 1]^+$, 5), 262 ($[M - CH_3O]^+$, 12), 206 (76), 162 (21), 75 ($[C_2H_3OS]^+$, 100); ^{1}H NMR δ 4.78 (br d, 1 H, NH), 4.27 (d, 1 H, $CH(OMe)_2$), 4.07–3.76 (m, 1 H, $CHCH_2S$), 3.44 (s, 6 H, 2 OCH_3), 3.19 and 2.94 (AB part of ABX spectrum, 2 H, ^2J = 14.4 Hz, J = 4.0 Hz, J = 7.8 Hz, $CHCH_2S$), 2.34 (s, 3 H, $SCOCH_3$), 1.43 (s, 9 H, $C(CH_3)_3$).

***N*-[(2,2,2-Trichloroethoxy)carbonyl]-*S*-acetyl-L-cysteinal Dimethyl Acetal (20).** The same procedure was followed as described for **16**. Compound **18** (585 mg, 1.88 mmol) gave via tosylate **19** after column chromatography (EtOAc/*n*-hexane, 80/20, v/v) 475 mg (69%) of **20**. The yield was based on the alcohol **16**: R_f 0.38 (EtOAc/*n*-hexane, 1/1, v/v); ^{1}H NMR δ 5.33 (br d, 1 H, NH), 4.67 (s, 2 H, CH_2CCl_3), 4.38 (d, 1 H, $CH(OMe)_2$), 4.01 (m, 1 H, $CHCH_2S$), 3.32 (s, 6 H, 2 OCH_3), 3.11–2.93 (AB part of ABX spectrum, 2 H, $CHCH_2S$), 2.35 (s, 3 H, $SCOCH_3$).

***N*-[(*tert*-Butyloxy)carbonyl]-*S*-acetyl-L-cysteine Methyl Ester (25a).** The same procedure was followed as described for **16**. L-BOC-Ser-OMe (3.8 g, 17.4 mmol) gave via tosylate **24a** after column chromatography (EtOAc/*n*-hexane, 25/75, v/v) 3.85 g (80%) of **25a**: mp 46–47 °C (EtOAc/*n*-hexane); R_f 0.51 (EtOAc/*n*-hexane, 50/50, v/v); $[\alpha]^{22}_D$ −44.2° (c = 2.6, MeOH); IR (KBr) ν (cm^{-1}) 3360 (NH), 1730 (C=O), 1680 (C=O); CIMS (100 eV) *m/z* (relative intensity) 278 ($[M + 1]^+$, 6), 222 (66), 178 (100), 162 (96); ^{1}H NMR δ 5.23 (br d, 1 H, NH), 4.61–4.38 (m, 1 H, CHCOOMe), 3.74 (s, 3 H, OCH_3), 3.52–3.16 (AB part of ABX spectrum, 2 H, CH_2S), 2.33 (s, 3 H, $SCOCH_3$), 1.42 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{11}H_{19}NO_5S$ (MW 277.340): C, 47.64; H, 6.90; N, 5.50. Found: C, 47.81; H, 6.89; N, 5.02.

***N*-[(*tert*-Butyloxy)carbonyl]-*S*-acetyl-D-cysteine Methyl Ester (25b).** The same procedure was followed as described for **16**. D-BOC-Ser-OMe (7.7 g, 35.2 mmol) gave via tosylate **24b** after column chromatography (EtOAc/*n*-hexane, 25/75, v/v) 8.2 g (84%) of **25b**: $[\alpha]^{22}_D$ +45.9° (c = 2.7, MeOH). Further spectroscopic data and the melting point are identical with **25a**.

General Procedure for the Preparation of the Chloromethyl Sulfides. *N*-[(*tert*-Butyloxy)carbonyl]-*S*-(chloromethyl)-L-cysteine Dimethyl Acetal (22). To a stirred solution of thioacetate **16** (1.0 g, 3.4 mmol) in methanol (15 mL) was added dropwise a 1 N MaOMe solution in methanol (3.5 mL). After completion of the reaction, as was monitored by TLC (EtOAc/*n*-hexane, 1/2, v/v), the methanol was removed by evaporation in vacuo. The residue was dissolved in dichloromethane and subsequently washed with 0.1 N HCl and brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated in vacuo to give 860 mg (100%) crude **17**. The thiol was not further purified but dissolved in bromochloromethane (30 mL), and triethylbenzylammonium chloride (TEBAC) (77 mg, 0.34 mmol) and powdered KOH (267 mg, 4.76 mmol) were added successively. After 15 min the reaction was complete. The reaction mixture was filtered, and the filtrate was subsequently washed with water, 1 N HCl, and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give 1.0 g (98%) of the chloromethyl sulfide **22**, which was not further purified: oil; R_f 0.54 (EtOAc/*n*-hexane, 1/2, v/v); ^{1}H NMR δ 4.93 (br d, 1 H, NH), 4.78 (s, 2 H, SCH_2Cl), 4.27 (d, 1 H, $HC(OMe)_2$), 4.13–3.70 (m, 1 H, $CHCH_2S$), 3.45 (s, 6 H, 2 OCH_3), 3.23–2.55 (AB part of ABX spectrum, 2 H, $CHCH_2S$), 1.47 (s, 9 H, $C(CH_3)_3$).

***N*-[(2,2,2-Trichloroethoxy)carbonyl]-*S*-(chloromethyl)-L-cysteine Dimethyl Acetal (23).** The same procedure was followed as described for **22**. Compound **20** (475 mg, 1.29 mmol) and NaOMe (1.35 mL 1 N methanolic solution) gave, via the thiol **21**, 244 mg (50%) of **23**: R_f 0.44 (EtOAc/*n*-hexane, 1/1, v/v); ^{1}H NMR δ 5.44 (br d, 1 H, NH), 4.78 (s, 2 H, SCH_2Cl), 4.69 (s, 2 H, CH_2CCl_3), 4.37 (d, 1 H, $HC(OMe)_2$), 4.15–3.77 (m, 1 H, $CHCH_2S$), 3.41 (s, 6 H, 2 OCH_3), 3.18–2.67 (AB part of ABX spectrum, 2 H, $CHCH_2S$).

***N*-[(*tert*-Butyloxy)carbonyl]-*S*-(chloromethyl)-L-cysteine Methyl Ester (26a).** The same procedure was followed as described for **22**. Compound **25a** (6.5 g, 23 mmol) gave, via the thiol derivative, 5.9 g (89%) of the chloromethyl sulfide **26a**: oil; R_f 0.52 (EtOAc/*n*-hexane, 1/1, v/v); CIMS (100 eV) *m/z* (relative intensity) 286 ($[M + 3]^+$, 3.65), 284 ($[M + 1]^+$, 9.72), 230 (17), 228 (40), 192 (28), 186 (22), 184 (49), 148 (100); ^{1}H NMR δ 5.30 (br d, 1 H, NH), 4.71 (s, 2 H, SCH_2Cl), 4.70–4.51 (m, 1 H, CHCOOMe), 3.78 (s, 3 H, OCH_3), 3.29 and 3.15 (AB part of ABX spectrum, 2 H, ^2J = 14.0 Hz, J = 4.9 Hz, J = 5.7 Hz, SCH_2CH), 1.42 (s, 9 H, $C(CH_3)_3$).

***N*-[(*tert*-Butyloxy)carbonyl]-*S*-(chloromethyl)-D-cysteine Methyl Ester (26b).** The same procedure was followed as described for **22**. Compound **25b** (6.5 g, 23 mmol) gave, via the thiol derivative, 6.0 g (92%) of the chloromethyl sulfide **26b**. Identical spectroscopic data as for **26a**.

5-Methoxy-3-[2-[*N*-[[2-(trimethylsilyl)ethoxy]carbonyl]-*N*-hydroxyamino]ethyl]indole (28). 2-(Trimethylsilyl)ethyl chloroformate[15] (8.12 g, 45 mmol) was added at room temperature dropwise to a stirred solution of **11** (6.2 g, 30 mmol) in CH_2Cl_2/dioxane (150 mL). After completion of the reaction (2 h), as was monitored by TLC ($CHCl_3$/MeOH, 93/7, v/v), most of the solvent was removed by evaporation in vacuo. The residue was dissolved in dichloromethane and subsequently washed with saturated $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was subjected to column chromatography (EtOAc/*n*-hexane, 40/60, v/v) to give 7.94 g (76%) of **28**: R_f 0.41 ($CHCl_3$/MeOH, 93/7, v/v); EIMS (70 eV) *m/z* (relative intensity) 350 (M^+, 15), 233 ($[M - C_5H_{13}OSi]^+$, 23), 218 (27), 174 ($[C_{11}H_{12}NO]^+$, 26, 173 (60), 160 ($[C_{10}H_{10}NO]^+$, 100); ^{1}H NMR δ 7.96 (br s, 1 H, NH), 7.26 (d, 1 H, ^3J = 9.0 Hz, C(7)H), 7.11–6.80 (m, 3 H, C(2), C(4), and C(6)H), 6.71 (br s, 1 H, OH), 4.14–3.80 (m, 4 H, CH_2N and CH_2O), 3.88 (s, 3 H, OCH_3), 3.12 (t, 2 H, C(3)-CH_2), 0.91–0.72 (m, 2 H, CH_2Si), 0.00 (s, 9 H, $Si(CH_3)_3$).

General Procedure for the Coupling of TEOC-Protected *N*-Hydroxytryptamines with Chloromethyl Sulfides. Compound 32. Sodium hydride was added to a cooled (−10 °C) stirred

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solution of **27**[1] (960 mg, 3 mmol) in dry DME (15 mL) in an argon atmosphere. The reaction mixture was allowed to warm to room temperature (H_2 evolution occurred). To the resulting clear solution was added NaI (450 mg, 3 mmol) at once, and then a solution of **22** (1123 mg, 3.75 mmol) in DME (15 mL) was added. After completion of the reaction (5 h), as was monitored by TLC (EtOAc/*n*-hexane, 1/1, v/v), the alkylated product **29** was not isolated but Bu_4NF (9 mL, 1 N solution in THF) was added. The reaction mixture was stirred overnight, after which it was diluted with EtOAc (50 mL) and subsequently washed with saturated $NaHCO_3$, 1 N HCl, and brine. The organic layer was dried ($MgSO_4$), and the solvent was evaporated in vacuo. The crude reaction product was subjected to column chromatography (EtOAc/*n*-hexane, 30/70, v/v) to give 988 mg (75%) of **32**: oil; R_f 0.44 (EtOAc/*n*-hexane, 1/1, v/v); $[\alpha]^{22}_D$ −23.6° (*c* = 2.75, methanol); CIMS (100 eV) *m/z* (relative intensity) 440 ($[M + 1]^+$, 60), 352 ($[C_{16}H_{21}N_3O_4S + 1]^+$, 67), 189 ($[C_{11}H_{13}N_2O]^+$, 37), 176 (100), 144 ($[C_{10}H_{10}N]^+$, 61), 130 ($[C_9H_8N]^+$, 70); ^1H NMR δ 8.16 (br s, 1 H, NH), 7.67–7.02 (m, 5 H, indole C(2)H and C(4)–C(7)H), 5.98 (br s, 1 H, HNO), 5.05 (br d, 1 H, NHBOC), 4.91 (s, 2 H, OCH_2S), 4.42 (d, 1 H, $CH(OMe)_2$), 4.09–3.85 (m, 1 H, $CHCH_2S$), 3.40 (s, 6 H, 2 OCH_3), 3.40–2.64 (m, 6 H, indole C(3)CH_2CH_2N and $CHCH_2S$), 1.48 (s, 9 H, $C(CH_3)_3$).

Compound 30a. Procedure A. The same procedure was followed as described for **32**. Compound **27** (1 g, 3.13 mmol), NaH (82 mg, 3.34 mmol), NaI (470 mg, 3.13 mmol), and **26a** (1 g, 3.5 mmol) gave after column chromatography (EtOAc/*n*-hexane, 35/65, v/v) 248 mg (35%) of **35**, 610 mg (34%) of **30a**, and 593 mg (59%) of starting material **27**.

Compound 35: CIMS (100 eV) *m/z* (relative intensity) 202 ($[M + 1]^+$, 70), 146 (100), 102 ($[M - BOC + 1]^+$, 79); ^1H NMR δ 7.02 (br s, 1 H, NH), 6.17 (s, 1 H, C=CH), 5.77 (d, 1 H, *J* = 1.5 Hz, C=CH), 3.83 (s, 3 H, OCH_3), 1.47 (s, 9 H, $C(CH_3)_3$).

Compound 30a: oil; R_f 0.34 (EtOAc/*n*-hexane, 1/2, v/v); $[\alpha]^{22}_D$ −17.6° (*c* = 2.1, methanol); CIMS (100 eV) *m/z* (relative intensity) 568 ($[M + 1]^+$, 1), 567 (M^+, 2), 468 (9), 440 (15), 144 ($[C_{10}H_{10}N]^+$, 68), 130 ($[C_9H_8N]^+$, 48), 57 ($[C_4H_9]^+$, 100); ^1H NMR δ 8.04 (br s, 1 H, NH), 7.68–7.02 (m, 5 H, indole C(2)H and C(4)–C(7)H), 5.60 (br d, 1 H, NHBOC), 4.89 (s, 2 H, OCH_2S), 4.69–4.38 (m, 1 H, CHCOOMe), 4.12–3.72 (m, 4 H, CH_2N and $SiCH_2CH_2O$), 3.76 (s, 3 H, OCH_3), 3.26–2.90 (m, 4 H, indole C(3)-CH_2 and $CHCH_2S$), 1.41 (s, 9 H, $C(CH_3)_3$), 1.00–0.68 (m, 2 H, CH_2Si), 0.00 (s, 9 H, $Si(CH_3)_3$).

Procedure B. Sodium hydride (356 mg, 14.8 mmol) was added to a cooled (−10 °C) stirred solution of **27**[1] (5 g, 15.6 mmol) in dry DME (75 mL) in an argon atmosphere. The reaction mixture was allowed to warm to room temperature (H_2 evolution occurred). The resulting clear solution was added dropwise to a stirred solution of **26a** (5.9 g, 20.8 mmol) and NaI (5 g, 33.3 mmol) in DME (75 mL). After stirring for 24 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc and subsequently washed with 0.1 N HCl and brine. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$) to give 7.5 g (85%) of **30a**. Spectroscopic data vide supra.

Compound 30b. Via procedure B as described for **30a** with **27**[1] (5 g, 15.6 mmol), NaH (356 mg, 14.8 mmol), chloromethyl sulfide **26b** (5.9 g, 20.8 mmol), and NaI (5 g, 33.3 mmol) in DME (150 mL) gave after column chromatography ($CHCl_3$) 7.4 g (84%) of **30b**: $[\alpha]^{22}_D$ +21.4° (*c* = 3.7, methanol); further spectroscopic data are identical with that of **30a**.

Compound 31. Via procedure B as described for **30a** with **28** (1.6 g, 4.6 mmol), NaH (105 mg, 4.37 mmol), the chloromethyl sulfide **26b** (2 g, 6.9 mmol), and NaI (1.5 g, 10 mmol) in DME (30 mL) gave after column chromatography ($CHCl_3$) 2.43 g (88%) of **31**: oil; R_f 0.52 ($CHCl_3$/MeOH, 97/3, v/v); $[\alpha]^{22}_D$ +16.7° (*c* = 3.6, methanol); CIMS (100 eV) *m/z* (relative intensity) 598 ($[M + 1]^+$, 0.23), 597 (M^+, 0.22), 543 (0.33), 499 (0.75), 470 (1.3), 57 ($[C_4H_9]^+$, 100); ^1H NMR δ 7.93 (br s, 1 H, NH), 7.23 (d, 1 H, *J* = 9.0 Hz, C(7)H), 7.03–6.74 (m, 3 H, C(2), C(4), and C(6)H), 5.61 (br d, 1 H, HNBOC), 4.88 (s, 2 H, OCH_2S), 4.67–4.42 (m, 1 H, CHCOOMe), 4.14–3.59 (m, 4 H, CH_2N and $SiCH_2CH_2O$), 3.87 (s, 3 H, indole C(5)-OCH_3), 3.78 (s, 3 H, $COOCH_3$), 3.18–2.97 (m, 4 H, indole C(3)-CH_2 and $CHCH_2S$), 1.40 (s, 9 H, $C(CH_3)_3$), 1.00–0.64 (m, 2 H, $SiCH_2$), 0.00 (s, 9 H, $Si(CH_3)_3$).

General Procedure for the Removal of the TEOC Group. Compound 33a. A solution of **30a** (6.2 g, 10.9 mmol), Bu_4NCl (9 g, 33 mmol), and $KF{\cdot}2H_2O$ (4.1 g, 44 mmol) in dry acetonitrile (200 mL) was stirred for 10 h at 55 °C. The solvent was evaporated in vacuo. The residue was dissolved in EtOAc and successively washed with water, saturated NH_4Cl, and brine. The organic layer was dried ($MgSO_4$), and the solvent was evaporated in vacuo. The crude reaction product was subjected to column chromatography ($CHCl_3$) to give 3.94 g (85%) of **33a**: oil; R_f 0.38 (EtOAc/*n*-hexane, 1/1, v/v); $[\alpha]^{22}_D$ −8.6° (*c* = 1.85, methanol), CIMS (100 eV) *m/z* (relative intensity) 424 ($[M + 1]^+$, 27), 368 (34), 338 (8), 324 (15), 189 ($[C_{11}H_{13}N_2O]^+$, 47), 144 ($[C_{10}H_{10}N]^+$, 100), 130 ($[C_9H_8N]^+$, 72), 57 ($[C_4H_9]^+$, 89); ^1H NMR δ 8.06 (br s, 1 H, NH), 7.63–7.00 (m, 5 H, indole C(2)H and C(4)–C(7)H), 6.08 (br s, 1 H, HNO), 5.91 (br d, 1 H, NHBOC), 4.82 (s, 2 H, OCH_2S), 4.71–4.51 (m, 1 H, CHCOOMe), 3.71 (s, 3 H, OCH_3), 3.37–2.82 (m, 6 H, indole C(3)-CH_2CH_2 and $CHCH_2S$), 1.41 (s, 9 H, $C(CH_3)_3$).

Compound 33b. Via the same procedure as described for **33a** with **30b** (6.2 g, 10.9 mmol), Bu_4NCl (9 g, 33 mmol) and $KF{\cdot}2H_2O$ (4.1 g, 44 mmol) in dry acetonitrile (200 mL) gave after column chromatography ($CHCl_3$) 4.00 g (86%) of **33b**: $[\alpha]^{22}_D$ +9° (*c* = 3.2, methanol); further spectroscopic data are identical with that of **33a**.

Compound 34. Via the same procedure as described for **33a** with **31** (2.25 g, 3.75 mmol), Bu_4NCl (3.07 g, 11.25 mmol) and $KF{\cdot}2H_2O$ (1.4 g, 15 mmol) gave after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 1.38 g (81%) of **34**: oil; R_f 0.42 ($CHCl_3$/MeOH, 97/3, v/v); $[\alpha]^{22}_D$ +5.8° (*c* = 4.5, methanol); CIMS 100)V) *m/z* (relative intensity) 454 ($[M + 1]^+$, 9), 453 (M^+, 3), 398 (18), 354 (12), 219 (28), 191 (33), 174 ($[C_{11}H_{12}NO]^+$, 100), 160 ($[C_{10}H_{10}NO]^+$, 54); ^1H NMR δ 8.02 (br s, 1 H, NH), 7.26 (d, 1 H, C(7)H), 7.09–6.80 (m, 3 H, C(2), C(4), and C(6)H), 6.11 (br s, 1 H, HNO), 5.94 (br d, 1 H, NHBOC), 4.90 and 4.85 (AB spectrum, 2 H, ^2J = 11.9 Hz, OCH_2S), 4.68–4.51 (m, 1 H, CHCOOMe), 3.86 (s, 3 H, OCH_3), 3.71 (s, 3 H, $COOCH_3$), 3.41–2.90 (m, 6 H, indole C(3)-CH_2CH_2 and $CHCH_2S$), 1.44 (s, 9 H, $C(CH_3)_3$).

Cyclization Attempt of 32. Compound 36. A solution of **32** (110 mg, 0.25 mmol) and TFA (114 mg, 1 mmol) in dichloromethane (12 mL) was stirred for 2 days. The reaction mixture was washed with 0.1 N $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$) to give unidentified products, 28 mg (25%) starting material (**32**), and 21 mg (24%) of diastereomer a and 21 mg (24%) of diastereomer b of **36**.

Diastereomer a: CIMS (100 eV) *m/z* (relative intensity) 352 ($[M + 1]^+$, 23), 320 (56), 189 ($[C_{11}H_{13}N_2O]^+$, 39), 176 (100), 144 ($[C_{10}H_{10}N]^+$, 65), 130 ($[C_9H_8N]^+$, 88); ^1H NMR δ 8.27 (br s, 1 H, indole NH), 7.67–7.03 (m, 5 H, C(2), C(4)-C(7)H), 6.46 (br s, 1 H, NH), 6.21 (br s, 1 H, HNO), 5.37 (d, 1 H, *J* = 6 Hz, OCH(OMe)), 4.90 and 4.81 (AB spectrum, 2 H, ^2J = 12 Hz, OCH_2S), 3.92 (m, 1 H, $NCHCH_2$), 3.49 (s, 3 H, OCH_3), 3.31 (t, 2 H, CH_2NO), 3.08–2.68 (m, 4 H, $NCHCH_2$, indole C(3)-CH_2).

Diastereomer b: CIMS (100 eV) *m/z* (relative intensity) 352 ($[M + 1]^+$, 18), 320 (41), 189 ($[C_{11}H_{13}N_2O]^+$, 21), 176 (68), 144 ($[C_{10}H_{10}N]^+$, 88), 130 ($[C_9H_8N]^+$, 100); ^1H NMR δ 8.24 (br s, 1 H, indole NH), 7.64–7.05 (m, 5 H, C(2), C(4)-C(7)H), 6.29 (br s, 1 H, NH), 5.93 (br s, 1 H, HNO), 5.11 (d, 1 H, *J* = 2.2 Hz, OCH(OMe)), 4.88 (s, 2 H, OCH_2S), 3.71 (br t, 1 H, $NCHCH_2$), 3.49 (s, 3 H, OCH_3), 3.32 (t, 2 H, CH_2NO), 3.04 (t, 2 H, indole C(3)-CH_2), 2.82–2.51 (m, 2 H, $NCHCH_2$).

General Procedure of Cyclization. (1*R*,13b*S*)-1-[[(*tert*-Butyloxy)carbonyl]amino]-1,2,7,8,13,13b-hexahydro-[1,6,2]-oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole (38a) and (1*R*,13b*R*)-1-[[(*tert*-Butyloxy)carbonyl]amino]-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]-pyrido[3,4-*b*]indole (39a). To a cooled (−70 °C) stirring solution of **33a** (2 g, 4.73 mmol) in dichloromethane (200 mL) in an argon atmosphere was added dropwise DIBAL (6.5 mL of a 1.5 M solution in toluene, diluted with 20 mL dichloromethane) in 30 min. After completion of the reaction (30 min) as was monitored by HPLC (Waters RCM 8×10, reversed phase, CH_3CN/H_2O, 60/40), the reaction mixture was cooled to −90 °C and TFA (8 g, 70 mmol) was added at once. After the reaction mixture was stirred for 30 min it was poured into 250 mL of a 0.5 N aqueous HCl solution. The organic layer was separated, and the water

layer was washed with dichloromethane. The combined organic layers were washed with water and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (EtOAc/*n*-hexane, 20/80, v/v) to yield 604 mg (34%) of **38a** and 425 mg (24%) of **39a**.

Compound 38a: amorphous white solid, crystallization attempts failed; R_f 0.56 (EtOAc/*n*-hexane, 1/2, v/v); $[\alpha]^{22}_D$ +7.4° (*c* = 2.15, methanol); CIMS (100 eV) *m/z* (relative intensity) 376 ($[M + 1]^+$, 3), 375 (M^+, 6), 344 (7), 232 (10), 202 (31), 137 (32), 135 (97), 133 (100); ^{1}H NMR (400 MHz) δ 9.98 (br s, 1 H, NH), 7.45–7.42 (m, 2 H, C(9)H and C(12)H), 7.18–7.05 (m, 2 H, C(10)–C(11)H), 6.24 (br d, 1 H, *J* = 8.6 Hz, HNBOC), 5.26 (d (A part of AB spectrum), 1 H, ^2J = 11.4 Hz, C(4)H_A), 4.77 (dd, (B part of AB spectrum), 2 H, ^2J = 11.4 Hz and *J* = 1.6 Hz, C(4)H_B), 4.52–4.49 (m, 1 H, C(1)H), 4.13 (br s, 1 H, C(13b)H), 3.78 (br d, 1 H, ^2J = 14.8 Hz, C(7)H), 3.54 (m, 1 H, C(2)H), 3.07 (m, 1 H, C(2)H), 2.96 (m, 1 H, C(7)H), 2.82 (m, 1 H, C(8)H), 2.77 (m, 1 H, C(8)H), 1.52 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (400 MHz) δ 156.28 (C=O), 136.59 (C(12a)), 132.57 (C(13a)), 126.00 (C(8b)), 121.61 (C11)), 119.21 (C(10)), 118.00 (C(9)), 111.52 (C(12)), 107.49 (C(8a)), 80.45 ($OC(Me)_3$), 74.84 (C(4)), 73.44 (C(13b)), 54.89 (C(1)), 54.59 (C(7)), 32.79 (C(2)), 28.40 ($C(CH_3)_3$), 21.14 (C(8)).

Compound 39a: mp 214–216 °C (EtOAc/*n*-hexane); R_f 0.40 (EtOAc/*n*-hexane, 1/2, v/v); $[\alpha]^{22}_D$ +93.8° (*c* = 1.6, methanol); UV (MeOH) λ_{max} 224, 273.5 (sh), 282, 289.5 nm; CIMS (100 eV) *m/z* (relative intensity) 376 ($[M + 1]^+$, 19), 375 (M^+, 26), 320 (44), 276 (54), 232 (35), 202 (24), 186 (100), 149 (45), 57 (50); ^{1}H NMR (400 MHz) δ 8.56 (br s, 1 H, NH), 7.42 (d, 1 H, ^3J = 7.7 Hz, C(12)H), 7.27 (d, 1 H, *J* = 7.7 Hz, C(9)H), 7.10–6.98 (m, 2 H, C(10)–C(11)H), 5.69 (br d, 1 H, *J* = 10.4 Hz, HNBOC), 4.94 and 4.81 (AB spectrum, 2 H, ^2J = 9.1 Hz, C(4)H_2), 4.66 (m, 2 H, C(1)H), 4.15 (br s, 1 H, C(13b)H), 3.60 (m, 1 H, C(7)H), 3.32 (d, 1 H, *J* = 14.5 Hz, C(2)H), 3.15 (m, 1 H, C(7)H), 2.97 (m, 1 H, C(8)H), 2.83–2.76 (dd, 2 H, C(2)H and C(8)H), 1.17 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{19}H_{25}N_3O_3S$ (MW 375.427): C, 60.78; H, 6.71; N, 11.19. Found: C, 60.62; H, 6.60; N, 11.02.

(1*S*,13b*R*)-1-[[(*tert*-Butyloxy)carbonyl]amino]-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole (38b) and (1*S*,13b*S*)-1-[[(*tert*-Butyloxy)carbonyl]amino]-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole (39b). In an analogous fashion **33b** (2 g, 4.73 mmol), DIBAL (2 equiv), and TFA (8 g) gave after column chromatography (EtOAc/*n*-hexane, 20/80, v/v) 621 mg (35%) of **38b** and 327 mg (18%) of **39b**.

Compound 38b: amorphous white solid; $[\alpha]^{22}_D$ −8.3° (*c* = 3.75, methanol); further spectroscopic data are identical with that of **38a**.

Compound 39b: mp 214–216 °C (EtOAc/*n*-hexane); $[\alpha]^{22}_D$ −94.2° (*c* = 3.8, methanol); further spectroscopic data are identical with that of **39a**.

(1*S*,13b*R*)-1-[[(*tert*-Butyloxy)carbonyl]amino]-10-methoxy-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole (41) and (1*S*,13b*S*)-1-[[(*tert*-Butyloxy)carbonyl]amino]-10-methoxy-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole (40). In an analogous fashion **34** (1.25 g, 2.76 mmol), DIBAL (2 equiv), and TFA (5 mL) gave after column chromatography ($CHCl_3$) 637 mg (57%) of **41** and 268 mg (24%) of **40**.

Compound 41: mp 145–146 °C (CH_2Cl_2/*n*-hexane); R_f 0.78 ($CHCl_3$/MeOH, 97/3, v/v); $[\alpha]^{22}_D$ −23.1° (*c* = 5.1, methanol); CIMS (100 eV) *m/z* (relative intensity) 406 ($[M + 1]^+$, 83), 405 (M^+, 47), 374 ($[M - CH_3O]^+$, 12), 350 (51), 320 (29), 306 (36), 262 (27), 232 (65), 216 ($[C_{12}H_{12}N_2O]^+$, 100); ^{1}H NMR δ 9.82 (br s, 1 H, NH), 7.32 (dd, 1 H, *J* = 9.0 Hz, C(12)H), 6.89 (s, 1 H, C(9)H), 6.81 (dd, 1 H, *J* = 9.0 Hz, C(11)H), 6.22 (br d, 1 H, *J* = 9.1 Hz, HNBOC), 5.26 (d (A part of AB spectrum), 1 H, ^2J = 11.4 Hz, C(4)H_A), 4.80 (dd (B part of AB spectrum), 1 H, ^2J = 11.4 Hz, *J* = 1.8 Hz, C(4)H_B), 4.62–4.37 (m, 1 H, C(1)H), 4.12 (br s, 1 H, C(13b)H), 3.84 (s, 3 H, OCH_3), 3.77–3.34 (m, 2 H, C(7)H and C(2)H), 3.22–2.61 (m, 4 H, C(7)H, C(2)H, and C(8)H_2), 1.49 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{20}H_{27}N_3O_4S$ (MW 405.518): C, 59.24; H, 6.71; N, 10.36. Found: C, 59.11; H, 6.74; N, 10.31.

Compound 40: mp 184–220 °C dec; R_f 0.53 ($CHCl_3$/MeOH, 97/3, v/v); $[\alpha]^{22}_D$ −55.3° (*c* = 4.05, methanol); CIMS (100 eV) *m/z* (relative intensity) 406 ($[M + 1]^+$, 57), 405 (M^+, 44), 350 (51), 320 (17), 306 (50), 262 (32), 232 (17), 216 ($[C_{12}H_{12}N_2O]^+$, 100); ^{1}H NMR δ 8.46 (br s, 1 H, NH), 7.17 (d, 1 H, *J* = 9.0 Hz, C(12)H), 6.91–6.71 (m, 2 H, C(9)H and C(11)H), 5.70 (br d, 1 H, HNBOC), 4.97 and 4.81 (AB spectrum, 2 H, ^2J = 9.0 Hz, C(4)H_2), 4.72–4.56 (m, 1 H, C(1)H), 4.14 (br s, 1 H, C(13b)H), 3.86 (s, 3 H, OCH_3), 3.61 (m, 1 H, C(7)H), 3.34 (m, 1 H, C(2)H), 3.13 (m, 1 H, C(7)H), 2.94 (m, 1 H, C(8)H), 2.83–2.76 (m, 2 H, C(2)H and C(8)H), 1.20 (s, 9 H, $C(CH_3)_3$). Anal. Calcd for $C_{20}H_{27}N_3O_4S$ (MW 405.518): C, 59.24; H, 6.71; N, 10.36. Found: C, 58.99; H, 6.62; N, 10.27.

Removal of the BOC group. (1*R*,13b*S*)-1-Amino-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole (42a). A solution of **38a** (604 mg, 1.61 mmol), chlorotrimethylsilane (351 mg, 3.22 mmol), and NaI (483 mg, 3.22 mmol) in acetonitrile (200 mL) was stirred at room temperature during 3 h. The solvent was evaporated in vacuo, and the residue was dissolved in dichloromethane and subsequently washed with water and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was subjected to column chromatography (EtOAc/*n*-hexane, 1/1, v/v) to yield 423 mg (95%) of **42a**: mp 147–149 °C (CH_2Cl_2/*n*-hexane); R_f 0.24 ($CHCl_3$/MeOH, 97/3, v/v); $[\alpha]^{22}_D$ −28.8° (*c* = 1.7, methanol); CIMS (100 eV) *m/z* (relative intensity) 276 ($[M + 1]^+$, 27), 275 (M^+, 20), 232 (21), 203 (27), 202 (32), 186 (91), 172 (40), 171 (100), 169 (35), 144 (35); ^{1}H NMR (400 MHz) δ 10.05 (br s, 1 H, NH), 7.46 (d, 1 H, *J* = 7.7 Hz, C(12)H)), 7.32 (d, 1 H, *J* = 8.1 Hz, C(9)H), 7.15–7.04 (m, 2 H, C(10)–C(11)H), 4.93 (br s, 2 H, C(4)H_2), 3.71–3.60 (br d, 3 H, C(13b)H, C(1)H, and C(7)H), 3.13–2.77 (m, 5 H, C(2)H_2, C(7)H, and C(8)H_2), 1.59 (br s, 2 H, NH_2); ^{13}C NMR (400 MHz) δ 135.78 (C(12a)), 133.73 (C(13a)), 126.08 (C(8b)), 121.28 (C(11)), 118.98 (C(10)), 118.06 (C(9)), 110.98 (C(12)), 106.79 (C(8a)), 73.08 (C(4)), 69.02 (C(13b)), 59.70 (C(1)), 54.98 (C(7)), 37.97 (C(2)), 20.81 (C(8)). Anal. Calcd for $C_{14}H_{17}N_3OS$ (MW 275.374): C, 61.06; H, 6.22; N, 15.26. Found: C, 60.99; H, 6.10; N, 15.11.

(−)-Debromoeudistomin L ((−)-1e). Via the same procedure as described for **38a** with **39b** (327 mg, 0.87 mmol), chlorotrimethylsilane (190 mg, 1.74 mmol) and NaI (260 mg, 1.74 mmol) gave after column chromatography ($CHCl_3$/MeOH, 98/2, v/v) 225 mg (94%) of **1e**: amorphous white solid; crystallization attempts were unsuccessful; R_f 0.06 ($CHCl_3$/MeOH, 97/3, v/v); $[\alpha]^{22}_D$ −115.3° (*c* = 3.0, methanol); UV (MeOH) λ_{max} 223, 273.5 (sh), 282, 289 nm; CIMS (100 eV) *m/z* (relative intensity) 276 ($[M + 1]^+$, 3), 275 (M^+, 1), 232 (11), 231 (14), 212 (19), 211 (21), 203 (82), 202 (100), 186 (34), 172 (22), 171 (32), 169 (37), 144 (44); ^{1}H NMR (400 MHz) δ 8.33 (br s, 1 H, NH), 7.47 (d, 1 H, *J* = 7.6 Hz, C(12)H), 7.32 (d, 1 H, *J* = 8.0 Hz, C(9)H), 7.17–7.13 (m, 2 H, C(10)–C(11)H), 4.92 and 4.80 (AB spectrum, 2 H, ^2J = 9.0 Hz, C(4)H_2), 4.08 (br s, 1 H, C(13b)H), 3.57 (m, 1 H, C(7)H), 3.51 (br s, 1 H, C(1)H), 3.31 (d, 1 H, ^2J = 14.4 Hz, C(2)H), 3.13 (m, 1 H, C(7)H), 2.94 (m, 1 H, C(8)H), 2.84 (dd, 1 H, ^2J = 14.3 Hz, *J* = 5.7 Hz, C(2)H), 2.81 (m, 1 H, C(8)H), 1.85 (br s, 2 H, NH_2); ^{13}C NMR (400 MHz) δ 136.90 (C(12a)), 130.67 (C(13a)), 126.32 (C(8b)), 122.13 (C(11)), 119.82 (C(10)), 118.26 (C(9)), 111.16 (C(12)), 110.96 (C(8a)), 71.36 (C(4)), 69.93 (C(13b)), 53.98 (C(7)), 50.73 (C(1)), 33.99 (C(2)), 20.67 (C(8)).

(1*S*,13b*R*)-1-Amino-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole (42b). Via the same procedure as described for **38a** with **38b** (621 mg, 1.66 mmol), chlorotrimethylsilane (362 mg, 3.32 mmol) and NaI (500 mg, 3.32 mmol) gave after column chromatography (EtOAc/*n*-hexane, 1/1, v/v) 404 mg (89%) of **42b**: mp 146–149 °C (CH_2Cl_2/*n*-hexane); $[\alpha]^{22}_D$ +23.2° (*c* = 3.8, methanol); further spectroscopic data are identical with that of **42a**.

(+)-Debromoeudistomin L ((+)-1e). Via the same procedure as described for **38a** with **39a** (425 mg, 1.13 mmol), chlorotrimethylsilane (246 mg, 2.26 mmol) and NaI (340 mg, 2.26 mmol) gave after column chromatography ($CHCl_3$/MeOH, 98/2, v/v) 303 mg (98%) of (+)-**1e**: amorphous white solid; crystallization attempts were unsuccessful; $[\alpha]^{22}_D$ +111.4° (*c* = 2.1, methanol); further spectroscopic data are identical with that of (−)-**1e**.

(1*S*,13b*S*)-1-Amino-10-methoxy-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2′,3′:1,2]pyrido[3,4-*b*]indole ((−)-1f). Via the same procedure as described for **38a** with **40** (155 mg, 0.38

mmol), chlorotrimethylsilane (83 mg, 0.76 mmol) and NaI (114 mg, 0.76 mmol) gave after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 111 mg (95%) of (-)-**1f**: amorphous white solid; crystallization attempts were unsuccessful; R_f 0.36 ($CHCl_3$/MeOH, 93/7, v/v); $[\alpha]^{22}_D$ -76.6° (c = 2.7, methanol); CIMS (100 eV) m/z (relative intensity) 306 ($[M + 1]^+$, 13), 276 (37), 232 (100), 216 ($[C_{12}H_{12}N_2O_2]^+$, 19), 201 (49), 200 ($[C_{12}H_{12}N_2O]^+$, 22), 199 (20), 174 (30); ^1H NMR (400 MHz) δ 8.22 (br s, 1 H, NH), 7.19 (d, 1 H, J = 9.0 Hz, C(12)H), 6.92-6.76 (m, 2 H, C(9)H and C(11)H), 4.93 and 4.81 (AB spectrum, 2 H, ^2J = 9.0 Hz, C(4)H_2), 4.06 (br s, 1 H, C(13b)H), 3.83 (s, 3 H, OCH_3), 3.56 (m, 1 H, C(7)H), 3.42 (m, 1 H, C(1)H), 3.27 (m, 1 H, C(2)H), 3.09 (m, 1 H, C(7)H), 2.95 (m, 1 H, C(8)H), 2.83 (dd, 1 H, C(2)H), 2.81 (m, 1 H, C(8)H), 1.87 (br s, 2 H, NH_2).

(1*S*,13b*R*)-1-Amino-10-methoxy-1,2,7,8,13,13b-hexahydro-[1,6,2]oxathiazepino[2',3':1,2]pyrido[3,4-*b*]indole (43). Via the same procedure as described for **38a** with **41** (110 mg, 0.27 mmol), chlorotrimethylsilane (59 mg, 0.54 mmol) and NaI (81 mg, 0.54 mmol) gave after column chromatography (EtOAc/*n*-hexane, 40/60, v/v) 65 mg (78%) of **43**: crystallized from CH_2Cl_2/*n*-hexane; mp 104-105 °C; R_f 0.24 ($CHCl_3$/MeOH, 93/7, v/v); $[\alpha]^{22}_D$ +3° (c = 2.0, methanol); CIMS (100 eV) m/z (relative intensity) 306 ($[M + 1]^+$, 48), 262 (30), 233 (38), 232 (54), 216 ($[C_{12}H_{12}N_2O_2]^+$, 100), 201 (95), 200 ($[C_{12}H_{12}N_2O]^+$, 51), 199 (35); ^1H NMR (400 MHz) δ 9.87 (br s, 1 H, NH), 7.23 (d, 1 H, J = 9.0 Hz, C(12)H)), 6.94-6.73 (m, 2 H, C(9)H and C(11)H), 4.94 (br s, 2 H, C(4)H_2), 3.87 (s, 3 H, OCH_3), 3.77-3.51 (br m, 3 H, C(13b)H, C(1)H, and C(7)H), 3.13-2.77 (m, 5 H, C(2)H_2, C(7)H, and C(8)H_2), 1.69 (br s, 2 H, NH_2).

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Registry No. (-)-**1e**, 110597-53-0; (+)-**1e**, 120330-76-9; (-)-**1f**, 126645-51-0; **7**, 16620-52-3; **9**, 68935-49-9; **11**, 126645-25-8; **12**, 126645-26-9; **12** (R_2 = OH), 2766-43-0; **13**, 126645-27-0; **13** (R_2 = OH), 88050-18-4; **14**, 126645-28-1; **14** ((+)-MTPA ester), 126663-64-7; **15**, 126645-29-2; **16**, 126645-30-5; **17**, 126645-31-6; **18**, 126645-32-7; **19**, 126645-33-8; **20**, 126645-34-9; **21**, 126645-35-0; **22**, 126645-36-1; **23**, 126645-37-2; **24a**, 56926-94-4; **24b**, 126645-21-4; **24b** (R_3 = OH), 95715-85-8; **25a**, 126645-38-3; **25b**, 126645-22-5; **26a**, 126645-39-4; **26b**, 126645-23-6; **27**, 125109-08-2; **28**, 126645-40-7; **29**, 126645-41-8; **30a**, 126645-42-9; **30b**, 126645-24-7; **31**, 126645-43-0; **32**, 126645-44-1; **33a**, 126645-45-2; **33b**, 126645-47-4; **33b**, 126645-47-4; **34**, 126645-46-3; **35**, 55477-80-0; **35** (isomer 1), 126645-48-5; **36** (isomer 2), 126645-49-6; **38a**, 126722-18-7; **38b**, 126722-19-8; **39a**, 120296-29-9; **39b**, 120330-77-0; **40**, 126645-50-9; **41**, 126722-20-1; **42a**, 126783-64-0; **42b**, 126722-21-2; **43**, 126722-22-3.

Repetitive Imidazole Synthesis Using an Immobilized Imidazole Template

Darshan Ranganathan,* Ramesh Rathi, and Shashi Sharma

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

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A model representing the chemical simulation of the ATP-imidazole cycle programmed to continuous production of the daughter imidazoles from the immobilized parent imidazole template is presented. 6-Chloropurine was anchored to polystyrene by reaction with Ⓟ-CH_2Cl. Hydrolysis of the product purine followed by alkylation with phenacyl bromide afforded 1-phenacyl-9-polymer-bound hypoxanthine, which on treatment with benzylamine and *p*-TsOH produced the expected daughter molecule, 1-benzyl-5-phenylimidazole in 30% yield and the polymer-bound 5-amino-4-(benzylcarbamoyl)imidazole, which, in turn, was transformed to the template 9-polymer-bound hypoxanthine by treatment with MsOH followed by formamide. To prove the concept of the continuous generation of the daughter molecule, the regenerated parent template was processed through a second cycle using the same protocol when the expected daughter product 1-benzyl-5-phenylimidazole was obtained in 14% yield. Polymer-bound adenine when subjected to a similar protocol failed to yield any daughter molecule. Endeavours to prepare polymer-linked 4-oxoquinazoline and anthranilic acid are also reported here.

The ATP-imidazole cycle associated with the biosynthesis of ATP, GTP, and histidine exemplifies a unique synthetic strategy of Nature, wherein a daughter imidazole is produced from a mobile parent imidazole template in a cyclic pathway.[1] We have recently[2] shown that the salient features of the ATP-imidazole cycle could be demonstrated using either hypoxanthine or adenine as the carrier molecule. It was also demonstrated that the operating part of the cycle, namely, the vicinal disposition of an amino and a carboxyl group, could be transplanted onto a more amenable anchor. Thus, anthranilic acid via transformation to 4-oxoquinazoline performed as an excellent template for the production of N-protected 5-substituted imidazoles.

It could be readily perceived that were such parent templates to be linked to a polymer backbone, the daughter product alone would be in the mobile phase, thus making continuous use of the immobilized template possible. In the present work we have endeavored to anchor the already established templates, hypoxanthine, adenine, and 4-oxoquinazoline, to a polymer support and to demonstrate the capability of these systems in generating daughter molecules.

Macroporous polystyrene crosslinked with 2% divinylbenzene was chloromethylated with chloromethyl methyl ether in the presence of catalytic amounts of $SnCl_4$.[3] The extent of incorporation of the functional group was, in this case, estimated on the basis of weight

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