Recl. Trav. Chim. Pays-Bas **114**, 27–34 (1995)
SSDI 0165-0513(94)00079-4

0165-0513/95/01027-08$09.50

Transformations of the tetracyclic skeleton of eudistomins by neighboring-group participation in the Mitsunobu reaction

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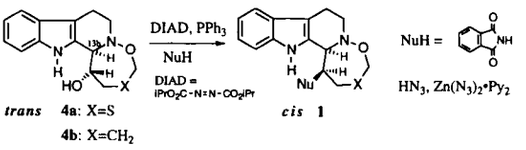
(Received August 8, 1994)

Abstract. Mitsunobu reaction mediated introduction of nitrogen nucleophiles into *trans* 1-hydroxy eudistomins afforded in high yields rearranged products instead of the anticipated *cis* eudistomins due to neighboring group participations. Transannular interaction in the 6,5,6,7-membered tetracyclic ring system of the sulfur atom in the 1,6,2-oxathiazepine ring, to give a thiiranium ion containing intermediate, was followed by intermolecular attack of the present nucleophiles to give a 6,5,6,6-membered tetracyclic ring system, now with a 1,5,2-oxathiazine ring. Substitution of the hydroxyl group in a *trans* 1-hydroxy dethia carba eudistomin derivative (*i.e.* with a 1,2-oxazepine ring) also gave rearranged products due to transannular interaction from the bridgehead nitrogen atom, to give via an aziridinium ion intermediate,products with a 6,5,7,6-membered tetracyclic ring system containing an 1,2-oxazine ring.

Introduction

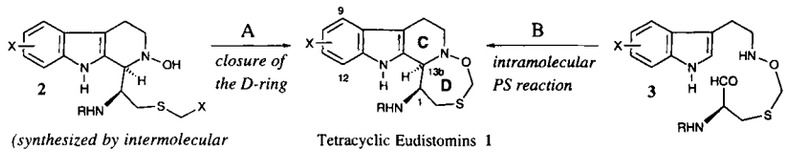
Tetracyclic eudistomins (*i.e.* **1**, R = H in Scheme I), first isolated from the colonial tunicate *Eudistoma Olivaceum*, may have potential as antiviral or antitumor drugs[1]. After the first isolation in 1984 by *Rinehart* et al., a few total syntheses have been reported. *Nakagawa* and *Still*[2] used the diastereoselective *inter*molecular Pictet-Spengler (PS) reaction to give **2**. However, closure of the seven membered 1,6,2-oxathiazepine ring was accomplished in a maximum 22% yield (route A, Scheme 1). *Kirkup* and our group used the *intra*molecular PS reaction from **3** to close the CD ring systems in a simultaneous fashion in high yields (route B, Scheme 1)[3]. However, the intramolecular PS approach resulted in an unfavorable *trans*[4] diastereoselectivity (d.e. 24–100%)[5]. Our previously published structure-activity relationship study revealed that biological activity is only displayed by the natural 1 *S*, 13b*S*(*cis*) diastereomer.[6] Therefore a high-yield *cis* diastereoselective route is desirable for future biological and structure-activity relationship investigations.



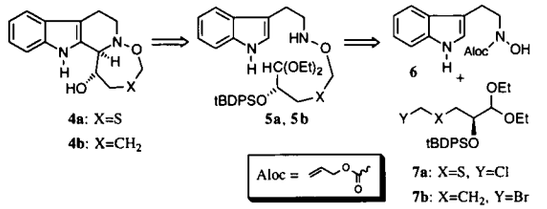
Scheme 2. Mitsunobu reaction mediated introduction of nucleophiles with inversion in trans *1-hydroxy eudistomins to give* cis *eudistomins*

It was reasoned that we could take advantage of the *trans* diastereoselectivity in the intramolecular PS approach. As depicted in Scheme 2, diastereoselective synthesis of a *trans*-1-hydroxy eudistomin derivative **4** followed by the introduction of the amino functionality by an S_N2-type process, such as the Mitsunobu reaction, should give eudistomins 5 with the natural C(1)H-C(13b)H *cis* configuration. Herein we describe the results of this attempted diastereoselective approach, leading to eudistomin derivatives with a rearranged tetracyclic skeleton.

† Deceased 20th November 1993



Scheme 1. Strategies for closure of the oxathiazepine ring in eudistomins



Scheme 3. Retrosynthetic analysis for the synthesis of the required 1-hydroxy-eudistomin derivatives

As outlined in Scheme 2, in addition to access to the natural eudistomins (X = S) the possibility of synthesizing the dethia eudistomin analog (X = CH_2) was also investigated.

Mainly because of its well-documented, exclusive, S_N2 type substitution,the Mitsunobu reaction was chosen for introduction of the amino group[7]. Also, activation of the hydroxyl group takes place *in situ* in the Mitsunobu approach, avoiding an extra synthetic step. Appropriate nitrogen nucleophiles, which can be conveniently transformed into a primary amine group are phthalimide[8] and hydrazoic acid[9] or the easy-to-handle salt zinc dipyridinezinc azide[10].

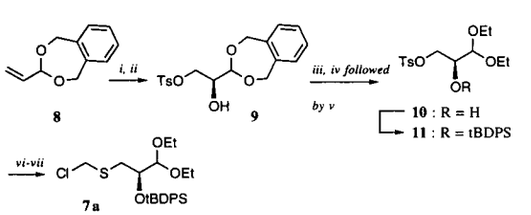
In Scheme 3, the retrosynthetic approach to the required *trans*-1-hydroxy eudistomins **4** is presented. The precursor-protected acetals **5** can be built up from the *N*-hydroxytryptamine derivative **6** and the fragments **7**.

Results and discussion

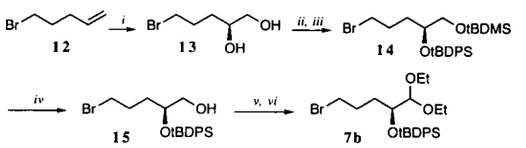
Synthesis of the fragments 7a, 7b

Both synthons **7a** and **7b** were synthesized by application of the novel Sharpless asymmetric dihydroxylation (AD) procedure[11].

Synthesis of (*R*)-2-(*tert*-butyldiphenylsilyloxy)-3-(chloromethylthio)propanal diethyl acetal **7a** (Scheme 4) was accomplished starting from the known AD of acrolein benzene-1,2-dimethanol acetal **8** to give the corresponding diol in high yields with an e.e. of 97% after one crystallization[12]. After selective transformation of the primary hydroxyl group into the tosylate to give **9**, the benzodioxepine moiety, which is essential to achieve high e.e.'s in the AD of acrolein type acetals, was removed by catalytic hydrogenation. Protection of the resulting aldehyde as a diethyl acetal gave **10** in nearly quantitative yield from **9**[13]. The remaining secondary alcohol was protected as a *tert*-butyldiphenylsilyl (tBDPS) ether to give **11** in 94% yield. Transformation of the tosylate **11** into the chloromethyl sulfide **7a** was accomplished using our previously described procedure via the thioacetate[3c]. Liberation of the thiol by transesterification with sodium methanolate was followed by treatment of the thiol with bromochloromethane and powdered KOH, employing tri-



Scheme 4. Asymmetric synthesis of (R)-2-(tert-*butyldiphenylsilyloxy)-3-(chloromethylthio)propanal diethyl acetal* **7a**. *Reagents*: (i) *AD-mix* α, *tBuOH* / H_2O = 1 / 1, 4°C; (ii) *TsCl, pyridine, 0°C;* (iii) *Pd / C* H_2, *EtOH;* (iv) $HC(OEt)_3$, *TsOH, EtOH;* (v) *tBDPS-Cl, imidazole, DMF*; (vi) *CsSAc, DMF;* (vii) *NaOMe, MeOH;* (viii) $BrCH_2Cl$, *KOH(s),* Et_3BnNCl



Scheme 5. Sharpless AD-based synthesis of (S)-5-bromo-2-(tert-*butyldiphenyl-silyloxy)pentanal diethyl acetal* **7b**. *Reagents:* (i) *AD-mix* α, $^tBuOH / H_2O$ = 1 / 1, 4°C; (ii) *tBDMS-Cl, imidazole, DMF;* (iii) *tBDPS-Cl, imidazole, DMF;* (iv) *PPTS, EtOH, 40°C, 12 h.;* (v) $(COCl)_2$, *DMSO,* CH_2Cl_2, Et_3N; (vi) $HC(OEt)_3$, *EtOH, TsOH*

ethylbenzylammonium chloride as a phase-transfer catalyst to give the chloromethyl sulfide **7a** in an overall yield of 48% from the tosylate **11**.

The synthesis of (*S*)-5-bromo-2-(*tert*-butyldiphenylsilyloxy)-pentanal diethyl acetal **7b** (Scheme 5) started from the commercially available 5-bromo-1-pentene **12**. Treatment of **12** with Sharpless' AD cocktail (AD-mix α, see ref. 11) afforded diol **13** in an outstanding yield of 94% but with a disappointing e.e. of 65%[14].

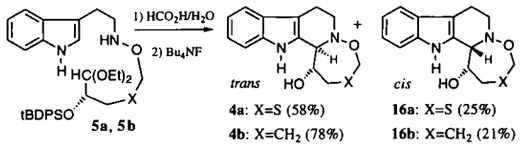
The primary hydroxyl group in **13** was protected as the *tert*-butyldimethylsilyl (tBDMS) ether followed by protection of the secondary hydroxyl group as a tBDPS ether to give **14** in 64% overall yield. Selective removal of the tBDMS group employing the weakly acidic pyridinium *p*-toluenesulfonate (PPTS) proceeded sluggishly and the primary alcohol **15** was obtained, after purification by column chromatography, in only 53% yield[15]. Subsequent Swern oxidation and protection of the obtained aldehyde as a diethyl acetal by treatment with triethyl orthoformate in ethanol gave **7b** in 94% overall yield from **15**. From the results described hereafter it can be concluded that even in the aldehyde stage the optical purity is preserved[16].

Nucleophilic coupling of 3-[2-[(allyloxycarbonyl)-hydroxy-amino]ethyl]indole (6) *with the chiral fragments* 7a *and* 7b

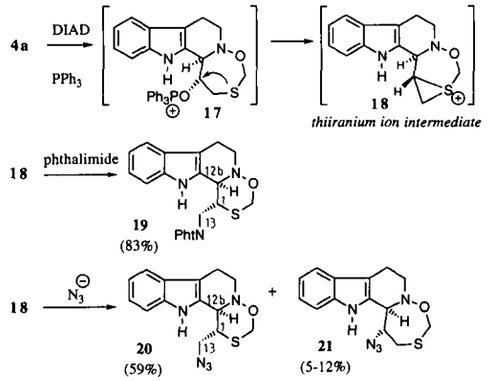
N_b-Aloc-N_b-hydroxytryptamine **6** was synthesized from N_b-hydroxytryptamine[3c] and *N*-(allyloxycarbonyloxy)succinimide (Aloc-ONSu) in 86% yield. Both N_b-Aloc protected N_b-alkoxytryptamines **5a,5b** (Scheme 3) were synthesized by gradually adding a solution of the sodium alkoxide of **6** to a solution of the halogenides **7a,7b** in freshly distilled 1,2-dimethoxyethane. Sodium iodide was added to generate *in situ* the more reactive alkyl iodides. The iodomethyl sulfide from **7a** was consumed within 3 hours at room temperature whereas the primary alkyl iodide from **7b** needed stirring at 50°C for three days to reach 50% conversion. Removal of the Aloc protective groups by treatment with palladium(II)acetate, triphenylphosphine and triethylammonium formate afforded **5a** and **5b** in overall yields of 65% and 44%, respectively, from **7a,7b**[17].

Pictet-Spengler (PS) cyclization

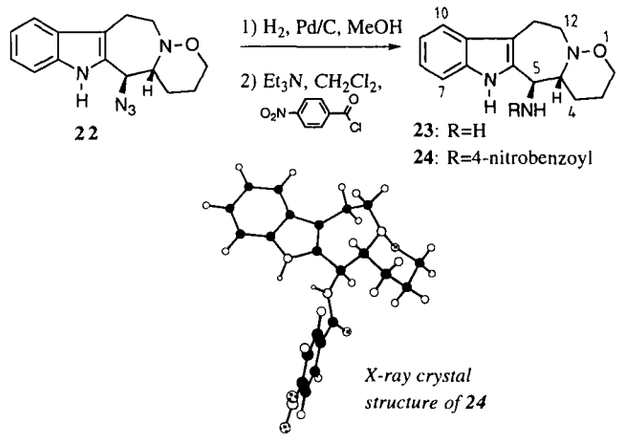
The PS reaction of the α-(*tert*-butyldiphenylsilyloxy) diethyl acetals **5a,5b** proceeded smoothly in formic acid/water (9/1, v/v) at room temperature within 1 hour. After work-up, the tBDPS groups were removed by treat-



Scheme 6. Intramolecular Pictet-Spengler cyclization



Scheme 7. Mitsunobu reaction induced rearrangement of the 1,6,2-oxathiazepine ring



Scheme 8. Structure proof for compound **22** *by X-ray crystal structure; determination of compound* **24**

ment with tetrabutylammonium fluoride to give the *cis/trans* tetracyclic compounds **16a / 4a** and **16b / 4b** in yields of 82% and 99%, in ratios of 30/70[18] and 21/78, respectively, as determined by analytical HPLC (Scheme 6). Separation of the diastereomers was readily accomplished by flash column chromatography.

Cis/trans assignments of the new dethia eudistomin derivatives **4b** and **16b** were made on the basis of 400-MHz ^{1}H-NMR spectroscopy data. Similar to the ^{1}H-NMR data of the naturally derived eudistomin analogs **4a** and **16a** (Scheme 6), a downfield shift was observed for the indole NH proton (*i.e.* $\Delta\delta$ = 1.1 ppm) in the ^{1}H-NMR spectra of the desthia *trans* diastereomer **4b**, due to the presence of a hydrogen bond between the equatorially orientated 1-hydroxy group and the indole NH proton[19]. The NOESY spectrum of the *cis* diastereomer **16b** suggested the same conformation of the 1,2-oxazepine ring as is found for the [1,6,2]-oxathiazepine ring in natural eudistomins[20]; for H(13b)β[21], connectivities were found with both H(2)β and H(7)β, indicating that these protons are all axially orientated in space (see Scheme 1 for numbering). Also, connectivity between H(1)β and the indole N proton was present, indicating that H(1)β occupies an equatorial position.

Introduction of the amino group via the Mitsunobu reaction

Initial Mitsunobu reactions were carried out with alcohol **4a**(X = S) and phthalimide. The yield of phthalimide introduction was optimized to 83%. However, instead of the desired *cis* eudistomin of the type **1**, formation of the ring contracted product **19** had occurred (Scheme 7).

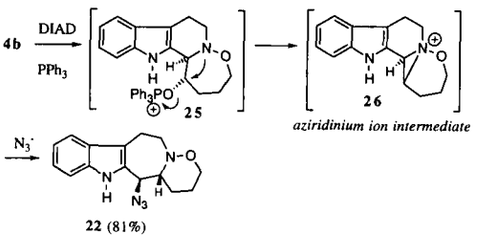
Apparently, after formation of the phosphonium salt **17** transannular anchimeric assistance had taken place from the sulfur atom positioned β with respect to the phosphonium leaving group[22]. Evidently, this *intra*molecular nucleophilic attack of the sulfur atom, to give the thiiranium ring containing intermediate **18**, is faster than formation of the desired product by *inter*molecular attack of the available nitrogen nucleophile. In **18**, nucleophilic attack at the thiiranium ring is possible at the secondary or tertiary (electrophilic) carbon atoms. With phthalimide as the nucleophile only product **19** was isolated, originating from attack at the less hindered secondary carbon atom to give the more favored six-membered ring. When the small azide nucleophile was used, both possible products **20** and **21** were isolated.

That a rearrangement had occurred within the 7-membered 1,6,2-oxathiazepine ring, to give a six-membered 1,5,2-oxathiazine ring, was evident from the 400 MHz ^{1}H-NMR data of **19**. If the anticipated *cis* eudistomin skeleton had been formed, one should have expected H(1) as a multiplet in the δ4.5-5 ppm region. The double doublet at δ4.86 ppm must, however, be part of an AB system due to the large geminal coupling constant of 14.1 Hz. The proton present at δ4.86 has a geminal relationship to the proton which resonates at δ4.15 ppm. Also *both* these geminal protons have a NOE contact with the proton at the saturated bridgehead carbon atom [*i.e.* C(12b)] therefore excluding the possibily that these geminal protons are located at C(2) in the eudistomin skeleton. The e.e.'s of the tetracyclic structures **19, 20** and **21** have not been determined.

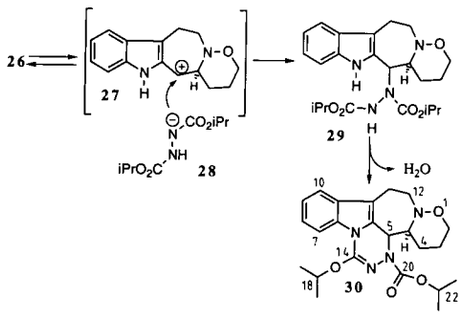
The Mitsunobu reaction of alcohol **4b** with hydrazoic acid was accomplished in 81% yield. However, comparison of the 90 MHz NMR spectrum of the isolated azide (**22**) with the ^{1}H-NMR spectrum of the *trans* dethia carba-eudistomin azide, synthesized by *Kirkup* and coworkers, revealed some differences suggesting the formation of the alternative product **22**[23]. The incontrovertible proof of structure **22** was given by X-ray crystal structure determination (Scheme 8). For this purpose, the azide group was reduced by catalytic hydrogenation with Pd/C to give **23** in 49% yield followed by treatment with 4-nitrobenzoyl chloride to give **24** in 63% yield of which a single crystal was obtained suitable for X-ray crystal structure determination.

Apparently, as described above for **4a** (Scheme 7), transannular neighboring-group participation had occurred. After formation of the phosphonium leaving group in **25**, the bridgehead nitrogen (which is highly nucleophilic due to the α-effect of the alkoxy substituent)[24] attacks to form the pentacyclic aziridinium intermediate **26** (Scheme 9). Subsequent attack of the azide anion seems to take place exclusively at the benzylic position (*vide infra*) yielding the azepine **22** in 81% yield[25].

The optical purity of **23**, determined by analytical HPLC[26], was 78%, corresponding with an e.e. of 56%. The first chiral intermediate **13** had an e.e. of 65%, implying that in



Scheme 9. Mitsunobu reaction induced rearrangement of the 1,2-oxazepine ring



Scheme 10. Incorporation of 1,2-bis(isopropoxycarbonyl)hydrazine after the Mitsunobu reaction induced rearrangement of the 1,2-oxazepine ring

the synthesis sequence of **13** to **23** (8 steps) only 9% of the optical purity was sacrificed.

Finally, we report that the Mitsunobu reaction of phthalimide with alcohol **4b** resulted in a similar outcome. In the isolated product **30** (42% yield) the elements of 1,2-bis(isopropoxycarbonyl)hydrazine **28** were present as determined by ^{13}C-, ^{1}H-NMR and mass spectroscopy. This type of side reaction is known and it was reported that this process only occurs when the reacting alcohol can form *stable* carbocation intermediates[27]. Apparently, after formation of the aziridium ion **26** ring opening occurs to yield the relatively stable secondary and benzylic carbocation in **27** (Scheme 10). Attack of hydrazide **28** gives the intermediate compound **29**, immediately followed by an intramolecular condensation to give **30**.

The reason that this side reaction is only found with the imide-type nucleophile and not with the azide ion, is probably a combination of two factors: the presence of an intermediate carbocation and the difference in pK_a of the nucleophiles. Firstly, the phosphonium salt **25** (see Scheme 9) *rapidly* forms the aziridinium intermediate **26**. Rearrangement towards the carbocation-containing **27** is now faster than reaction with the present nucleophiles[28].

The position of the equilibrium shown in Scheme 11 is decisive for the outcome of the Mitsunobu reaction.

In the case of NuH = imide the more nucleophilic **28** is present in sufficient concentrations to form the hydrazide adduct **29** whereas, with NuH = hydrazoic acid, the equilibrium is immediately shifted to the right, leading to product **22** exclusively.

An interesting adventitious circumstance is the resemblance of the skeleton of the tetracyclic azepines **22-24** (Scheme 8) with the naturally occurring ngouniensines **31**, which were isolated as the major indole alkaloids of *Strychnos ngouniensis* (Chart 1)[29]. The herein described

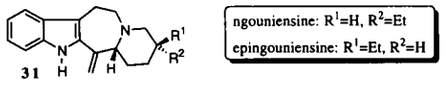


Chart 1. Naturally occurring ngouniensines

Mitsunobu reaction induced rearrangement of tetracyclic pyrido[3,4-*b*]indole skeletons might be a feasible approach to the synthesis of the series of N_b-oxo-ngouniensine natural products.

The biological activities of the unique eudistomin derivatives with a rearranged tetracyclic skeleton described herein will be published elsewhere.

Scheme 11

Experimental

Proton magnetic resonance spectra were measured on a Bruker WH-90, Bruker AC-100 or a Bruker AM-400 spectrometer. Chemical shift values are reported as δ-values relative to tetramethylsilane as an internal standard; deuteriochlorofom was used as solvent. Mass spectra were obtained with a double-focussing VG 7070E spectrometer. High resolution mass spectra were taken for compounds **4b, 16b, 19, 20** and **23** as a final proof. For the determination of optical rotations a Perkin-Elmer 241 polarimeter was used. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. All solvents were commercially obtained and used unpurified unless stated otherwise. Thin-layer chromatography (TLC) was carried out using silica gel F-254 plates (thickness 0,25 mm). Spots were visualized with a UV hand lamp, iodine vapor, ninhydrine solution containing 3 ml acetic acid and 0.3 g ninhydrin in 100 ml 1-butanol, or Cl_2-TDM[30]. Column chromatography was carried out using silica 60H (Merck). Analytical HPLC analysis was carried out with a LKB 2150 system equipped with a Waters RCM 8×10, reversed phase C-18 column and a Pye Unicam LC-UV detector. All compounds described were purified by column chromatography when needed and were pure according to TLC, NMR and HPLC.

*(S)-2-hydroxy-3-(p-tolysulfonyloxy)propanal diethyl acetal (**10**).*

To **9**[12] (8.6 g,23.6 mmol) in ethanol (150 ml) under a nitrogen atmosphere was added 10% Pd(C) (500 mg) and the resulting suspension was stirred in a hydrogen atmosphere until all starting material had been consumed (2-48 h) according to TLC ($R_{f(9)}$ 0.38, $R_{f(aldehyde)}$ 0.21, EtOAc/hexanes, 1/1, v/v). The Pd(C) catalyst was removed by filtration over hyflo and subsequently triethyl orthoformate (25 ml) and TFA (0,2 ml) were added. After standing for 1,5 h satd $NaHCO_3$ (50 ml) was added and the volatiles were removed *in vacuo*. After purification of the residue by column chromatography (EtOAc/hexanes, 1/2, v/v) 7.4 g (99%) of **10** was obtained as a colorless oil. R_f 0.46 (EtOAc/hexanes, 1/1, v/v). EIMS-(70eV), *m/z* (relative intensity): 317 ($[M-1]^+$, 0.01), 273 ($[M-OC_2H_5]^+$, 0.4), 103 ($[HC(OC_2H_5)_2]^+$, 100), 91 ($[C_7H_7]^+$, 26), 75 ($[C_3H_7O_2]^+$, 50). ^{1}H-NMR (90 MHz) δ: 7.80 and 7.35 (AB, 4H, J_{AB} 8.4 Hz, C_6H_4), 4.47 (d, 1H, *J*5.7 Hz, OCHO), 4.20 and 4.11 (AB part of ABX spectrum, 2H, J_{AX} 3.4 Hz, J_{BX} 5.5 Hz and J_{AB} 10.2 Hz, OCH_2CH), 3.95-3.36 (m, 5H, $2xOCH_2CH_3$ and OCH_2CH), 2.42 (s, 4H, H_3CPh and OH), 1.20 and 1.17 (dt, 6H, *J* 7.0 Hz, $2xOCH_2CH_3$).

*(R)-2-(tert-Butyldiphenylsilyl)-3-(p-tolylsulfonyloxy)propanal diethyl acetal (**11**).*

To 10 (1.41 g, 4.4 mmol) and imidazole (0.6 g, 8.8 mmol) in dimethylformamide (25 ml), tert-butyldiphenylsilyl chloride (1.46 g, 5.3 mmol) was added. After standing at room temperature overnight, the reaction mixture was diluted with EtOAc (100 ml) and successively washed with citric acid (20% in water), water (2x) and brine. After drying ($MgSO_4$) the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/4, v/v) to yield 2.29 g (94%) of **11** as a colorless oil. R_f 0.37 (EtOAc/hexanes, 1/4, v/v). α_D^{22} −8.09 (*c* 5.26, MeOH). EIMS (70eV), *m/z* (relative intensity): 353 ($[M-203]^+$, 14), 199 ($[M-Ph_2SiOH]^+$, 100), 103 ($[HC(OC_2H_5)_2]^+$, 31), 91 ($[C_7H_7]^+$, 9), 75 ($[C_3H_7O_2]^+$, 10). ^{1}H-NMR (90 MHz) δ: 7.76-7.56 and 7.39-7.19 (m, 14H, $2xC_6H_5$ and C_6H_4), 4.24 (d, 1H, *J* 4.6 Hz, OCHO), 4.16-3.74 (m, 3H, OCH_2CH), 3.67-3.08 (m, 4H, $2xOCH_2CH_3$), 2.40 (s, 3H, H_3CPh), 1.16 and 0.92 (dt, 6H, *J* 7.3 Hz, $2xOCH_2CH_3$), 1.04 and 1.00 [ds, 9H, $C(CH_3)_3$].

*(R)-2-(tert-Butyldiphenylsilyloxy)-3-(chloromethylthio)propanal diethyl acetal (**7a**).*

The chloromethyl sulfide **7a** was synthesized via the corresponding thioacetate as described in Ref. 3c. The thioacetate was obtained from **11** and purified by column chromatography (EtOAc/hexanes, 1/9, v/v) in 70% yield (3.5 g scale) as a yellowish oil. R_f 0.53 (EtOAc/hexanes, 1/4, v/v). α_D^{22} −30.0 (*c* 2.6, MeOH). ^{1}H-NMR (90 MHz) δ: 7.78-7.62 and 7.44-7.30 (m, 10H, $2xC_6H_5$), 4.24 (d, 1H, *J* 4.4 Hz, OCHO), 3.98-3.81 (m, 1H, CH_2CH), 3.72-3.12 (m, 6H, $2xOCH_2CH_3$ and CH_2CH), 2.24 (s, 3H, $COCH_3$), 1.17 and 0.95 (dt, 6H, *J* 7.2 Hz, $2xOCH_2CH_3$), 1.04 [s, 9H, $C(CH_3)_3$]. Liberation of the thiol was accomplished in 70% yield. ^{1}H-NMR (90 MHz) δ:

7.82-7.67 and 7.47-7.30 (m, 10H, 2xC_6H_5), 4.50 (d, 1H, *J* 5.6 Hz, OCHO), 3.95-3.80 (m, 1H, CH_2CH), 3.76-3.24 (m, 4H, 2xOCH_2CH_3), 2.70-2.55 (m, 2H, CH_2CH), 1.53 (dd, 1H, *J* 7.8 Hz and *J* 9.0 Hz, SH), 1.18 and 1.00 (dt, 6H, *J* 7.2 Hz, 2xOCH_2CH_3), 1.07 [s, 9H, $C(CH_3)_3$].
Alkylation of the thiol by treatment with bromochloromethane/KOH/triethylbenzyl-ammoniumchloride gave chloromethyl sulfide **7a** in 97% yield. ^{1}H-NMR (90 MHz) δ: 7.80-7.67 and 7.47-7.31 (m, 10H, 2xC_6H_5), 4.55 (s, 2H, SCH_2Cl), 4.36 (d, 1H, *J* 4.6 Hz, OCHO), 4.04-3.88 (m, 1H, CH_2CH), 3.75-3.16 (m, 4H, 2xOCH_2CH_3), 3.09-2.74 (m, 2H, CH_2CH), 1.19 and 0.97 (dt, 6H, *J* 7.1 Hz, 2xOCH_2CH_3), 1.05 [s, 9H, $C(CH_3)_3$].

(S)-5-bromopentane-1,2-diol (**13**)

Asymmetric approach: To a well stirred solution of *tert*-butyl alcohol (100 ml) and water (100 ml) was added potassium osmate(VI) dihydrate (14.5 mg, 0.039 mmol), hydroquinidine 1,4-phthalazinediyl diether (150 mg, 0.19 mmol), potassium carbonate (8.2 g, 59 mmol) and potassium ferricyanide (19.3 g, 59 mmol). After a clear two-layer system appeared, the solution was cooled to 0°C. To this well-stirred, cold, two-phase system was added 5-bromo-1-pentene **12** (2.4 ml, 3.0 g, 20 mmol) in one portion. After stirring in the refrigerator at 4°C overnight sodium sulfite (30.0 g, 24 mmol) was added to the bright yellow suspension, and the reaction mixture was allowed to warm up to room temperature. After stirring for an additional hour EtOAc (200 ml) and brine (25 ml) were added to the, now almost colorless, reaction mixture. The organic phase was separated and the water phase was subsequently extracted with 3 portions of EtOAc. The combined organic phases were washed with brine and dried ($MgSO_4$). After removal of the solvent *in vacuo* 3.43 g (94%) of crude 13 was obtained as a yellowish oil. To determine the e.e. (*vide infra*) a small part of the reaction mixture was further purified by column chromatography (MeOH/CH_2Cl_2, 3/97, v/v) to obtain pure 13 as a colorless oil. R_f 0.26 (MeOH/CH_2Cl_2, 7/93, v/v). α_D^{22} −10.7 (*c* 3.92, MeOH, e.e. 65%). ^{1}H-NMR (90 MHz) δ: 3.87-3.32 (m, 5H, OCH_2CH and $BrCH_2$), 3.24 (br s, 2H, exchangeable, 2xOH), 2.20-1.44 (m, 4H, $BrCH_2CH_2CH_2$). EIMS(70eV), *m/z* (relative intensity): 153 ([M-CH_3O]$^+$, 17), 151 ([M-CH_3O]$^+$, 17), 71 (84), 43 ([C_2H_3O]$^+$, 100).

Symmetric approach (to obtain both enantiomers to facilitate the e.e. determination). To a stirred solution of 5-bromo-1-pentene **12** (0.25 ml, 0.32 g, 2.1 mmol) and 4-methylmorpholine *N*-oxide (0.42 g, 3.55 mmol) in THF/H_2O (2/1, v/v, 10 ml), osmium tetroxide (2.6 ml of a 2.5% solution in *tert*-butyl alcohol) was added. After stirring for 12 h sodium sulfite (0.4 g, 3.2 mmol) was added and the reaction mixture was filtered over hyflo. After evaporation of the volatiles *in vacuo* the residue was subjected to column chromatography (MeOH/CH_2Cl_2, 3/97, v/v) to yield 35 mg (9%) of racemic **13**. The reason for the low yield is probably the quality of the used osmium tetroxide solution.

Determination of the enantiomeric purity. Both optically active and racemic **28** were converted into their di-(*R*)-MTPA esters following the procedure described by *Mosher* and coworkers.[13] Determination of the e.e. by ^{1}H-NMR (400 MHz) gave an e.e. of 64%, calculated from the double doublets at 4.56 ppm (*R*-enantiomer) and 4.28 ppm (*S*-enantiomer). ^{19}F-NMR (376 MHz, 325 K) gave an e.e. of 66%, calculated from the singlets at 8.50/8.28 ppm (*R*-enantiomer) and 8.36/8.31 ppm (*S*-enantiomer).

*(S)-5-Bromo-1-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)-pentane* (**14**)

To a stirred solution of **13** (2.84 g, 15.5 mmol) in dimethylformamide (25 ml) was added imidazole (1.6 g, 23 mmol) and *tert*-butyldimethylsilyl chloride (2.34 g, 15.5 mmol). After standing of the reaction mixture overnight *tert*-butylchlorodiphenylsilane (4.27 g, 15.5 mmol) together with another portion of imidazole (1.6 g, 23 mmol) were added. After additional stirring overnight the volatiles were evaporated under high vacuum. The residue was dissolved in EtOAc (50 ml) and subsequently washed with 2 portions of 10% citric acid, satd $NaHCO_3$ and brine. After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/8, v/v) affording 5.0 g (64%) of **14** as a colorless oil. R_f 0.69 (EtOAc/hexanes, 1/4, v/v). ^{1}H-NMR (90 MHz) δ: 7.87-7.71 (m, 4H, 2xPhH_2), 7.55-7.43 (m, 6H, 2xPhH_3), 4.10-3.35 (m, 5H, OCH_2CH and $BrCH_2$), 2.18-1.64 (m, 4H, $BrCH_2CH_2CH_2$), 1.18 [s, 9H, $C(CH_3)_3$], 0.93 [s, 3H, $C(CH_3)_3$], 0.04 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$).

*(S)-5-Bromo-2-(*tert*-butyldiphenylsilyloxy)-pentan-1-ol* (**15**)

To **14** (5.0 g, 9.8 mmol) in dry ethanol (25 ml) was added PPTS (0.82 g, 3.3 mmol). After standing of the reaction mixture overnight no conversion of the starting material was detected by TLC. Subsequent heating of the reaction mixture overnight at 40°C gave complete consumption of the starting material. The volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/4, v/v) to give 2.19 g (53%) of **15** as a colorless oil. R_f 0.31 (EtOAc/hexanes, 1/4, v/v). R_f 0.45 (EtOAc/hexanes, 1/2, v/v). α_D^{22} +5.9 (*c* 2.56, acetone). ^{1}H-NMR (90 MHz) δ: 7.69-7.47 (m, 4H, 2xPhH_2), 7.43-7.22 (m, 6H, 2xPhH_3), 3.82-3.62 (m, 1H, $HOCH_2CH$), 3.42-3.05 (m, 4H, $BrCH_2$ and $HOCH_2$), 1.75-1.43 (m, 4H, $BrCH_2CH_2CH_2$), 0.96 [s, 9H, $C(CH_3)_3$]. CIMS(70eV), *m/z* (relative intensity): 391 ([M-CH_3O]$^+$, 0.07), 389 ([M-CH_3O]$^+$, 0.06), 199 (100).

*(S)-5-Bromo-2-(*tert*-butyldiphenylsilyloxy)-pentanal diethyl acetal* (**7b**)

Oxalyl chloride (0.29 ml, 0.42 g, 3.31 mmol) was dissolved in dichloromethane (25 ml) employing flame-dried glass equipment under an argon atmosphere. After cooling to −75°C, dry DMSO (0.47 ml, 0.51 g, 6.54 mmol) was added over a 5-minute period and the reaction mixture was stirred for 5 min at that temperature. Subsequently **15** (0.92 g, 2.2 mmol), dissolved in dry dichloromethane (5 ml), was added and after additional stirring for 10 min, triethylamine (1.5 ml, 1.1 g, 10.9 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was washed with 10% citric acid, satd $NaHCO_3$, and brine. After drying (Na_2SO_4) the volatiles were evaporated *in vacuo* to yield the crude aldehyde. R_f 0.58 (EtOAc/hexanes, 1/2, v/v). R_f 0.50 (EtOAc/hexanes, 1/6, v/v). ^{1}H-NMR (90 MHz) δ: 9.59 (d, 1H, *J* 1.3 Hz, HCO), 7.72-7.32 (m, 10H, 2xC_6H_5), 4.11-4.02 (m, 1H, CH), 3.56-3.23 (m, 2H, $BrCH_2$), 1.87-1.76 (m, 4H, CH_2CH_2), 1.11 [s, 9H, $C(CH_3)$]. The aldehyde was dissolved in dry ethanol (25 ml), and triethyl orthoformate (2 ml) and $TsOH \cdot H_2O$ ($\approx$ 5 mg) were added. After standing for 3 h satd $NaHCO_3$ (10 ml) was added and the volatiles were evaporated *in vacuo*. The residue was dissolved in EtOAc (50 ml) and washed with water and brine and then dried ($MgSO_4$). After evaporation of the solvent *in vacuo* the residue was subjected to column chromatography (EtOAc/hexanes, 1/8, v/v) to yield 1.02 g (94%) of **7b** as a colorless oil. R_f 0.63 (EtOAc/hexanes, 1/6, v/v). α_D^{22} −5.40 (*c* 2.24, MeOH). ^{1}H-NMR (90 MHz) δ: 7.78-7.66 (m, 4H, 2xPhH_2), 7.42-7.30 (m, 6H, 2xPhH_3), 4.24 [d, 1H, *J* 4.8Hz, $CH(EtO)_2$], 3.84-3.03 [m, 7H, $BrCH_2$, $CHCH(OEt)_2$ and 2xOCH_2CH_3], 2.05-1.50 (m, 4H, $BrCH_2CH_2CH_2$), 1.19 and 0.95 (dt, 6H, *J* 7.1 Hz, 2xOCH_2CH_3), 1.06 [s, 9H, $C(CH_3)_3$]. CIMS(70eV), *m/z* (relative intensity): 449 ([M-CH_3O]$^+$, 0.8), 447 ([M-CH_3O]$^+$, 0.7), 161 (71), 103 ([$HC(OC_2H_5)_2$]$^+$, 100).

3-[2-[(Allyloxycarbonyl)hydroxyamino]ethyl]indole (**6**)

To 3-[2-(hydroxyamino)ethyl]indole[3c] (6.14 g, 35.7 mmol) in dioxane/dichloromethane (150 ml, 1/1, v/v) was added Aloc-ONSu (7.81 g, 39.3 mmol), causing a slight raise in temperature. After 3 h, all starting material had been consumed as indicated by TLC ($CHCl_3$/MeOH, 93/7, v/v). The reaction mixture was concentrated to dryness, dissolved in EtOAc (150 ml) and washed with satd $NaHCO_3$ (2×50 ml) and brine. After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/1, v/v) to yield 8.0 g (86%) of **6** as colorless crystals. mp 79-82°C. R_f 0.40 (EtOAc/hexanes, 1/1, v/v). ^{1}H-NMR (90 MHz) δ: 8.82 (br s, 1H, indole-NH), 7.76-7.52 [m, 1H, indole-C(7)H], 7.42-7.03 [m, 4H, indole-C(2)H and C(4)-C(6)H_3], 5.96-5.54 (m, 1H, H_2C=C*H*-CH_2), 5.19-5.07 (m, 2H, H_2C=CH-CH_2), 4.42 (dt, 2H, *J* 5.8 Hz and *J* 1.0 Hz, H_2C=CH-CH_2), 4-2.5 (very br s, 1H, NOH), 3.94-3.76 [m, 2H, C(3)CH_2CH_2N], 3.20-3.04 [m, 2H, C(3)CH_2CH_2N]. Anal. calcd. for $C_{14}H_{16}N_2O_3 \cdot 1/2H_2O$ (269): C 62.44. H 6.36. N 10.40; found: C 62.66. H 6.19. N 10.34%.

*(S)-2-(*tert*-Butyldiphenylsilyloxy)-3-[[2-(1H-indol-3-yl)ethyl]amino-oxy]methylthiol-propanal diethyl acetal* (**5a**)

Nucleophilic coupling. NaH (72 mg of a 80% oil dispersion, 2.4 mmol) was added to a stirred solution of **6** (630 mg, 2.4 mmol) in freshly distilled DME (20 ml). The suspension was stirred until a clear solution appeared (10–30 min) (hydrogen gas evolved). This solution was added dropwise (over a period of 2–3 h) to a stirred solution of chloromethyl sulfide **7a** (1.12 g, 2.4 mmol) and NaI (360 mg, 2.4 mmol) in freshly distilled DME (50 ml) (after approx. 30 sec. after the addition of NaI, the formation of iodomethyl sulfide was observ-

able by precipitation of the formed NaCl). After additional stirring for 1 h, satd $NaHCO_3$ (5 ml) was added and the suspension was concentrated *in vacuo*. The residue was dissolved in EtOAc (50 ml) and subsequently washed with water and satd NH_4Cl. The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexanes, 1/3, v/v) to give 1.66 g (83%) of N_b-protected **5a** as a colorless oil. R_f 0.18 (EtOAc/hexanes, 1/4, v/v). CIMS-(70eV),*m/z* (relative intensity): 644 ($[M+1\text{-}OC_2H_5]^+$, 0.9), 199 ($[C_{13}H_{11}SiO]^+$, 100), 144 ($[C_{10}H_{10}N]^+$, 11), 130 ($[C_9H_8N]^+$, 27), 103 ($[HC(OC_2H_5)_2]^+$, 38). ^{1}H-NMR (90 MHz) δ: 8.02 (br s, 1H, indole-NH), 7.80-7.56 and 7.39-6.95 [m, 15H, $2xC_6H_5$, indole-C(2)H and C(4)-C(7)H_4], 5.98-5.56 (m, 1H, $H_2C=CH$-CH_2), 5.32-5.07 (m, 2H, H_2C=CH-CH_2), 4.82 (s, 2H, OCH_2S), 4.47-4.32 (m, 3H, H_2C=CH-CH_2 and SCH_2CHCH), 3.96-2.89 (m, 11H, $2xOCH_2CH_3$, indole-C(3)CH_2CH_2 and SCH_2CHCH), 1.16 and 0.94 (dt, 6H, *J* 6.9 Hz, $2xOCH_2CH_3$), 1.05 [s, 9H, $C(CH_3)_3$].

Removal of the Aloc group: The above obtained N_b-Aloc protected product was dissolved in acetonitrile/water (20 ml, 4/1, v/v) and triethylammonium formate (8 g, 19 mmol) was added. An argon stream was passed through the resulting solution for 15 min to remove oxygen, palladium(II) acetate (12 mg, 0.05 mmol) and triphenylphosphine (70 mg, 0.26 mmol) were added. After heating under reflux for 45 min, all starting material had been consumed and subsequently the volatiles were removed *in vacuo*. The residue was dissolved in EtOAc (75 ml) and washed with water (2×50 ml) and dried with brine and $MgSO_4$. The solvent was removed *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/4, v/v) to give 1.13 g (78%) of **5a** as a colorless oil. R_f 0.18 (EtOAc/hexanes, 1/4, v/v). CIMS(70eV), *m/z* (relative intensity): 576 ($[M-30]^+$, 4), 144 ($[C_{10}H_{10}N]^+$, 15), 130 ($[C_9H_8N]^+$, 79), 103 ($[HC(OC_2H_5)_2]^+$, 100). ^{1}H-NMR (90 MHz) δ: 8.00 (br s, 1H, indole-NH), 7.81-7.54 and 7.37-6.96 [m, 15H, $2xC_6H_5$ and indole-C(2)H and C(4)-C(7)H_4], 5.76 (br s, 1H, HNO), 4.69 (s, 2H, OCH_2S), 4.40 (d, 1H, *J* 4.2 Hz, SCH_2CHCH), 4.00-3.86 (m, 1H, SCH_2CHCH), 3.71-2.80 (m, 10H, indole-C(3)CH_2CH_2, SCH_2CHCH and $2xOCH_2CH_3$), 1.16 and 0.97 (dt, 6H, *J* 6.9 Hz, $2xOCH_2CH_3$), 1.07 [s, 9H, $C(CH_3)_3$].

*(S)-2-(*tert*-Butyldiphenylsilyloxy)-5-[[2-(1H-indol-3-yl)ethyl]amino-oxy]-pentanal diethyl acetal (***5b***)*

Nucleophilic coupling: The same procedure was followed as described for **5a**. NaH (120 mg of a 80% oil dispersion, 4.0 mmol), **7b** (2,0 g, 4.0 mmol), NaI (100 mg, 0.7 mmol) and **6** (1.0 g, 3.8 mmol) were stirred, after the addition of the sodium alkoxide from **6** at room temperature, for 3 days at 50°C and gave after work-up and purification by column chromatography (EtOAc/hexanes, 3/7, v/v) 1.28 g (50%) of **5b** as an oil. R_f 0.38 (EtOAc/hexanes, 1/2, v/v). CIMS(70eV), *m/z* (relative intensity): 569 ($[M\text{-}HC(OC_2H_5)_2]^+$, 0.2), 144 ($[C_{10}H_{10}N]^+$, 3), 130 ($[C_9H_8N]^+$, 5), 103 ($[HC(OC_2H_5)_2]^+$, 4), 91 ($[C_7H_7N]^+$, 14), 41 ($[C_3H_5]^+$, 100). ^{1}H-NMR (90 MHz) δ: 8.07 (br s, 1H, indole-NH), 7.80-7.58 [m, 5H, indole-C(7)H and $2xPhH_2$], 7.39-6.99 [m, 10H, $2xPhH_3$ and indole C(2)H and C(4)-C(6)H_3], 6.04-5.62 (m, 1H, $H_2C=CH$-CH_2), 5.34-5.10 (m, 2H, H_2C=CH-CH_2), 4.49 (dt, 2H, *J* 1.2 Hz and *J* 5.6 Hz, H_2C=CH-CH_2), 4.23 [d, 1H, *J* 4.6 Hz, $HC(OEt)_2$], 3.86-2.97 [m, 11H, indole-C(3)-$CH_2CH_2NOCH_2$-, $CHCH(OEt)_2$ and $2xOCH_2CH_3$], 1.89-1.53 (m, 4H, $OCH_2CH_2CH_2CH$-), 1.17 and 0.94 (dt, 6H, *J* 7.2 Hz, $2xOCH_2CH_3$), 1.06 [s, 9H, $C(CH_3)_3$], together with 1.18 g (59%) recovered iodoalkane **7b**.

Removal of the Aloc protective group: The same procedure was followed as described for **5a** to give after purification by column chromatography (EtOAc/hexanes, 1/2, v/v) 980 mg (88%) of **5b** as a colorless oil. R_f 0.26 (EtOAc/hexanes, 1/2, v/v). ^{1}H-NMR (90 MHz) δ: 8.07 (br s, 1H, indole-NH), 7.80-7.57 [m, 5H, indole-C(7)H and $2xPhH_2$], 7.38-7.00 [m, 10H, $2xPhH_3$ and indole C(2)H and C(4)-C(6)H_3], 5.45 (very br s, ONH), 4.24 [d, 1H, *J* 4.8 Hz, $HC(OEt)_2$], 3.81-2.91 [m, 11H, indole-C(3)-$CH_2CH_2NOCH_2$, $CHCH(OEt)_2$ and $2xOCH_2CH_3$], 1.84-1.46 (m, 4H, $OCH_2CH_2CH_2CH$-), 1.25 and 0,94 (dt, 6H, *J* 7.2 Hz, $2xOCH_2CH_3$), 1.05 [s, 9H, $C(CH_3)_3$].

*(1S,13bR)-(***4a***) and (1S,13bS)-1-Hydroxy-1,2,7,8,13,13b-hexahydrol [1,6,2]oxathiazepinol[2',3':1,2]pyrido[3,4-b]indole (***16a***)*

In HCO_2H/H_2O (9/1, v/v, 90 ml) was dissolved **5a** (770 mg, 1.27 mmol). After 1 h the reaction mixture was diluted with EtOAc (100 ml) and neutralized by the careful addition of $NaHCO_3$. The organic layer was then washed with brine and dried ($MgSO_4$), followed by evaporation of the volatiles *in vacuo*. The residue was dissolved in dry THF (25 ml) and tetrabutylammonium fluoride (1.5 ml of a 1 M solution in THF) was added. After 30 min the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/4, v/v) to yield 190 mg (54%) of 4a. α_D^{22} −26.8 (*c* 4.78, EtOAc), and 100 mg (28%) of **16a** α_D^{22} +166.5 (*c* 3.40, EtOAc). Further spectroscopical and analytical data were identical to those published previously (see Ref. 6).

*(1S,13bR)-(***4b***) And (1S,13bS)-1-hydroxy-1,2,3,4,7,8,13,13b-octahydro[1,2]-oxazepino[2',3':1,2]pyrido[3,4-b]indole (***16b***).*

5b (1.2 g, 2.04 mmol) was dissolved in a mixture of formic acid/water (9/1, v/v, 100 ml). After standing at room temperature for 30 min, all starting material had been consumed. The volatiles were evaporated at high vacuum and the residue was dissolved in EtOAc (50 ml) and subsequently washed with satd $NaHCO_3$, water and brine. After drying ($MgSO_4$) and evaporation of the solvent *in vacuo* the residue was dissolved in dry THF (15 ml) and tetrabutylammonium fluoride (2.5 ml of a 1 M solution in THF) was added. After completion of the reaction (30 min) the solvent was evaporated *in vacuo*. The product ratio was determined at this stage by analytical HPLC (acetonitrile/water, 3/7, v/v, flow 1 ml/min, λ 280 nm), retention time (min): **16b** (4.5) and **4b** (5.6). Ratio **16b/4b** 18/82. The residue was subjected to column chromatography (EtOAc/hexanes, 1/2, v/v) to give 413 mg (78%) of **4b** as a white solid. R_f 0.39 (EtOAc/hexanes, 1/1, v/v), 0.22 (EtOAc/hexanes, 1/2, v/v). α_D^{22} −23.2 (*c* 3.40, EtOAc). CIMS(70eV), exact mass calcd for $C_{15}H_{18}N_2O_2$ *m/z*: 258.1368 ($[M]^+$); found: 258.1467; relative intensity: 258 ($[M]^+$, 100), 241 ($[M\text{-}OH]^+$, 12), 169 (78), 144 ($[C_{10}H_{10}N]^+$, 42), 130 ($[C_9H_8N]^+$, 7). ^{1}H-NMR (400 MHz) (all assignments are based on NOESY) δ: 9.00 (br s, 1H, indole NH), 7.47 [d, 1H, *J* 7.7 Hz, C(12)H), 7.32 (d, 1H, *J* 8.0 Hz, C(9)H], 7.14 [t, 1H, *J* 7.4 Hz, C(10)H], 7.07 [t, 1H, *J* 7.4 Hz, C(11)H], 4.12-4.08 [m, 1H, C(1)Hβ], 3.78-3.71 [br m, 3H, C(13b)Hα and C(4)H_2], 3.05-2.92 [m, 2H, C(7)Hα and C(8)Hα], 2.78 [br d, 1H, *J* 13.4 Hz, C(8)Hβ], 2.05-1.95 [m, 2H, C(3)H_2], 1.80-1.73 [m, 2H, C(2)H_2]. Anal. calcd for $C_{15}H_{18}N_2O_2$: C 69.75, H 7.02, N 10.84, found: C 69.59, H 6.95, N 10.57%.

Together with 110 mg (21%) of **16b** as a white solid. R_f 0.30 (EtOAc/hexanes, 1/1, v/v). α_D^{22} +62.3 (*c* 3.10, EtOAc). CIMS(70eV), exact mass calcd for $C_{15}H_{18}N_2O_2$ *m/z*: 258.1368 ($[M]^+$); found: 258.1467; relative intensity: 258 ($[M]^+$, 85), 241 ($[M\text{-}OH]^+$, 12), 227 (41), 169 (84), 149 (100), 144 ($[C_{10}H_{10}N]^+$, 51), 130 ($[C_9H_8N]^+$, 8) ^{1}H-NMR (400 MHz) (all assignments are based on NOESY) δ: 7.91 (br s, 1H, indole NH), 7.46 [d, 1H, *J* 7.7 Hz, C(12)H], 7.29 [d, 1H, *J* 8.0 Hz, C(9)H], 7.15 [t, 1H, *J* 7.4 Hz, C(10)H], 7.09 [t, 1H, *J* 7.4 Hz, C(11)H], 4.31 [br s, 1H, C(1)Hβ], 4.13-4.08 [m, 2H, C(13b)Hβ and C(4)Hα], 3.75 [dt, 1H, *J* 10.6 Hz and *J* 7.6 Hz, C(4)Hβ], 3.56-3.54 [m, 1H, C(7)Hα], 3.08-3.01 [m, 1H, C(7)Hβ], 2.99-2.91 [m, 1H, C(8)Hβ], 2.78 [br d, 1H, *J* 15.2 Hz, C(8)Hα], 2.32-2.24 [m, 1H, C(3)Hα], 2.17-2.09 [m, 1H, C(2)Hα], 2.04-1.95 [m, 2H, C(2)Hβ and OH], 1.69-1.62 [m, 1H, C(3)Hβ].

Introduction of the amino group via the Mitsunobu reaction

*(1R,12bR)-1-(Phthalimidomethyl)-6,7,12,12b-tetrahydro-1H-[1,5,2]-oxathiazinol[2',3':1,2]pyrido[3,4-blindole (***19***).*

To **4a** (100 mg, 0.36 mmol, e.e. 30%), phthalimide mg, 0.54 mmol) and triphenylphosphine (190 mg, 0.72 mmol) in dry THF (0.5 ml), diisopropyl azodicarboxylate (DIAD, 0.11 ml, 110 mg, 0.54 mmol) was added dropwise with a syringe over a period of 5 min causing a slight exothermic reaction. The progress of the reaction was monitored by HPLC (acetonitrile/water, 3/7, v/v, flow 1 ml/min, λ 254 nm), retention time (min): phthalimide (3.0), triphenylphosphine oxide (4.0), 4a (4.8), 19 (6.4) and triphenylphosphine (8.8). After 2 h the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/3, v/v) to yield 129 mg (84%) of **19** as a white amorphous solid which failed to crystallize. R_f 0.47 (EtOAc/hexanes, 1/1, v/v). α_D^{22} +77.6 (*c* 1.65, MeOH), CIMS(70 eV) exact mass calcd for $C_{22}H_{19}N_3O_3S$ *m/z*: 405.1147 ($[M]^+$); found: 405.1149. *m/z* (relative intensity): 405 ($[M]^+$, 0.3), 186 ($[C_{11}H_{10}N_2O]^+$, 3), 144 ($[C_{10}H_{12}N]^+$, 4.3), 130 ($[C_9H_{10}N]^+$, 7.2), 41 (100). ^{1}H-NMR (400 MHz) (all assignments are based on NOESY) δ: 8.34 (very br s, 1H, indole-NH), 7.90–7.85 (m, 2H, Pht-H_2), 7.73–7.70 (m, 2H, Pht-H_2), 7.49 [d, 1H, *J* 7.6 Hz, C(8)H], 7.31 [d, 1H, *J* 7.9 Hz, C(11)H], 7.14 [dt, *J* 7.1 Hz and *J* 1.2 Hz, C(9)H], 7.09 [dt, 1H, *J* 7.8 Hz and *J* 0.9 Hz, C(10)H], 5.67 [very br s, 1H, C(3)Hα], 4.86 [dd 1H, *J* 14.1 Hz and *J* 9.6 Hz, C(13)H], 4.69 [very br s, 1H, C(3)Hβ], 4.32 [s, 1H, C(12b)Hα], 4.15 [dd, 1H, *J* 14.0

Hz and *J* 5.3 Hz, C(13)H], 3.94–3.90 [m, 1H, C(1)Hβ], 3.86 [dd, 1H, *J* 13.0 Hz and *J* 4.0 Hz, C(6)Hβ], 3.24–3.16 [m, 1H, C(7)Hβ], 3.12 [ddd, 1H, *J* 12.7 Hz, *J* 11.7 Hz and *J* 5.3 Hz, C(6)Hα], 2.66 [dd, 1H, *J* 15.0 Hz and *J* 4.7 Hz, C(7)Hα].

(1R,12bR)-1-(Azidomethyl)-6,7,12,12b-tetrahydro[1,5,2]oxathiazino[2',3' : 1,2]-pyrido[3,4-b]indole (**20**) *and (1S,13bR)-1-azido-1,2,7,8,13,13b-tetrahydro[1,6,2]-oxathiazepino[2',3' : 1,2]pyrido[3,4-b]indole* (**21**):

To **4a** (50 mg, 0.18 mmol), $Zn(N_3)_2 \cdot 2Py$ (167 mg, 0.54 mmol) and triphenylphosphine (190 mg, 0.72 mmol) in dry toluene (1.0 ml), diisopropyl azodicarboxylate (0.14 ml, 150 mg, 0.74 mmol) was added dropwise via a syringe over a period of 5 min causing a slight exothermic reaction. The progress of the reaction was monitored by TLC (EtOAc/hexanes, 1/2, v/v). After 2 h the volatiles were evaporated in vacuo and the residue was subjected to column chromatography (EtOAc/hexanes, 1/4) to yield 7 mg (13%) of 21. R_f 0.58 (EtOAc/hexanes, 1/2, v/v). ^{1}H-NMR (90 MHz) δ: 8.07 (br s, 1H, indole-NH), 7.53-7.00 [m, 4H, indole-C(9)-C(12)H$_4$], 5.29 and 5.00 [br AB, 2H, J_{AB} 11.4 Hz, C(4)H$_2$], 4.43 [br d, 1H, *J* 5.0 Hz, C(13b)H], 4.04–3.93 (m, 2H), 3.77–3.58 (m, 1H), 3.57–3.25 (m, 1H), 3.20–2.47 (m, 3H). Together with 23 mg (42%) of 20. R_f 0.44 (EtOAc/hexanes, 1/2, v/v). IR (NaCl), ν (cm^{-1}) 2110 (N_3). CIMS(70 eV) exact mass calcd for $C_{14}H_{15}N_5OS$ *m/z*: 301.0997 ([M]$^+$); found: 301.0995. *m/z* (relative intensity): 301 ([M]$^+$, 32), 259 ([M-N_3]$^+$, 100), 144 ([$C_{10}H_{10}N$]$^+$, 12), 130 ([C_9C_8N]$^+$, 4). ^{1}H-NMR (400 MHz) (all assignments are based on NOE difference spectroscopy) δ: 8.03 (br s, 1H, indole-NH), 7.49 [d, 1H, *J* 7.8 Hz, C(8)H], 7.34 [d, 1H, *J* 8.0 Hz, C(11)H], 7.18 [dt, 1H, *J* 7.5 Hz and *J* 1.1 Hz, C(9)H], 7.11 [dt, 1H, *J* 7.4 Hz and *J* 0.9 Hz, C(10)H], 5.30 [br s, 1H, C(3)Hα], 5.06 [very br s, 1H, C(3)Hβ], 4.45 [d, 1H, *J* 4.9 Hz, C(12b)Hα], 4.04–3.99 [m, 2H, C(1)Hβ and C(13)H], 3.71 [br s, 1H, C(6)Hβ], 3.40 [br s, 1H, C(13)H], 3.15–3.04 [m, 2H, C(7)Hβ and C(6)Hα], 2.68 [br d, 1H, *J* 10.5 Hz, C(7)Hα] and 15 mg (30%) of recovered 4a.

(5R,R)-5-Azido-2,3,4,4a,5,6,11,12-octahydro[1,2]oxazino[2',3' : 1,2]-azepino[4,5-b]indole (**22**).

The same procedure was used as described for **19** using **4b** (195 mg, 0.76 mmol), hydrazoic acid (0.7 ml of 1.6 m solution in benzene[31]), triphenylphosphine (300 mg, 1.15 mmol) and diisopropyl azodicarboxylate (0.23 ml, 230 mg, 1.14 mmol). Work-up and purification by column chromatography (EtOAc/hexanes, 1/4, v/v) afforded 174 mg (81%) of **22** as a white solid. R_f 0.52 (EtOAc/hexanes, 1/2, v/v). IR (KBr pellet) ν (cm^{-1}) 2105 (N_3). ^{1}H-NMR (90 MHz) δ: 8.33 (br d, 1H, indole-NH), 7.53–7.00 [m, 4H, C(7)-C(10)H$_4$], 5.07 [br d, 1H, *J* 9.4 Hz, C(5)H], 3.68–2.68 [m, 5H, NCH_2CH_2 and C(4a)H], 2.36–1.43 (m, 4H, $CH_2CH_2CH_2O$).

(5R,4aR)-5-Amino-2,3,4,4a,5,6,11,12-octahydro[1,2]oxazino[2',3' : 1,2]-azepino[4,5-b]indole (**23**).

To **22** (90 mg, 0.32 mmol) in methanol (25 ml) was added 10% Pd(C) (500 mg) and the resulting suspension was stirred in a hydrogen atmosphere for 30 min The Pd(C) catalyst was removed by filtration over hyflo and the volatiles were evaporated *in vacuo*. The residue was subjected to column chromatography (MeOH/$CHCl_3$/Et_3N, 5/94.75/0.25, v/v/v) to yield 40 mg (49%) of **23** as a white solid. R_f 0.24 (MeOH/$CHCl_3$, 7/93, v/v). α_D^{22} +1.6 (*c* 4.95, MeOH). CIMS(70 eV), exact mass calcd for $C_{15}H_{19}N_3O$ *m/z*: 257.1528 ([M]$^+$); found: 257.1528; relative intensity: 257 ([M]$^+$, 21), 241 ([M-NH_2]$^+$, 10), 169 (70), 158 ([$C_{10}H_{10}N_2$]$^+$, 100), 144 ([$C_{10}H_{10}N$]$^+$, 13), 130 ([C_9H_8N]$^+$, 23). ^{1}H-NMR (400 MHz) δ: 8.91 (br s, 1H, indole-NH), 7.47 [d, 1H, *J* 7.7 Hz, C(7)H], 7.31 [d, 1H, *J* 7.8 Hz, C(10)H], 7.12 [t, 1H, *J* 7.4 Hz, C(9)H], 7.07 [t, 1H, *J* 7.3 Hz, C(8)H], 4.09 [br s, 1H, C(5)H], 4.00–3.97 (m, 2H, $NOCH_2$), 3.54–3.41 [m, 2H, C(12)*H* H and C(11)*H* H], 3.04–2.86 [m, 3H, C(12)H*H*, C(11)H*H* and C(4a)H], 2.07–2.04 (m, 1H, CH_2CHH), 1.77–1.66 (m, 5H, NH_2 and CH_2CHH). ^{13}C NMR (100 MHz) δ: 138.13 C(6a), 133.66 C(5a), 128.33 C(10b), 121.12 C(8), 119.06 C(9), 117.85 C(10), 111.45 C(10b), 110.66 C(7), 69.62 C(2), 68.56 C(5), 57.72 C(12), 49.45 C(4a), 27.18 C(3), 24.42 C(4), 19.52 C(11). Anal. calcd. for $C_{20}H_{27}N_3O_3 \cdot 1/4H_2O$: C 68.81, H 7.51, N 16.05; found: C 68.96, H 7.50, N 14.37%.

(5R,4aR)-5-[(4-Nitrobenzoyl)amino]-2,3,4,4a,5,6,11,12-octahydro[1,2]oxazino-[2',3' : 1,2]azepino[4,5-b]indole (**24**).

To **23** (18 mg, 0.07 mmol) dissolved in dichloromethane (1 ml) was added 4-nitrobenzoyl chloride (19 mg, 0.10 mmol) and triethylamine (19 μl, 14 mg, 0.14 mmol). After stirring the reaction mixture for 2 h, the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/2, v/v) to give 18 mg (63%) of **24** as yellow crystals (mp 252°C, decomp., crystallized from CH_2Cl_2/EtOH by very slow evaporation of CH_2Cl_2). R_f 0.30 (EtOAc/hexanes, 1/1, v/v). EIMS (70 eV), *m/z* (relative intensity): 406 ([M]$^+$, 19), 195 (74), 28 (100). ^{1}H-NMR (400 MHz) δ: 8.39 (br s, 1H, indole-NH), 8.28 (d, 2H, *J* 8.7 Hz, O_2NPhH_2), 7.94 (d, 2H, *J* 8.7 Hz, O_2NPhH_2), 7.50 [d, 1H, *J* 7.8 Hz, C(7)H], 7.31 [d, 1H, *J* 8.0 Hz, C(10)H], 7.29 (br d, 1H, NH), 7.18 [t, 1H, *J* 7.3 Hz, C(9)H], 7.12 [t, *J* 7.4 Hz, C(8)H], 5.38 [dd, 1H, *J* 8.0 Hz and *J* 5.5 Hz, C(5)H], 4.15 (dt, 1H, *J* ≈ 11 Hz, NOC*H* H), 3.85–3.78 [m, 2H, C(4a)H and C(12)*H* H], 3.71 (dt, 1H, *J* 11.3 Hz and *J* 2.1 Hz, NOCH*H*), 3.44 [ddd, 1H, *J* 12.2 Hz, *J* 6.7 Hz and *J* 2.5 Hz, C(12)H*H*], 3.15 [ddd, 1H, *J* 15.9 Hz, *J* 6.6 Hz and *J* 2.2 Hz, C(11)*H* H], 2.96 [ddd, 1H, *J* 16.1 Hz, *J* 10.3 Hz and *J* 2.4 Hz, C(11)H*H*], 1.92–1.78 (m, 3H, CH_2CHH), 1.65–1.58 (m, 1H, CH_2CH*H*).

Compound **30**.

To **4b** (100 mg, 0.39 mmol), phthalimide (81 mg, 0.59 mmol), and triphenylphosphine (200 mg, 0.76 mmol) in dry THF (0.5 ml) was added diisopropyl azodicarboxylate (0.115 ml, 120 mg, 0.59 mmol) gradually over a period of 5 min, causing a slight exothermic reaction. After stirring for 1.5 h, the volatiles were evaporated *in vacuo* and the residue was subjected to column chromatography (EtOAc/hexanes, 1/4, v/v) to yield 70 mg (42%) of **30** as a colorless oil. R_f 0.31 (EtOAc/hexanes, 1/2, v/v). CIMS(70 eV), *m/z* (relative intensity): 426 ([M+1]$^+$, 100). ^{1}H-NMR (400 MHz. To sharpen up the severely broadened spectrum recorded at 58°C) δ: 7.84–7.79 [m, 1H, C(7)H], 7.47–7.42 [m, 1H, C(10)H], 7.24–7.19 [m, 2H, C(9)H and C(8)H], 6.07 [br s, 1H, C(5)H], 5.32 [heptet, 1H, *J* 6.1 Hz, $OCH(Me)_2$], 5.02 [heptet, 1H, *J* 6.2 Hz, $OCH(Me)_2$], 4.01–3.92 [m, 2H, OCH_2], 3.59 [ddd, 1H, *J* 12.9 Hz, *J* 4.9 Hz and *J* 1.6 Hz, C(12)*H* H], 3.18 (t, 1H, *J* 13.7 Hz, C(11)*H* H), 2.87–2.82 [br m, 1H, C(4a)H], 2.73 [dd, 1H, *J* 15.6 Hz and *J* 4.2 Hz, C(11)H*H*], 2.58 [t, 1H, *J* 12.1 Hz, C(12)H*H*], 2.01 [br s, 1H, C(3)*H* H], 1.94–1.82 [m, 2H, C(4)H$_2$], 1.59 (d, 3H, *J* 6.1 Hz, CH_3), 1.46 (d, 3H, *J*, 6.3 Hz, CH_3), 1.51–1.44 [m, 1H, C(3)H*H*], 1.36 (d, 3H, *J* 6.2 Hz, CH_3), 1.32 (d, 3H, *J* 6.2 Hz, CH_3). ^{13}C NMR (100 MHz) δ: 154.54 C(20), 147.84 C(14), 135.77 C(6a), 133.41 C(5a), 129.10 C(10a), 123.24 C(9), 122.73 C(8), 118.35 C(10), 115.39 C(10b), 115.18 C(7), 72.74 C(22), 70.22 C(2), 69.84 C(18), 64.61 C(5), 57.46 C(12), 50.11 C(4a), 25.59 C(3), 23.35 C(4), 22.27 CH_3, 22.14 CH_3, 22.00 CH_3, 21.45 CH_3, 19.88 C(11).

Acknowledgment

We thank Mr. *Ad Swolfs* and Mr. *Peter van Galen* for taking and discussing the 400-MHz NMR and Mass spectra.

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