# Synthesis of the Aziridinomitosene Skeleton by Application of Guanidinium Ylide-Mediated Aziridination

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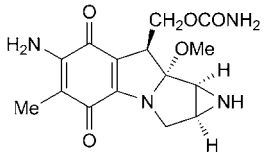
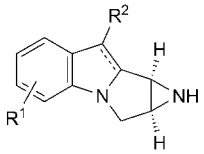
An aziridinomitosene skeleton, a basic core of mitomycin antibiotics, was straightforwardly prepared from *N*-(*p*-toluenesulfonyl)indole-2-carboxaldehyde in 16% overall yield by successive reactions of guanidinium ylide-mediated aziridination, $InCl_3$-catalyzed epimerization of *trans*-3-(indol-2-yl)aziridine-2-carboxylate, leading to the *cis*-derivative, and dehydrative cyclization.

**Introduction.** – Mitomycins are antibiotics isolated from *Streptomyces* species [1], and mitomycin C, among them, has clinically been used as an anticancer drug [2]. Aziridinopyrroloindole, composed of a 6-5-5-3 ring system, is the core skeleton of mitomycin antibiotics and is generally called as either aziridinomitosane or aziridinomitosene depending upon the saturation of the indole unit. Many groups have attempted at the synthesis of mitomycin antibiotics due to their interesting biological activities, and *Kishi* and co-workers [3], and *Fukuyama* and *Yang* [4] have skillfully achieved total syntheses of natural mitomycins. Although various synthetic approaches to aziridinomitosane [5] and aziridinomitosene [6] skeletons have also been examined, the use of bond connection between C(3) and N(4) (*cf.* the atom numbering of aziridinomitosene in *Scheme 1*) in the final construction of the ring system has never been reported to the best of our knowledge. We have established a unique guanidinium ylide-mediated aziridination reaction of an aromatic [7][8] or unsaturated [9] aldehyde, in which *trans*-3-(indol-2-yl)aziridine-2-carboxylate (*trans*-**2**; *Scheme 1*) could be obtained, when indole-2-carboxaldehyde (**1**; *Scheme 1*) is used as an aldehyde source. Herein, we describe a straightforward construction of a model aziridinomitosene skeleton from 3-(indol-2-yl)aziridine-2-carboxylate.



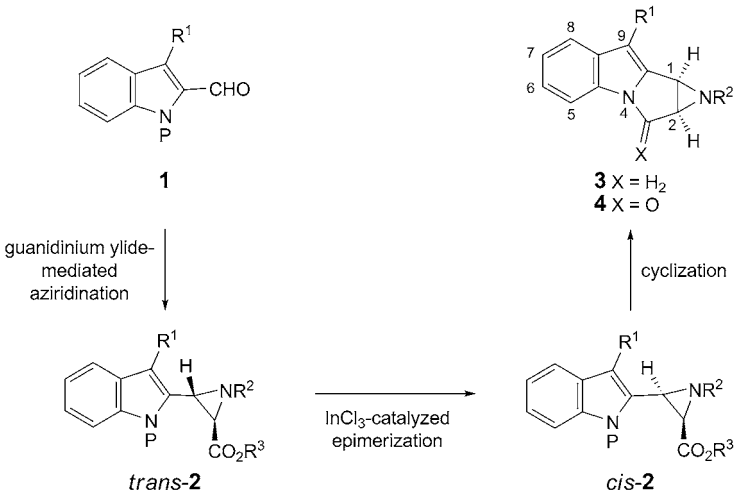

Mitomycin C




Aziridinomitosane (dihydro-indole unit)
Aziridinomitosene (indole unit)

**Results and Discussion.** – Our synthetic strategy toward the aziridinomitosene skeleton **3** or **4** is outlined in *Scheme 1*, in which three reactions are combined: *i*)

Scheme 1. *Synthetic Strategy for Aziridinomitosenes*

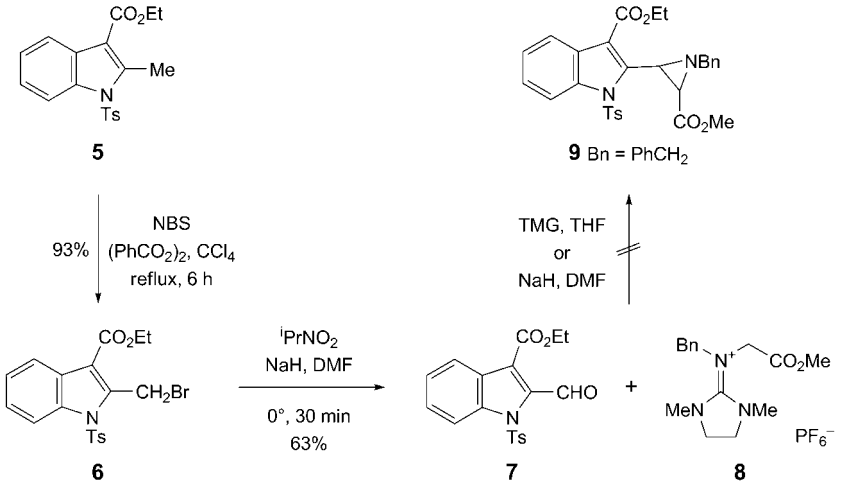



guanidinium ylide-mediated aziridination of *N*-protected (P) indole-2-carboxaldehyde **1**, *ii*) $InCl_3$-catalyzed epimerization of *trans*-aziridine *trans*-**2** to yielding the *cis*-derivative *cis*-**2**, and *iii*) a dehydrative C(3) and N(4) bond formation, leading to cyclization of *cis*-**2** for the construction of the second pyrrolo component of the aziridinomitosene skeleton.

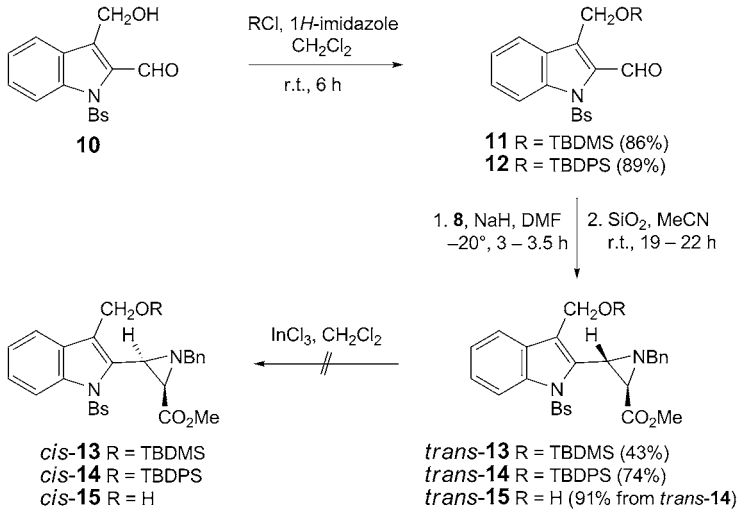
First, we focused on the preparation of 9-substituted aziridinomitosene, in which a appropriate substituent could be converted to the carbamoyloxymethyl moiety present in mitomycins. However, attempts for the aziridination between ethyl 2-formyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indole-3-carboxylate (**7**), which was prepared from ethyl 2-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indole-3-carboxylate (**5**) [10] in two steps as shown in *Scheme 2*, and a guanidinium salt **8** under standard reaction conditions, using either tetramethylguanidine (TMG) in THF or NaH in DMF, unfortunately failed.

It had been found, that in the guanidinium ylide-mediated aziridination, aziridine products were less effectively formed, when an aromatic aldehyde carrying a strong electron-withdrawing group (EWG) such as CN or $NO_2$ was subjected to the reaction [8]. Therefore, regarding the above-mentioned results it can be speculated that the presence of ester and Ts functionalities at C(3) and N(4), respectively, would cause double deactivation in the reactivity of the starting aldehyde **7**. Therefore, the ester group at C(3) was changed to a $CH_2OH$ moiety. The 1*H*-indole-2-carboxaldehydes **11** and **12**, in which the $CH_2OH$ function was protected with either a (*tert*-butyl)(dimethyl)silyl (TBDMS) or a (*tert*-butyl)(diphenyl)silyl (TBDPS) group, were prepared from *N*-benzenesulfonyl (Bs)-substituted 3-(hydroxymethyl)-1*H*-indole-2-carboxaldehyde **10** [11] (*Scheme 3*). Aziridination of the TBDMS-protected 1*H*-indole-2-carboxaldehyde **11** [12] with guanidinium salt **8** together with NaH in DMF, followed by treatment with silica gel ($SiO_2$), afforded *trans*-3-(3-{[(*tert*-butyl)dimethylsilyloxy]-methyl}-1*H*-indol-2-yl)aziridine-2-carboxylate (*trans*-**13**; Bn = $PhCH_2$) in 43% yield as

Scheme 2. *Trials for Aziridination of Ethyl 2-Formyl-1*H*-indole-3-carboxylate* **7**




Scheme 3. *Aziridination of (Silyloxy)methyl-Substituted 1*H*-Indole-2-aldehydes and Trials for Epimerization of the* trans-*Aziridines Formed*

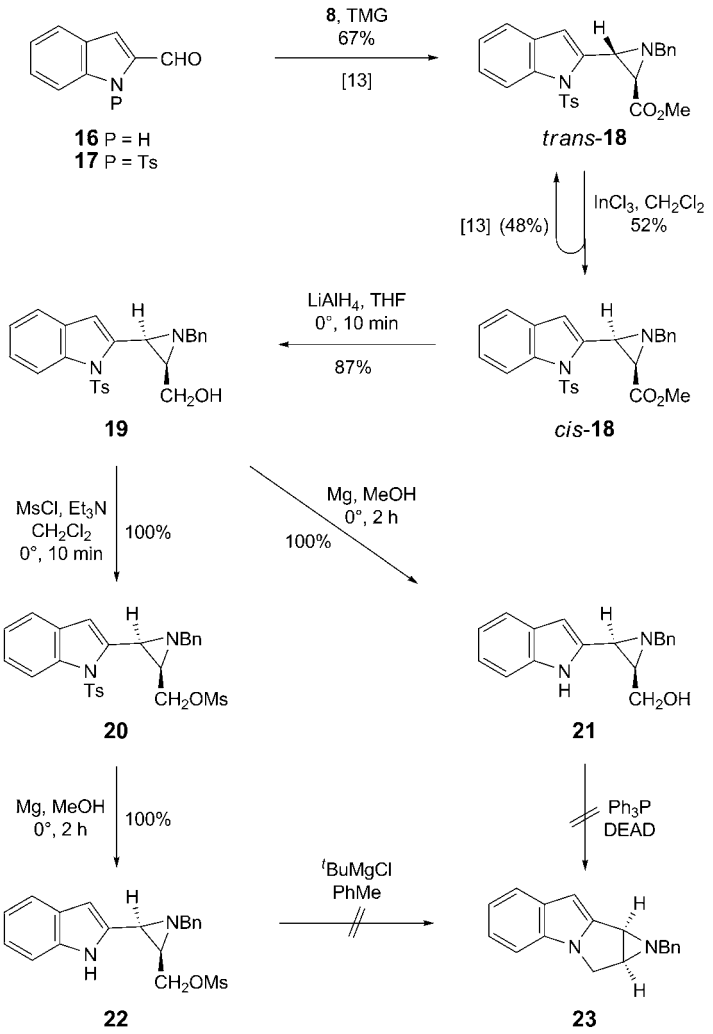



the sole isolable product, while the corresponding aziridine *trans*-**14** was more effectively obtained in 74% yield, when the TBDPS-protected aldehyde **12** was subjected to the guanidinium ylide-mediated aziridination. We have observed that a *Lewis* acid catalyzes a partial epimerization of *trans*-3-arylaziridine-2-carboxylate at C(3) to provide a *ca.* 1:1 equilibrium mixture of *trans*- and *cis*-isomers, and that $InCl_3$ was the most effective catalyst among *Lewis* acids examined [13]. However, application of the $InCl_3$-catalyzed epimerization to both the silyl-protected *trans*-aziridines *trans*-**13**

and -**14** was unsuccessful. The epimerization failed even in the case of a desilylated aziridine *trans*-**15**.

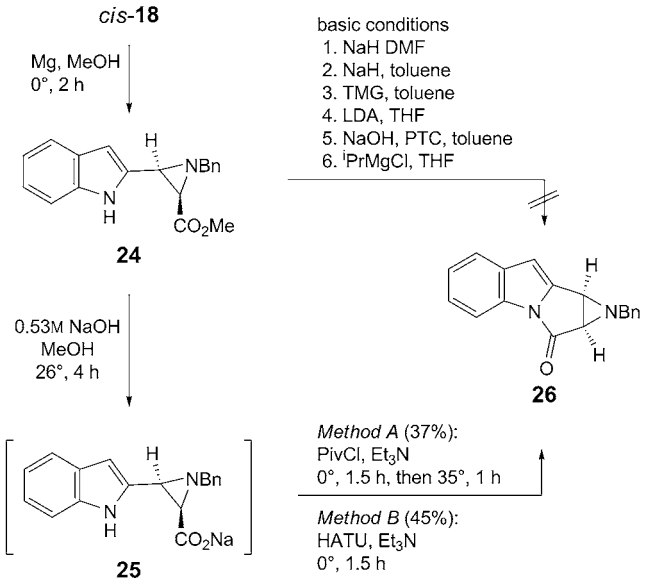
We have already reported that *N*-Ts-protected *trans*-3-(1*H*-indol-2-yl)aziridine-2-carboxylate *trans*-**18**, easily obtained from the aziridination of 1*H*-indole-2-carboxaldehyde **16** after *N*-Ts protection, was partially epimerized to *cis*-**18** by treatment with $InCl_3$ (*Scheme 4*) [13]. Therefore, we turned our attention to the preparation of the 9-unsubstituted aziridinomitosene skeleton (see **3** ($R^1 = H$, $R^2 = Bn$) or **4** ($R^1 = H$, $R^2 = Bn$) in *Scheme 1*).

Scheme 4. *Trials for Cyclization to Aziridinomitosene* **23**



First, the synthesis of aziridinomitosene skeleton **23** was targeted (*Scheme 4*). The ester function of *cis*-3-{1-[(4-methylphenyl)sulfonyl]-1*H*-indol-2-yl)}aziridine-2-carboxylate (*cis*-**18**) was reduced to the corresponding alcohol with $LiAlH_4$. The alcohol **19** was further converted to the methanesulfonate **20**. These two products, **19** and **20**, were *N*-deprotected with Mg in MeOH to provide the corresponding (1*H*-indole)aziridines **21** and **22**, respectively. However, treatment of either the aziridine-methanol **21** under *Mitsunobu* conditions, or the methanesulfonate **22** with *Grignard* reagent led to only decomposition of the starting materials. Since it could be assumed that failure for cyclization to the pyrroloindole skeleton was caused by its unstability under the reaction conditions, we decided to examine next conversion of *cis*-aziridine *cis*-**18** to the known aziridinomitosenone **26** (*Scheme 5*) [14].

Scheme 5. *Construction of Aziridinomitosenone* **26**




Attempts for direct cyclization of *cis*-**18**, after *N*-detosylation, under various basic conditions, did not result in formation of the desired lactam **26**. Gratifyingly, **26** was prepared from *cis*-**18** by successive *N*-detosylation, careful alkaline hydrolysis, and dehydrative cyclization either through the mixed anhydride formation using pivaloyl chloride (PivCl; *Method A*) or treatment with HATU (= *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) (*Method B*; *Scheme 5*). Treatment of (1*H*-indol-2-yl)aziridine **24** with 0.53M NaOH in MeOH at 26° for 4 h, which was the hydrolysis condition optimized after careful examination of the base concentration, gave a crude sodium carboxylate **25**. Since **25** was found to decompose after acidification, it was immediately treated with PivCl in the presence of $Et_3N$ at 0° for 1.5 h and then at 35° for 1 h to yield the aziridinomitosenone **26** in an overall yield of 37% from the *cis*-aziridine, *cis*-**18**. Furthermore, the cyclization step could be improved by the use of HATU as a dehydrating agent at 0° (up to 45%).

Successful construction of aziridinomitosenone **26**, as mentioned above, encouraged us to apply these reaction procedures to asymmetric synthesis; however, trials for asymmetric aziridination of *N*-Ts-protected indole-2-carboxaldehyde **17** using possible chiral guanidinium salts, including the *tert*-butyl ester and the bromide anion [7][8], unfortunately led to unsatisfactory combination of chemical yields (23–74%) and enantioselectivities (9–33% ee) in the formation of aziridine *trans*-**18**.

**Conclusions.** – We succeeded in a straightforward preparation of aziridinomitosene skeleton containing a lactam moiety by cyclization of *cis*-3-(1*H*-indol-2-yl)aziridine-2-carboxylate, which was prepared by guanidinium ylide-mediated aziridination of 1*H*-indole-2-carboxaldehyde, unfortunatly without success in application to chiral version.

## Experimental Part

*General.* Anh. DMF and $CH_2Cl_2$ were used as purchased from *Kanto Chemical*, and anh. THF was used as purchased from *Wako Chemical*. The org. extracts were dried ($MgSO_4$), and solvents were evaporated under reduced pressure. $SiO_2$ in aziridination: *Fuji Silisia FL100D*. TLC: *Merck Art 5715 DC-Fertigplatten Kieselgel 60 $F_{254}$*. Column chromatography (CC): *Kanto Chemical* $SiO_2$ *60* spherical. Flash chromatography (FC): *Kanto Chemical* $SiO_2$ *60* spherical for flash chromatography. M.p.: *Yanagimoto MPSI* apparatus; uncorrected. IR Spectra: Attenuated Total Reflectance (ATR) system on a *JASCO FT/IR-300E* spectrophotometer; $\tilde{\nu}$ in $cm^{-1}$. $^1H$- and $^{13}C$-NMR spectra: *JEOL JNM-ECP-400* instrument in $CDCl_3$; $\delta$ in ppm rel. to $Me_4Si$ as internal standard, *J* in Hz. MS: *JEOL JNM MS-GCMATE* for EI-MS; in *m*/*z* (rel. %); *JEOL JNM HX-100* for HR-FAB-MS.

*Ethyl 2-(Bromomethyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indole-3-carboxylate* (**6**). A mixture of *2-methyl-1*H*-indole* (**5** [10]; 0.769 g, 2.15 mmol), NBS (= *N*-bromosuccinimide; 0.384 g, 2.156 mmol), and benzoyl peroxide (0.011 g, 0.03 mmol) in $CCl_4$ (30 ml) was heated at reflux for 6 h, and the solvent was evaporated. Washing the residue with hexane gave **6** (0.877 g, 93%). Pale-yellow needles (recrystallized from hexane/AcOEt). M.p. 110.5–111.5°. IR: 1705 (C=O). $^1H$-NMR (400 MHz): 1.47 (*t*, *J* = 7.1, 3 H); 2.36 (*s*, 3 H); 4.46 (*q*, *J* = 7.1, 2 H); 5.57 (*s*, 2 H); 7.25 (br. *d*, *J* = 8.4, 2 H); 7.33 (br. *t*, *J* = 7.6, 1 H); 7.38 (br. *t*, *J* = 7.7, 1 H); 7.88 (*d*, *J* = 8.4, 2 H); 8.12 (*d*, *J* = 8.2, 1 H); 8.13 (*d*, *J* = 7.7, 1 H). $^{13}C$-NMR (100 MHz): 14.3; 21.6; 61.0; 113.4; 114.5; 122.5; 124.7; 126.2; 126.7; 127.2; 130.0; 135.2; 135.9; 142.4; 145.8; 163.8. EI-MS: 437 (15), 435 ($M^+$, 14), 356 (100, $[M-Br]^+$). Anal. calc. for $C_{19}H_{18}BrNO_4S$ (436.32): C 52.30, H 4.16, N 3.21; found: C 52.05, H 3.98, N 3.08.

*Ethyl 2-Formyl-1-[(4-methylphenyl)sulfonyl]-1*H*-indole-3-carboxylate* (**7**). A mixture of 2-nitropropane (0.3 ml, 3.38 mmol) and hexane-washed NaH (0.107 g, 2.67 mmol) in anh. DMF (7 ml) was stirred at 0° for 15 min, to which was added a soln. of **6** (0.77 g, 1.78 mmol) in anh. DMF (4 ml) at the same temp. The mixture was stirred at 0° for 30 min and extracted with AcOEt (20 ml × 3) after addition of $H_2O$ (10 ml). The combined org. phases was diluted with hexane (20 ml), washed with $H_2O$ (5 ml × 2) and brine (30 ml), dried, and evaporated. CC of the residue (hexane/toluene 1:8) afforded **7** (0.557 g, 84%). Colorless needles (recrystallized from hexane/AcOEt). M.p. 122–123°. IR: 1709 (C=O). $^1H$-NMR (400 MHz): 1.41 (*t*, *J* = 7.1, 3 H); 2.38 (*s*, 3 H); 4.42 (*q*, *J* = 7.1, 2 H); 7.30 (*d*, *J* = 8.5, 2 H); 7.38 (br. *t*, *J* = 7.6, 1 H); 7.49 (br. *t*, *J* = 7.9, 1 H); 7.92 (*d*, *J* = 8.5, 2 H); 8.10 (*d*, *J* = 8.1, 1 H); 8.14 (*d*, *J* = 8.6, 1 H); 10.57 (*s*, 1 H). $^{13}C$-NMR (100 MHz): 14.1; 21.6; 61.5; 114.4; 117.6; 123.0; 125.0; 126.2; 127.6; 127.7; 130.0; 134.7; 136.2; 139.1; 145.9; 163.0; 184.8. EI-MS: 371 (15, $M^+$), 91 (100). Anal. calc. for $C_{19}H_{17}NO_5S$ (371.41): C 61.44, H 4.61, N 3.77; found: C 61.40, H 4.49, N 3.73.

N-*Benzyl*-N′,N″-*ethylene*-N-*[(methoxycarbonyl)methyl]*-N′,N″-*dimethylguanidinium Hexafluorophosphate* (= N-*Benzyl*-N-*(2-methoxy-2-oxoethyl)-1,3-dimethylimidazolidin-2-iminium Hexafluorophosphate* = N-*(1,3-Dimethyl-2-imidazolidinylidene)*-N-*(2-methoxy-2-oxoethyl)benzenemethanaminium Hexafluorophosphate*; **8**). A mixture of 2-(benzylimino)-1,3-dimethylimidazolidine (1.502 g, 7.39 mmol), prepared from 2-chloro-1,3-dimethylimidazolinium chloride as described in [15], and $BrCH_2COOMe$ (0.75 ml, 8.13 mmol) in MeCN (14 ml) was stirred at r.t. for 3 h and evaporated. The

residual yellow oil was dissolved in $H_2O$ (150 ml) and mixed with $NH_4PF_6$ (1.471 g, 9.02 mmol). Separated precipitates were extracted with $CH_2Cl_2$ (80 ml × 3). The combined org. phases were washed with brine (80 ml), dried, and evaporated. Washing the residual solids with hexane/$Et_2O$ 1:1 (4 ml) gave **8** (2.067 g, 65%). Colorless prisms (recrystallized from AcOEt). M.p. 126–127°. IR: 1747 (C=O); 1585 (C=N). $^1$H-NMR (400 MHz): 3.13 (*s*, 6 H); 3.74 (*s*, 2 H); 3.78 (*s*, 3 H); 3.87 (*s*, 4 H); 4.50 (*s*, 2 H); 7.28–7.32 (*m*, 2 H); 7.34–7.42 (*m*, 3 H). $^{13}$C-NMR (100 MHz): 35.6; 48.6; 49.1; 52.8; 54.5; 129.0; 129.1; 129.3; 133.7; 163.7; 168.7. EI-MS: 276 ($M^+$, 10), 202 (14), 184 (17), 126 (26), 117 (21), 107 (29), 91 (100). Anal. calc. for $C_{15}H_{22}F_6N_3O_2P$ (421.32): C 42.76, H 5.26, N 9.97; found: C 42.79, H 5.18, N 9.94.

*3-({[(*tert*-Butyl)(dimethyl)silyl]oxy}methyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxaldehyde* (**11**). A mixture of *2-formyl-3-(hydroxymethyl)-1-(phenylsulfonyl)-1*H*-indole* (**10**; 1.00 g, 3.18 mmol), $^t$Bu-$Me_2$SiCl (TBDMSCl; 0.717 g, 4.76 mmol), and 1*H*-imidazole (0.349 g, 5.13 mmol) in anh. $CH_2Cl_2$ (22 ml) was stirred at r.t. for 3.5 h under Ar, and filtered through $SiO_2$. After evaporation of the filtrate, $Et_2O$ (20 ml) and sat. aq. $NH_4Cl$ soln. (10 ml) were added to the residue, and then the mixture was extracted with $Et_2O$ (20 ml × 3). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln. (10 ml) and brine (10 ml), dried, and evaporated. CC of the residue (hexane/AcOEt 10:1) afforded **11** (1.175 g, 86%) [12]. Pale-brown solids. M.p. 64–74°. IR: 1670 (C=O). $^1$H-NMR (400 MHz): 0.02 (*s*, 6 H); 0.86 (*s*, 9 H); 5.15 (*s*, 2 H); 7.30 (*t*, *J* = 7.6, 1 H); 7.37 (*t*, *J* = 7.9, 2 H); 7.47–7.58 (*m*, 2 H); 7.69 (*d*, *J* = 8.1, 2 H); 8.04 (*d*, *J* = 8.1, 1 H); 8.21 (*d*, *J* = 8.6, 1 H); 10.60 (*s*, 1 H). $^{13}$C-NMR (100 MHz): −5.5; 18.2; 25.8; 58.3; 115.4; 124.57; 124.59; 126.6; 129.0; 129.2; 129.3; 131.6; 134.2; 135.2; 137.0; 137.7; 185.0.

*3-({[(*tert*-Butyl)(diphenyl)silyl]oxy}methyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxaldehyde* (**12**). A mixture of **10** (1.50 g, 4.76 mmol), TBDPSCl (1.7 ml, 6.62 mmol), and 1*H*-imidazole (0.486 g, 7.13 mmol) in anh. $CH_2Cl_2$ (33 ml) was stirred at r.t. for 1 h under Ar and filtered through $SiO_2$. After evaporation of the filtrate, $Et_2O$ (30 ml) and sat. aq. $NH_4Cl$ soln. (10 ml) were added to the residue, and then the mixture was extracted with $Et_2O$ (20 ml × 3). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln. (10 ml) and brine (10 ml), dried, and evaporated. Washing the residue with hexane afforded **12** (2.34 g, 89%). Pale-brown solids (recrystallized from hexane/AcOEt). M.p. 124–125°. IR: 1684 (C=O). $^1$H-NMR (400 MHz): 1.01 (*s*, 9 H); 5.14 (*s*, 2 H); 7.24–7.38 (*m*, 7 H); 7.41 (br. *t*, *J* = 7.4, 2 H); 7.45–7.55 (*m*, 2 H); 7.55–7.61 (*m*, 4 H); 7.66 (br. *d*, *J* = 7.3, 2 H); 8.09 (*d*, *J* = 7.9, 1 H); 8.21 (*d*, *J* = 8.4, 1 H); 10.26 (*s*, 1 H). $^{13}$C-NMR (100 MHz): 19.2; 26.8; 58.5; 115.3; 124.3; 124.6; 126.6; 127.6; 128.9; 129.1; 129.3; 129.8; 132.1; 132.8; 134.0; 134.1; 135.5; 136.9; 137.5; 184.1. FAB-MS: 554 ($[M+H]^+$). Anal. calc. for $C_{32}H_{31}NO_4SSi$ (553.74): C 69.41, H 5.64, N 2.53; found: C 69.32, H 5.43, N 2.48.

*Methyl* rac-*(2*R*,3*R*)-3-[3-({[(*tert*-Butyl)(dimethyl)silyl]oxy}methyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl]-1-(phenylmethyl)aziridine-2-carboxylate* (*trans*-**13**). A mixture of NaH (60% in mineral oil, 0.156 g, 3.91 mmol) and **8** (1.02 g, 2.42 mmol) in anh. DMF (2.7 ml) was stirred at −20° for 20 min under Ar. To the mixture, a soln. of **11** (0.798 g, 1.86 mmol) in anh. DMF (2 ml) was slowly added, and the mixture was stirred at −20° for 3 h. After addition of $SiO_2$ (12 g) and MeCN (40 ml), the resulting suspension was stirred at r.t. further 19 h and filtered. After evaporation of the filtrate, the residue was diluted with AcOEt (51 ml) and hexane (17 ml), washed with $H_2O$ (2 ml × 5) and brine (10 ml), dried, and evaporated. FC of the residue (hexane/AcOEt 10:1) afforded *trans*-**13** (0.470 g, 43 %). Colorless needles (recrystallized from hexane). M.p. 126–127°. IR: 1736 (C=O). $^1$H-NMR (400 MHz) of a major invertomer: −0.05, −0.01 (2*s*, 3 H); 0.83 (*s*, 9 H); 2.94 (*d*, *J* = 2.6, 1 H); 3.71 (*s*, 3 H); 3.74 (*d*, *J* = 2.6, 1 H); 4.07, 4.54 (2*d*, *J* = 13.6, 1 H); 4.89, 4.94 (2*d*, *J* = 12.4, 1 H); 7.20–7.36 (*m*, 7 H); 7.41 (*t*, *J* = 7.8, 2 H); 7.53 (*t*, *J* = 7.4, 1 H); 7.65 (*d*, *J* = 7.5, 1 H); 7.86 (*d*, *J* = 7.5, 2 H); 8.11 (*d*, *J* = 8.4, 1 H). $^1$H-NMR (400 MHz) of a minor invertomer: 2.75 (*d*, *J* = 13.5, 1 H); 3.17 (br. *s*, 1 H); 3.77 (*s*, 3 H); 4.76, 4.82 (2*d*, *J* = 11.9, 1 H); 7.60 (*d*, *J* = 7.7, 1 H); 8.28 (*d*, *J* = 8.2, 1 H). EI-MS: 590 (1, $M^+$), 449 (73), 399 (24), 299 (13), 259 (16), 199 (47), 135 (100). Anal. calc. for $C_{32}H_{38}N_2O_5SSi$ (590.81): C 65.05, H 6.48, N 4.74; found: C 64.89, H 6.46, N 4.73.

*Methyl* rac-*(2*R*,3*R*)-3-[3-({[(*tert*-Butyl)(diphenyl)silyl]oxy}methyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl]-1-(phenylmethyl)aziridine-2-carboxylate* (*trans*-**14**). A mixture of NaH (60% in mineral oil, 0.304 g, 7.60 mmol) and **8** (1.98 g, 4.70 mmol) in anh. DMF (5 ml) was stirred at −20° for 30 min under Ar. To the mixture, a soln. of **12** (2.00 g, 3.61 mmol) in anh. DMF (4.1 ml) was slowly added, and the mixture was stirred at −20° for 3.5 h. After addition of $SiO_2$ (18 g) and MeCN (60 ml), the resulting suspension was stirred at r.t. further 22 h and filtered. After evaporation of the filtrate, the residue was diluted with

AcOEt (120 ml) and hexane (40 ml), washed with $H_2O$ (3 ml × 6) and brine (30 ml), dried, and evaporated. FC of the residue (hexane/$CH_2Cl_2$ 1:1 → hexane/AcOEt 10:1) afforded *trans*-**14** (1.90 g, 74 %). Yellow solids (recrystallized from hexane). M.p. 36–41°. IR: 1732 (C=O). $^1$H-NMR (400 MHz) of a major invertomer: 0.97 (*s*, 9 H); 2.72 (*d*, *J* = 2.4, 1 H); 3.54 (*d*, *J* = 2.4, 1 H); 3.61 (*s*, 3 H); 3.80, 3.95 (2*d*, *J* = 13.7, 1 H); 5.01, 5.07 (2*d*, *J* = 12.6, 1 H); 6.96–7.17 (*m*, 2 H); 7.13–7.45 (*m*, 13 H); 7.49 (*t*, *J* = 7.1, 1 H); 7.55–7.65 (*m*, 5 H); 7.82 (*d*, *J* = 8.1, 2 H); 8.15 (*d*, *J* = 8.4, 1 H). $^1$H-NMR (400 MHz) of a minor invertomer: 2.88 (*d*, *J* = 13.7, 1 H); 3.33 (*s*, 1 H); 3.70 (*s*, 3 H); 4.74, 4.90 (2*d*, *J* = 11.9, 1 H); 7.09 (*t*, *J* = 7.9, 1 H); 7.68 (*d*, *J* = 7.9, 2 H); 8.25 (*d*, *J* = 8.2, 1 H). $^{13}$C-NMR (100 MHz) of a major invertomer: 19.1; 26.6; 41.6; 42.8; 52.1; 53.9; 57.3; 114.3; 121.0; 122.8; 123.5; 125.0; 126.3; 126.8; 127.57; 127.60; 128.1; 128.2; 129.1; 129.58; 129.64; 129.7; 132.1; 133.2; 133.3; 133.6; 135.5; 136.3; 138.3; 138.9; 168.9. HR-FAB-MS: 715.2662 ($[M+H]^+$, $C_{42}H_{43}N_2O_5SSi^+$; calc. 715.2662).

*Methyl* rac-*(2*R,*3*R*)-3-[3-(Hydroxymethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl]-1-(phenylmethyl)-aziridine-2-carboxylate* (*trans*-**15**). A 1M soln. of TBAF in THF (2.16 ml, 21.6 mmol) was added to a soln. of *trans*-**14** (0.700 g, 0.98 mM) in anh. THF (1 ml). The mixture was stirred at r.t. for 0.5 h, the reaction was quenched with sat. $NH_4Cl$ aq. soln. (3 ml), and the mixture was extracted with AcOEt (10 ml × 3). The combined org. phases were washed with $H_2O$ (10 ml) and brine (10 ml), dried, and evaporated. FC of the residue (hexane/AcOEt 3:1 → 2:1) afforded *trans*-**15** (0.424 g, 91%). A yellow oil, solidified on keeping in the refrigerator. M.p. 42–47°. IR: 3362 (OH); 1732 (C=O). $^1$H-NMR (400 MHz): 2.75 (br. *d*, *J* = 2.9, 1 H); 3.80 (*s*, 3 H); 3.91 (*d*, *J* = 2.9, 1 H); 4.16, 4.46 (2*d*, *J* = 12.8, 1 H); 4.28 (*d*, *J* = 13.2, 1 H); 4.45 (br. *d*, *J* = 13.0, 1 H); 4.85 (br. *s*, 1 H); 7.20–7.27 (*m*, 1 H); 7.28–7.37 (*m*, 6 H); 7.41 (*t*, *J* = 7.8, 2 H); 7.48 (*t*, *J* = 7.9, 1 H); 7.53 (*t*, *J* = 7.5, 1 H); 7.75 (*d*, *J* = 7.3, 2 H); 8.15 (*d*, *J* = 8.4, 1 H). $^{13}$C-NMR (100 MHz): 41.8; 43.2; 52.6; 53.4; 55.0; 114.2; 119.0; 123.5; 123.7; 125.4; 126.2; 127.8; 128.67; 128.72; 129.0; 129.3; 133.1; 133.9; 135.9; 136.9; 138.7; 168.2. HR-FAB-MS: 477.1469 ($[M+H]^+$, $C_{26}H_{25}N_2O_5S^+$; calc. 477.1484).

rac-*[(2*R,*3*S*)-3-[1-[(4-Methylphenyl)sulfonyl]-1*H*-indol-2-yl}-1-(phenylmethyl)aziridin-2-yl]methanol* (**19**). A suspension of $LiAlH_4$ (0.186 g, 4.90 mM) in anh. THF (3 ml) was added to a soln. of *cis*-**18** (0.564 g, 1.22 mM) in anh. THF (5 ml) at 0° under Ar, and the mixture was stirred at the same temp. for 0.5 h. After successive addition of $H_2O$ (2 ml), 20% NaOH (2 ml), $H_2O$ (2 ml), and a 8:1 mixed soln. of $CH_2Cl_2$/MeOH (27 ml), the resulting mixture was stirred at 0° for 1 h and filtered through *Celite*. The filtrate was washed with brine (50 ml × 2), dried, and evaporated to give **19** (0.462 g, 87%). Colorless prisms (recrystallized from hexane/benzene). M.p. 156–157°. IR: 3232 (OH). $^1$H-NMR (400 MHz): 2.33 (*m*, 1 H); 2.36 (*s*, 3 H); 3.10–3.28 (*m*, 2 H); 3.33 (*d*, *J* = 6.2, 1 H); 3.70, 3.80 (2*d*, *J* = 13.2, 1 H); 6.63 (*s*, 1 H); 7.16–7.41 (*m*, 9 H); 7.44 (*t*, *J* = 7.5, 1 H); 7.69 (*d*, *J* = 8.4, 2 H); 8.13 (*d*, *J* = 8.2, 1 H). $^{13}$C-NMR (100 MHz): 21.5; 41.3; 60.1; 64.1; 110.8; 114.1; 120.7; 123.5; 124.4; 126.4; 127.4; 128.1; 128.5; 129.0; 129.9; 136.0; 136.4; 137.2; 138.4; 144.0. EI-MS: 432 (11, $M^+$). Anal. calc. for $C_{25}H_{24}N_2O_3S$ (432.54): C 69.42, H 5.59, N 6.48; found: C 69.33, H 5.33, N 6.49.

rac-*[(2*R,*3*S*)-3-[1-[(4-Methylphenyl)sulfonyl]-1*H*-indol-2-yl]-1-(phenylmethyl)aziridin-2-yl]methyl Methanesulfonate* (**20**). A soln. of methanesulfonyl chloride (MsCl; 10 µl, 0.133 mmol) in anh. $CH_2Cl_2$ (0.1 ml) and a soln. of $Et_3N$ (19 µl, 0.137 mmol) in anh. $CH_2Cl_2$ (0.1 ml) was successively added to a soln. of **19** (0.0413 g, 0.095 mmol) in anh. $CH_2Cl_2$ (0.1 ml) at 0°, and the mixture was stirred at the same temp. for 0.5 h. After addition of sat. aq. $NaHCO_3$ soln. (2 ml), the mixture was extracted with $CH_2Cl_2$ (10 ml × 3). The combined org. phases were washed with sat. aq. $NH_4Cl$ soln. (5 ml × 2), $H_2O$ (10 ml), and brine (10 ml), dried, and evaporated to give **20** (0.484 g, quant.) as a pale-yellow oil, which was used for the next step without any purification. $^1$H-NMR (400 MHz): 2.35 (*s*, 3 H); 2.41 (*dt*, *J* = 6.6, 6.2, 1 H); 2.71 (*s*, 3 H); 3.48 (*d*, *J* = 6.2, 1 H); 3.71 (*d*, *J* = 6.6, 2 H); 3.74, 3.79 (2*d*, *J* = 13.2, 1 H); 6.66 (*s*, 1 H); 7.18–7.42 (*m*, 9 H); 7.45 (*d*, *J* = 7.7, 1 H); 7.67 (*d*, *J* = 8.2, 2 H); 8.12 (*d*, *J* = 8.2, 1 H). $^{13}$C-NMR (100 MHz): 21.5; 37.3; 40.3; 44.4; 63.7; 68.5; 110.8; 114.1; 120.9; 123.7; 124.6; 126.4; 127.4; 128.3; 128.4; 128.7; 130.0; 135.6; 135.9; 137.3; 137.9; 145.4. EI-MS: 510 (4, $M^+$), 91 (100).

rac-*[(2*R,*3*S*)-3-(1*H*-Indol-2-yl)-1-(phenylmethyl)aziridin-2-yl]methanol* (**21**). A mixture of **19** (0.092 g, 0.212 mmol) and Mg turnings (0.259 g, 10.7 mmol) in dry MeOH (7 ml) was stirred at 0° for 2 h under Ar, and the reaction was quenched with sat. aq. $NH_4Cl$ soln. (4 ml) and $H_2O$ (1 ml). After dissolving the precipitates under microwave irradiation, the mixture was extracted with AcOEt (20 ml × 3). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (20 ml), dried,

and evaporated to give **21** (0.059 g, quant.) as a brown oil, which was used for the next step without any purification. IR: 3000 (OH); 1700 (C=O). $^1$H-NMR (400 MHz): 2.24 (*q*-like, $J = 6.2$, 1 H); 3.01 (*d*, $J = 6.2$, 1 H); 3.47 (*dd*, $J = 11.9$, 6.2, 1 H); 3.54 (*dd*, $J = 11.9$, 5.7, 1 H); 3.66, 3.71 (2*d*, $J = 13.4$, 1 H); 6.43 (*s*, 1 H); 7.06 (*t*, $J = 7.3$, 1 H); 7.11 (*t*, $J = 6.8$, 1 H); 7.15–7.23 (*m*, 1 H); 7.24–7.38 (*m*, 5 H); 7.52 (*d*, $J = 7.5$, 1 H); 8.71 (br. *s*, 1 H).

rac-*[(2*R,*3*S*)-3-(1*H*-Indol-2-yl)-1-(phenylmethyl)aziridin-2-yl]methyl Methanesulfonate* (**22**). A mixture of **20** (0.032 g, 0.063 mmol) and Mg turnings (0.037 g, 1.51 mmol) in dry MeOH (2 ml) was stirred at 0° for 2 h under Ar, and the reaction was quenched with sat. aq. $NH_4Cl$ soln. (2 ml) and $H_2O$ (1 ml). After dissolving the precipitates under microwave irradiation, the mixture was extracted with AcOEt (10 ml × 3). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln. (10 ml) and brine (10 ml), dried, and evaporated to give **22** (0.021 g, quant.) as a brown oil, which was used for the next step without any purification. IR: 3000 (OH); 1700 (C=O). $^1$H-NMR (400 MHz): 1.78–1.90 (*m*, 1 H); 1.88 (*s*, 3 H); 2.44 (*d*, $J = 6.2$, 1 H); 3.20, 3.27 (2*d*, $J = 13.5$, 1 H); 3.69 (*dd*, $J = 11.2$, 5.7, 1 H); 3.87 (*dd*, $J = 11.4$, 7.1, 1 H); 6.41 (*s*, 1 H); 6.90–7.40 (*m*, 8 H); 7.55–7.65 (*m*, 1 H); 7.83 (br. *s*, 1 H).

*Methyl* rac-*(2*R,*3*S*)–3-(1*H*-Indol-2-yl)1-(phenylmethyl)aziridine-2-carboxylate* (**24**). A mixture of *cis*-**18** (0.061 g, 0.133 mmol) and Mg turnings (0.078 g, 3.19 mmol) in dry MeOH (2.5 ml) was stirred at 0° for 2 h, and the reaction was quenched with sat. aq. $NH_4Cl$ soln. (2 ml) and $H_2O$ (1 ml). After dissolving the precipitates under microwave irradiation, the mixture was extracted with $CH_2Cl_2$ (10 ml × 2). The combined org. phases were washed with sat. aq. $NaHCO_3$ soln. (10 ml) and brine (10 ml), dried, and evaporated to give **24** as a brown oil, which was used for the next step without any purification. IR: 3400 (OH), 1736 (C=O). $^1$H-NMR (400 MHz): 2.69 (*d*, $J = 6.4$, 1 H); 3.23 (*d*, $J = 6.4$, 1 H); 3.62 (*s*, 3 H); 3.81 (*s*, 2 H); 6.54 (*d*, $J = 1.3$, 1 H); 7.06 (br. *t*, $J = 7.5$, 1 H); 7.14 (br. *t*, $J = 7.6$, 1 H); 7.24–7.40 (*m*, 6 H); 7.53 (*d*, $J = 7.9$, 1 H); 9.05 (br. *s*, 1 H).

rac-*(1a*R,*8b*S)-*1a,8b-Dihydro-1-(phenylmethyl)azireno[2′,3′:3,4]pyrrolo[1,2-*a*]indol-2(1*H*)-one* (**26**). *Method A*. A mixture of crude **24** (0.0264 g, 0.086 mmol) and NaOH (0.0112 g, 0.280 mmol) in anh. THF (0.5 ml) was stirred at r.t. for 2 h. After addition of $Et_3N$ (46 µl, 0.33 mmol) and pivaloyl chloride (PivCl; 36 µl, 0.292 mmol) at 0°, the mixture was stirred at the same temp. for 1.5 h and then at 35° for 1 h, and diluted with $Et_2O$ (10 ml). After filtration, the filtrate was washed with sat. aq. $NH_4Cl$ soln. (10 ml). The org. soln. was washed with brine (10 ml), dried, and evaporated. FC of the residue (hexane/AcOEt 3:1), followed by washing with hexane/$Et_2O$, afforded **26** (0.87 g, 37%). Pale-brown solids. M.p. 121–122° (lit. [14] m.p. 121–123°). IR: 1742 (C=O). $^1$H-NMR (400 MHz) of major invertomer: 3.18 (*d*, $J = 4.4$, 1 H); 3.39 (*d*, $J = 4.4$, 1 H); 3.69, 3.75 (2*d*, $J = 13.5$, 1 H); 6.47 (*s*, 1 H); 7.22 (*ddd*, $J = 7.5$, 7.5, 1.3, 1 H); 7.28–7.34 (*m*, 2 H); 7.36 (br. *d*, $J = 4.4$, 4 H); 7.47 (br. *d*, $J = 7.7$, 1 H); 7.90 (*d*, $J = 7.5$, 1 H). $^1$H-NMR (400 MHz) of minor invertomer: 3.29 (*d*, $J = 13.4$, 1 H); 3.59–3.60 (*m*, 2 H); 3.63–3.64 (*m*, 1 H); 3.88 (*d*, $J = 2.7$, 1 H); 6.59 (*s*, 1 H); 7.20–7.34 (*m*, 3 H); 7.53 (*d*, $J = 7.9$, 1 H); 7.96 (*d*, $J = 7.9$, 1 H). HR-FAB-MS: 274.1107 ($M^+$, $C_{18}H_{14}N_2O^+$; calc. 274.1106).

*Method B*. A mixture of crude **24** (0.0213 g, 0.0695 mmol) and NaOH (0.0086 g, 0.215 mmol) in anh. THF (0.2 ml) was stirred at r.t. for 1.5 h and evaporated. After dissolving the residue in anh. DMF (0.7 ml), the resulting soln. was added to HATU (0.0491 g, 0.129 mmol), stirred at 0° for 1.5 h under Ar, and evaporated. FC of the residue (hexane/$CH_2Cl_2$ 1:1), followed by washing with hexane/$Et_2O$, afforded **26** (0.086 g, 45%) as yellow solid, which was identical to the product obtained by *Method A*.

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*Received September 7, 2012*