

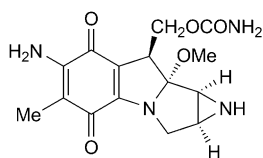
Synthesis of the Aziridinomitosenes Skeleton by Application of Guanidinium Ylide-Mediated Aziridination

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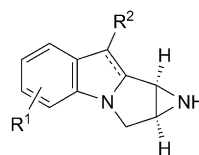
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An aziridinomitosenes skeleton, a basic core of mitomycin antibiotics, was straightforwardly prepared from *N*-(*p*-toluenesulfonyl)indole-2-carboxaldehyde in 16% overall yield by successive reactions of guanidinium ylide-mediated aziridination, InCl_3 -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 aziridinomitosenes or aziridinomitosenes 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 aziridinomitosenes [5] and aziridinomitosenes [6] skeletons have also been examined, the use of bond connection between C(3) and N(4) (*cf.* the atom numbering of aziridinomitosenes 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 aziridinomitosenes skeleton from 3-(indol-2-yl)aziridine-2-carboxylate.



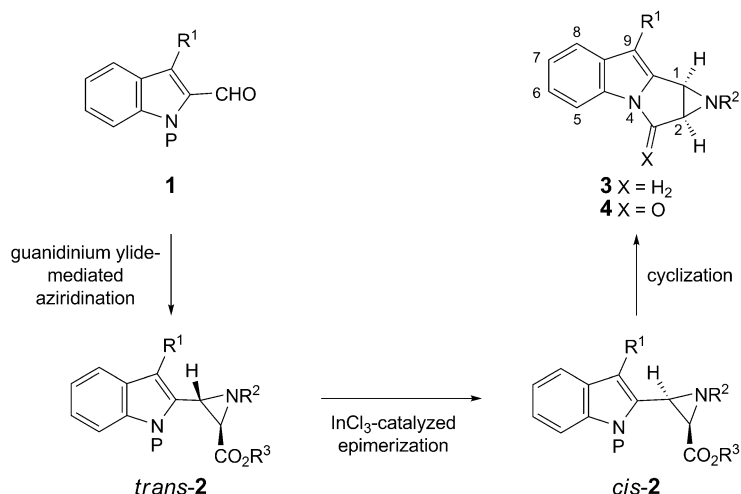
Mitomycin C



Aziridinomitosenes (dihydro-indole unit)
Aziridinomitosenes (indole unit)

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

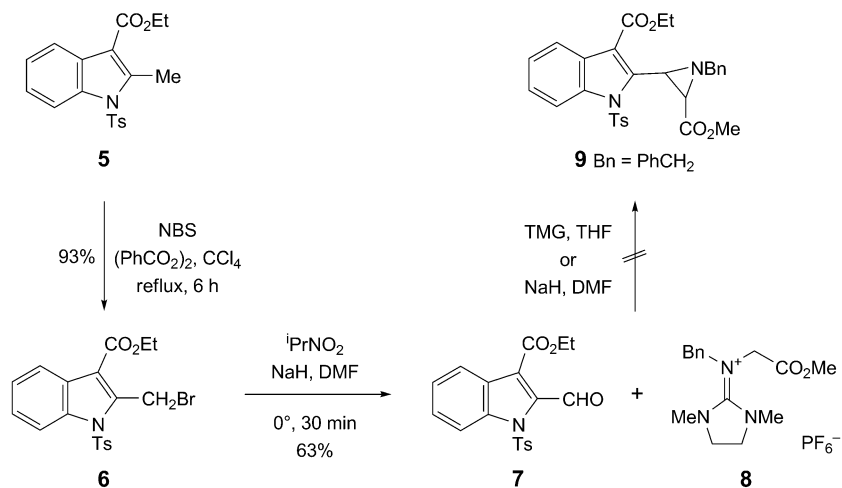
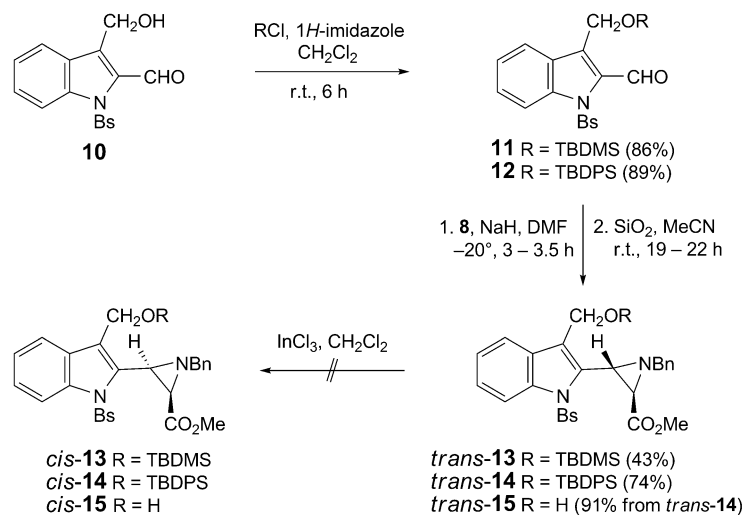
Scheme 1. Synthetic Strategy for Aziridinomitosenes



guanidinium ylide-mediated aziridination of *N*-protected (P) indole-2-carboxaldehyde **1**, ii) InCl₃-catalyzed epimerization of *trans*-aziridine *trans-2*, and iii) a dehydrative C(3) and N(4) bond formation, leading to cyclization of *cis-2* for the construction of the second pyrrole component of the aziridinomitosenes skeleton.

First, we focused on the preparation of 9-substituted aziridinomitosenes, 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 NO₂ 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 CH₂OH moiety. The 1*H*-indole-2-carboxaldehydes **11** and **12**, in which the CH₂OH 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 (SiO₂), afforded *trans*-3-(3-[[*tert*-butyl]dimethylsilyloxy]-methyl)-1*H*-indol-2-yl)aziridine-2-carboxylate (*trans-13*; Bn = PhCH₂) in 43% yield as

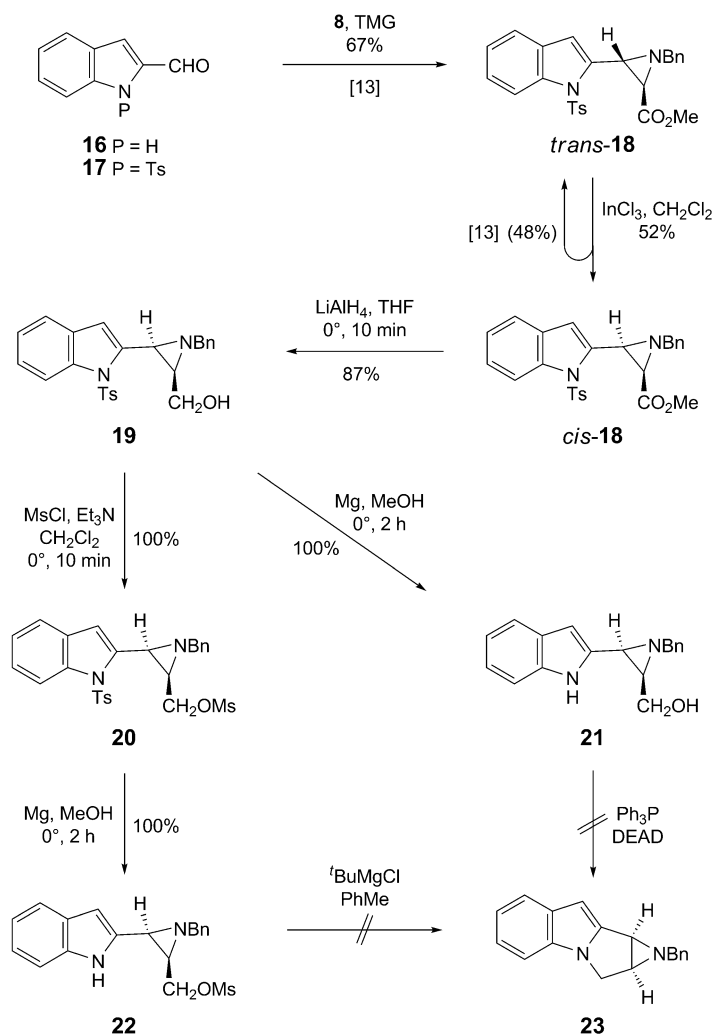
Scheme 2. Trials for Aziridination of Ethyl 2-Formyl-1H-indole-3-carboxylate **7**

 Scheme 3. Aziridination of (Silyloxy)methyl-Substituted 1H-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 InCl₃ was the most effective catalyst among *Lewis* acids examined [13]. However, application of the InCl₃-catalyzed epimerization to both the silyl-protected *trans*-aziridines *trans*-**13**

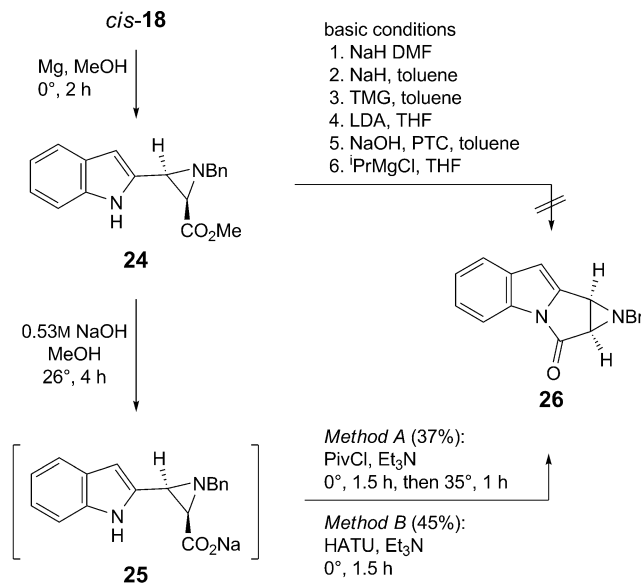
and **-14** was unsuccessful. The epimerization failed even in the case of a desilylated aziridine *trans*-**15**.

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 aziridinomitosenes skeleton (see **3** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Bn}$) or **4** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Bn}$) in Scheme 1).

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



First, the synthesis of aziridinomitosenone 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 LiAlH₄. 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 Et₃N 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 aziridinomitosenone 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, unfortunately without success in application to chiral version.

Experimental Part

General. Anh. DMF and CH₂Cl₂ were used as purchased from *Kanto Chemical*, and anh. THF was used as purchased from *Wako Chemical*. The org. extracts were dried (MgSO₄), and solvents were evaporated under reduced pressure. SiO₂ in aziridination: *Fuji Silisia FL100D*. TLC: *Merck Art 5715 DC-Fertigplatten Kieselgel 60 F₂₅₄*. Column chromatography (CC): *Kanto Chemical* SiO₂ 60 spherical. Flash chromatography (FC): *Kanto Chemical* SiO₂ 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 ¹³C-NMR spectra: *JEOL JNM-ECP-400* instrument in CDCl₃; δ in ppm rel. to Me₄Si 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 CCl₄ (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). ¹³C-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 C₁₉H₁₈BrNO₄S (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 H₂O (10 ml). The combined org. phases was diluted with hexane (20 ml), washed with H₂O (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). ¹³C-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 C₁₉H₁₇NO₅S (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 BrCH₂COOMe (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 H₂O (150 ml) and mixed with NH₄PF₆ (1.471 g, 9.02 mmol). Separated precipitates were extracted with CH₂Cl₂ (80 ml × 3). The combined org. phases were washed with brine (80 ml), dried, and evaporated. Washing the residual solids with hexane/Et₂O 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). ¹H-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). ¹³C-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 C₁₅H₂₂F₆N₃O₂P (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), ^tBu-Me₂SiCl (TBDMSCl; 0.717 g, 4.76 mmol), and 1*H*-imidazole (0.349 g, 5.13 mmol) in anh. CH₂Cl₂ (22 ml) was stirred at r.t. for 3.5 h under Ar, and filtered through SiO₂. After evaporation of the filtrate, Et₂O (20 ml) and sat. aq. NH₄Cl soln. (10 ml) were added to the residue, and then the mixture was extracted with Et₂O (20 ml × 3). The combined org. phases were washed with sat. aq. NaHCO₃ 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). ¹H-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). ¹³C-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), TBDPSCI (1.7 ml, 6.62 mmol), and 1*H*-imidazole (0.486 g, 7.13 mmol) in anh. CH₂Cl₂ (33 ml) was stirred at r.t. for 1 h under Ar and filtered through SiO₂. After evaporation of the filtrate, Et₂O (30 ml) and sat. aq. NH₄Cl soln. (10 ml) were added to the residue, and then the mixture was extracted with Et₂O (20 ml × 3). The combined org. phases were washed with sat. aq. NaHCO₃ 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). ¹H-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). ¹³C-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 C₃₂H₃₁NO₄SSi (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 SiO₂ (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 H₂O (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). ¹H-NMR (400 MHz) of a major invertomer: –0.05, –0.01 (2s, 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 (2d, *J* = 13.6, 1 H); 4.89, 4.94 (2d, *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). ¹H-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 (2d, *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 C₃₂H₃₈N₂O₅SSi (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 SiO₂ (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 H₂O (3 ml × 6) and brine (30 ml), dried, and evaporated. FC of the residue (hexane/CH₂Cl₂ 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). ¹H-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 (2d, *J* = 13.7, 1 H); 5.01, 5.07 (2d, *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). ¹H-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 (2d, *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). ¹³C-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]⁺, C₄₂H₄₃N₅O₅SSi⁺; calc. 715.2662).

Methyl rac-(2R,3R)-3-[3-(Hydroxymethyl)-1-(phenylsulfonyl)-1H-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 mmol) in anh. THF (1 ml). The mixture was stirred at r.t. for 0.5 h, the reaction was quenched with sat. NH₄Cl aq. soln. (3 ml), and the mixture was extracted with AcOEt (10 ml × 3). The combined org. phases were washed with H₂O (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). ¹H-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 (2d, *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). ¹³C-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]⁺, C₂₆H₂₅N₅O₅S⁺; calc. 477.1484).

rac-[(2R,3S)-3-[1-[(4-Methylphenyl)sulfonyl]-1H-indol-2-yl]-1-(phenylmethyl)aziridin-2-yl]methanol (19). A suspension of LiAlH₄ (0.186 g, 4.90 mmol) in anh. THF (3 ml) was added to a soln. of *cis*-**18** (0.564 g, 1.22 mmol) 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 H₂O (2 ml), 20% NaOH (2 ml), H₂O (2 ml), and a 8:1 mixed soln. of CH₂Cl₂/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). ¹H-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 (2d, *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). ¹³C-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 C₂₅H₂₄N₂O₃S (432.54): C 69.42, H 5.59, N 6.48; found: C 69.33, H 5.33, N 6.49.

rac-[(2R,3S)-3-[1-[(4-Methylphenyl)sulfonyl]-1H-indol-2-yl]-1-(phenylmethyl)aziridin-2-yl]methyl Methanesulfonate (20). A soln. of methanesulfonyl chloride (MsCl; 10 µl, 0.133 mmol) in anh. CH₂Cl₂ (0.1 ml) and a soln. of Et₃N (19 µl, 0.137 mmol) in anh. CH₂Cl₂ (0.1 ml) was successively added to a soln. of **19** (0.0413 g, 0.095 mmol) in anh. CH₂Cl₂ (0.1 ml) at 0°, and the mixture was stirred at the same temp. for 0.5 h. After addition of sat. aq. NaHCO₃ soln. (2 ml), the mixture was extracted with CH₂Cl₂ (10 ml × 3). The combined org. phases were washed with sat. aq. NH₄Cl soln. (5 ml × 2), H₂O (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. ¹H-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 (2d, *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). ¹³C-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-[(2R,3S)-3-(1H-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. NH₄Cl soln. (4 ml) and H₂O (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. NaHCO₃ 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). ¹H-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 (*2d*, *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-[*(2R,3S)*-3-(*1H*-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. NH₄Cl soln. (2 ml) and H₂O (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. NaHCO₃ 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). ¹H-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 (*2d*, *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-(*2R,3S*)-3-(*1H*-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. NH₄Cl soln. (2 ml) and H₂O (1 ml). After dissolving the precipitates under microwave irradiation, the mixture was extracted with CH₂Cl₂ (10 ml × 2). The combined org. phases were washed with sat. aq. NaHCO₃ 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). ¹H-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-(*1aR,8bS*)-*1a,8b*-Dihydro-1-(phenylmethyl)azireno[2',3':3,4]pyrrolo[1,2-*a*]indol-2(*1H*)-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 Et₃N (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 Et₂O (10 ml). After filtration, the filtrate was washed with sat. aq. NH₄Cl 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/Et₂O, afforded **26** (0.87 g, 37%). Pale-brown solids. M.p. 121–122° (lit. [14] m.p. 121–123°). IR: 1742 (C=O). ¹H-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 (*2d*, *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). ¹H-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*⁺, C₁₈H₁₄N₂O⁺; 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/CH₂Cl₂ 1:1), followed by washing with hexane/Et₂O, afforded **26** (0.086 g, 45%) as yellow solid, which was identical to the product obtained by *Method A*.

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