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Synthetic Process Development of Antitumor Agent KT6587, an Indolocarbazole Alkaloid K252a Derivative

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Abstract:

A facile and large-scale preparation process of an antitumor agent KT6587 (2), derived from an indolocarbazole alkaloid K252a (1), has been developed. The new synthetic process requires four steps: (i) selective *N*-silylation of the amide group of 1 with *tert*-butyldimethylsilyl chloride, (ii) methylation of the hydroxy group, (iii) deprotection under aqueous acidic conditions to afford 3, and (iv) reduction of the methoxycarbonyl group to obtain 2. The key strategic improvement is to obtain fine quality of the intermediate 3 in a reasonable yield with reproducibility. This new process improves the overall yield from 33% to 70% without tedious chromatographic separations and hazardous conditions. Multikilogram quantities of KT6587 (2) for early clinical evaluation have been obtained by this method.

Introduction

K252a (**1**, Figure 1) is an indolocarbazole alkaloid isolated from *Nocardiopsis* species which shows potent inhibitory activities against protein kinase C and cyclic nucleotide-dependent protein kinases.[1] Recently, **1** has been found to be also a potent inhibitor of *trk* tyrosine kinase activity in vitro.[2−5] However, experiments performed in mice bearing P388 leukemia suggested that **1** lacked antitumor activity.[6] Therefore, screening efforts have been continued, focusing on identifying the new analogues of **1** which retain the *trk* inhibitory property and also exhibit antitumor activity in vivo.

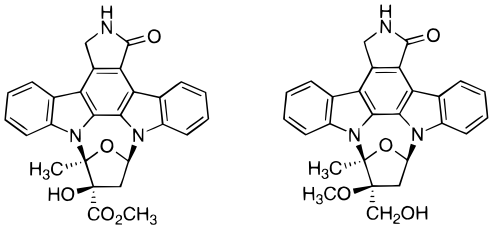

Figure 1. **Structures of K252a and KT6587.**

As a result, it was shown that KT6587 (**2**, Figure 1) inhibited potently the enzymatic activity of *trk* in tumor cells. Compound **2** also exhibited in vivo antitumor activity against mice tumors derived from NIH3T3 cells transfected with *trkA*, and **2** was expected to have therapeutic value against malignancies and other disorders caused by inappropriate *trk* activity.[7] Multikilogram quantities of **2** were required for researching pharmacological profiles and clinical trials.

The original synthesis consisted of the nonselective methylation of **1** with methyl iodide in the presence of sodium hydride in *N*,*N*-dimethylformamide, followed by a precise silica gel chromatographic separation to give **3** in 34% yield,[8] and subsequent reduction with sodium borohydride to give **2** in 97% yield (Scheme 1).[9] There are several problems in these procedures. The methylation of **1** contained an explosive risk between sodium hydride and *N*,*N*-dimethylformamide[10,11] and tedious chromatographic separation. The reduction of **3** was performed in low concentration using an excessive amount of sodium borohydride. The promise shown through the bioorganic and pharmaceutical studies of KT6587 (**2**) was sufficient to initiate industrialization studies of its synthesis.

Results and Discussion

From the viewpoint of the explosive risk in the combination of sodium hydride and *N*,*N*-dimethylformamide, alterna-

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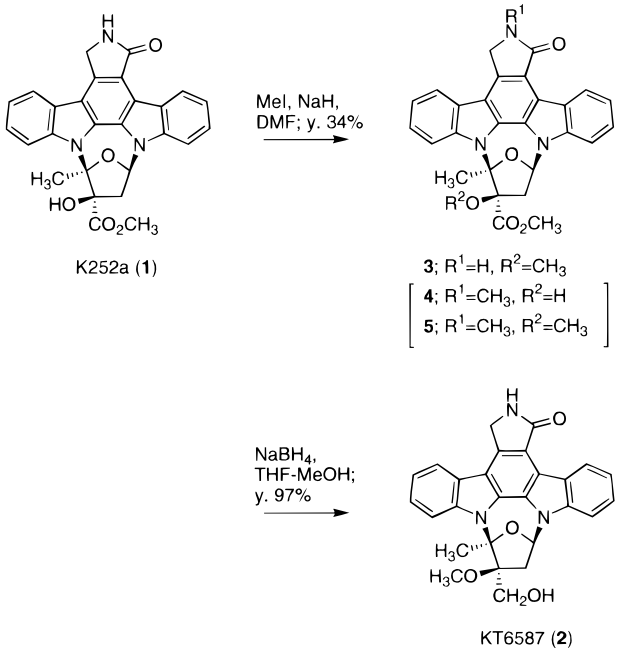
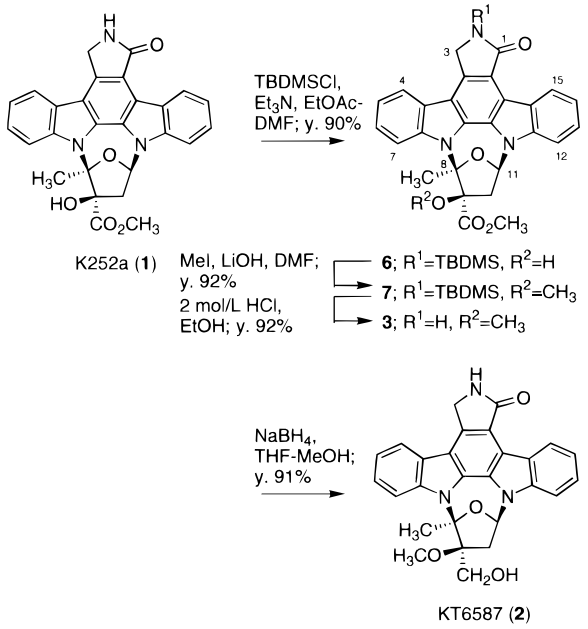
Scheme 1. **Original method[8,9]**



Scheme 2. **Improved method**



tive conditions for the methylation of K252a (**1**) were studied. With regard to reaction solvent, *N*,*N*-dimethylformamide was the most suitable because of its excellent solubilization of **1**. Sodium hydroxide as a base gave **3** in approximately 50% yield, similar to the original method. The optimized condition using sodium hydroxide and *N*,*N*-dimethylformamide (see Experimental Section) improved the yield of **3** to 74% and reduced the yields of byproducts **4** and **5**. However, the ratio of these compounds largely depended on the purity of **1**, with poor reproducibility. The purification by recrystallization did not succeed in removing the byproducts **4** and **5** efficiently, and the chromatographic separation using silica gel was necessary.

The main cause of the side reaction described above was the lack of selectivity in the methylation, because **1** has not only the hydroxy group but also the amide moiety. Among protecting groups being tried, the *tert*-butyldimethylsilyl group was the most suitable,[12,13] and this protecting group was selectively introduced to the amide moiety of **1**. Furthermore, the obtained compound **6** was stable under the following methylation conditions. The structure of *N*-silylated compound **6** was confirmed by NMR studies.[14] Then the synthetic route shown in Scheme 2 was investigated in detail at each step.

When we used *tert*-butyldimethylsilyl chloride in the presence of triethylamine in ethyl acetate containing 5% *N*,*N*-dimethylformamide compensating for the inferior solubility of **1**, the reaction proceeded smoothly and clearly to give **6** quantitatively. Through the workup procedures, washing with water and saturated brine, *N*,*N*-dimethylformamide was easily removed from the organic layer, and the crude solid of **6** was obtained after concentration under reduced pressure. Recrystallization from methanol and water gave **6** in 90% yield. This procedure has a significant reproducibility irrespective of the scale and the purity of the starting material **1**.

Table 1. **Effects of bases on the synthesis of 7[a]**

			conditions					
					yields (%)[c]			
base[b]	(equiv)	MeI (equiv)	temp (°C)	time (h)	**7**	**3**	**5**	unreacted **6** (%)[c]
NaOH	2.0	2.0	−5	4.0	97.8	0.7	1.1	0.4
NaOH	2.0	2.0	5	4.0	83.7	1.0	1.8	nd[d]
KOH	2.5	2.0	−5	5.0	78.1	1.9	6.8	0.3
LiOH	3.0	3.0	25	4.0	99.1	0.1	0.8	<0.1

[a] All reactions were performed in *N*,*N*-dimethylformamide. [b] Compound **7** was not obtained when using *i*-Pr_2NEt, DBU, or K_2CO_3. [c] Determined by quantitative HPLC analysis of the organic layer after workup. [d] Not detected.

Compound **6** was easily converted into the corresponding *O*-methylated compound **7** with methyl iodide and sodium hydroxide or lithium hydroxide as the base. Further studies on the quality of the reaction mixture when sodium hydroxide was used clarified that raising the reaction temperature from −5 to 5 °C decreased the yield of **7** and increased the amount of **3** and **5** by the desilylation (Table 1). On the other hand, the reaction proceeded smoothly at room temperature with lithium hydroxide to depress the amount of the undesirable compound **5**. As the workup procedure, quick neutralization with citric acid buffer solution to acidic pH (approximately 5.0) was necessary to depress the desilylation. By recrystallization from aqueous acetonitrile, the *O*-methylated compound **7** was obtained in 92% yield, and the residual **5** contained in **7** decreased to less than 0.3%.

(12) With regard to methoxymethyl, pivaloyl, or benzyl carbamates groups, the selectivities were not completely founded. In the case of carbamates, *N*-*tert*-butyl carbamate was obtained in 69% yield, but the *N*,*O*-di-*tert*-butyl carbamate was produced at 26%. In using other silyl groups such as triethylsilyl, triphenylsilyl, *tert*-butyldiphenylsilyl, or tri-*iso*-propylsilyl, no better results than those from using *tert*-butyldimethylsilyl were obtained.

(13) *N*-Silylation for the amide moiety was well used as a protecting group in the β-lactam chemistry. For an example, see: Ratctiffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31. Though the *N*-silylated derivative of 3-pyrrolin-2-one was synthesized,[17] our work is the first example for isoindolin-1-one or indolocarbazole compounds.

(14) NOEs between Si−CH_3 and 3-CH_2 were observed, although NOEs between Si−CH_3 and 15-CH were not observed. These results indicate that **6** is a 2-*N*-silylated, not an *O*-silylated compound.

Despite its insufficient solubilization of **7**, ethanol was used as the desilylation solvent in the presence of aqueous hydrochloric acid, and the reaction proceeded smoothly at 75 °C for 2 h to give **3**. In this case, the desilylated compound **3** was precipitated from the reaction mixture and was isolated easily by filtration (92% yield). The undesirable compound **5** was detected at approximately 0.1% at most, and **4** was not detectable by HPLC analysis. This strategic improvement made the procedures free from the need for chromatographic separation.

The reduction of the methoxycarbonyl group of **3** to a hydroxymethyl group was the final synthetic step to **2**. In the original method, the reduction of **3** was performed in a low concentration in a mixture of methanol and tetrahydrofuran with 20 equiv of sodium borohydride to consume **3** completely.[9] However, it seemed that the amount of sodium borohydride would decrease in the higher concentration and with its portionwise addition. The sudden exotherm and the uncontrolled gas evolution could be easily avoided as well. After quenching of the reaction with diluted hydrochloric acid, extraction with dichloromethane, passage of the organic layer through a small pad of silica gel, and crystallization from *N*,*N*-dimethylformamide and ethyl acetate gave the semipurified solid of **2** as an *N*,*N*-dimethylformamide solvate. This solvated form was clearly indicated by thermal analysis[15] and NMR studies.[16] This solvate could not be dried under reduced pressure to an acceptable residual solvent level. To remove *N*,*N*-dimethylformamide to the tolerated level in the drug bulk, the crude cake was suspended in water at the reflux temperature. As a result, high-quality compound **2** at more than 99.8% purity was obtained, and residual *N*,*N*-dimethylformamide was detected at not more than 100 ppm (91% yield from **3**).

In conclusion, an efficient four-step process for large-scale synthesis of the antitumor agent KT6587 has been developed. These procedures provided a higher total yield than the original synthesis and avoided the tedious chromatographic purification. Multikilogram quantities of the drug bulk have been produced successfully, using these procedures, for early clinical evaluations.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 MHz on AC-300 spectrometers, and signals are given in ppm using TMS as an internal standard. IR spectra were recorded on a Shimadzu FTIR-4300 spectrophotometer. SIMS spectra were recorded on a Hitachi M-80B mass spectrometer. HRFABMS were recorded on a JEOL JMS SX-102 mass spectrometer. All reagents and solvents were of commercial quality. Silica gel was Wako C-200.

HPLC Analyses. HPLC analysis was estimated using the following two sets of conditions. Conditions I: detector, ultraviolet absorption photometer (wavelength, 292 nm); column, GL Sciences Inc. Unisil Pack 250A (Unisil NQ C18 5 μm) 250 × 4.6 mm i.d.; mobile phase, mixture of 0.02 mol/L NH_4OAc and CH_3CN (1:9); flow rate, 1.0 mL/min; column temperature, 30 °C; t_R (min), **1** (3.7), **3** (4.9), **4** (4.4), **5** (5.6), **6** (6.7), **7** (12.7). Conditions II: detector, ultraviolet absorption photometer (wavelength, 292 nm); column, GL Sciences Inc. Unisil Pack 250A (Unisil NQ C18 5 μm) 250 × 4.6 mm i.d.; mobile phase, mixture of 0.02 mol/L phosphate buffer and CH_3CN (3:7); flow rate, 1.0 mL/min; column temperature, 30 °C; t_R (min), **2** (5.3), **3** (8.5).

(8*S*,9*R*,11*R*)-2-*tert*-Butyldimethylsilyl-9-hydroxy-9-methoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1*H*,8*H*,11*H*-2,7b,11a-triazadibenzo[*a*,*g*]cycloocta[*cde*]-trinden-1-one (6). To a suspension of **1** (K252a, 75.0 g, 160 mmol) in EtOAc (1200 mL), DMF (75 mL), and Et_3N (68 mL, 480 mmol) was added a solution of TBDMSCl (72.5 g, 480 mmol) in EtOAc (300 mL), and the mixture was stirred at 30 °C for 4 h. After the reaction was quenched with H_2O (1500 mL), the organic layer was washed with saturated brine twice (1500 mL each) and dried over Na_2SO_4, and then the filtrate was concentrated under reduced pressure. The resulting residue was crystallized from aqueous MeOH (1130 mL) and dried under vacuum to afford **6** as a pale yellow solid: 84.0 g (90%); mp 235−241 °C dec; ^{1}H NMR ($CDCl_3$/TMS) δ = 0.58 (s, 6H), 1.08 (s, 9H), 2.05 (dd, J = 13.8, 4.5 Hz, 1H), 2.20 (s, 3H), 3.21 (d, J = 5.0 Hz, 1H), 3.97 (s, 3H), 5.15 (d, J = 4.7 Hz, 2H), 6.44 (s, 1H), 7.20 (t, J = 5.1 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 7.54 (t, J = 7.3 Hz, 2H), 7.95 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 7.7 Hz, 1H), 9.25 (d, J = 8.0 Hz, 1H); IR (KBr) ν = 1746, 1670, 1585, 1458, 1347, 1275, 1202 cm^{-1}; SIMS 581 $(M + H)^+$; HRFABMS calcd for $C_{33}H_{35}N_3O_5Si$ *m*/*z* 582.2424 $(M + H)^+$, found 582.2442.

(8*S*,9*R*,11*R*)-2-*tert*-Butyldimethylsilyl-9-methoxy-9-methoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1*H*,8*H*,11*H*-2,7b,11a-triazadibenzo[*a*,*g*]cycloocta[*cde*]-trinden-1-one (7). To a solution of **6** (82.0 g, 141 mmol) in DMF (1640 mL) and MeI (26.4 mL, 423 mmol) was added LiOH (10.1 g, 423 mmol), and the mixture was stirred at 25 °C for 3 h. After being quenched with a chilled aqueous solution (1640 mL) containing citric acid monohydrate (44.8 g) and NaCl (65.6 g), the mixture was extracted twice with EtOAc (2050 and 820 mL). The organic layer was washed with H_2O (820 mL) and saturated brine twice (820 mL each) and dried over Na_2SO_4, and then the filtrate was concentrated under reduced pressure. The resulting residue was crystallized from aqueous CH_3CN (1800 mL) and dried under vacuum to afford **7** as a pale yellow solid: 77.1 g (92%); mp 260−272 °C dec; ^{1}H NMR ($CDCl_3$/TMS) δ = 0.56 (s, 6H), 1.07 (s, 9H), 2.10 (dd, J = 13.9, 4.9 Hz, 1H), 2.21 (s, 3H), 3.05 (s, 3H), 3.54 (dd, J = 13.7, 7.5 Hz, 1H), 4.01 (s, 3H), 5.14 (d, J = 4.7 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.33 (t, J =

(15) Thermogravimetry and differential thermal analysis (TG-DTA) was performed using a MacScience TG-DTA 2000, and the heating rate was 10.0 °C/min from 35 to 300 °C. The DTA curve showed the endothermic peak at 161.3 °C. The TG curve indicated that 13.9% of the weight proportion, which corresponds to the *N*,*N*-dimethylformamide portion in the 1:1 solvated form, diminished at 160 °C as described above.

(16) The ^{1}H NMR data of the solvated compound indicated the same molar amount of *N*,*N*-dimethylformamide as **1** was contained: ^{1}H NMR (DMSO-d_6) δ = 2.02 (dd, J = 13.6, 5.0 Hz, 1H), 2.23 (s, 3H), 2.72 (s, 3H), 2.88 (s, 3H), 2.97 (s, 3H), 3.04 (dd, J = 13.7, 7.6 Hz, 1H), 3.95 (br s, 2H), 5.01 (s, 2H), 5.32 (s, 1H), 7.08 (dd, J = 7.5, 5.0 Hz, 1H), 7.30 (m, 2H), 7.47 (m, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 7.7 Hz, 1H), 8.62 (s 1H), 9.21 (d, J = 7.9 Hz, 1H).

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7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.53 (t, J = 7.6 Hz, 2H), 7.89 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 9.23 (d, J = 8.1 Hz, 1H); IR (KBr) ν = 1732, 1664, 1589, 1456, 1350, 1272, 1098 cm^{-1}; SIMS 596 $(M + H)^+$; HRFABMS calcd for $C_{34}H_{37}N_3O_5Si$ m/z 596.2581 $(M + H)^+$, found 596.2572.

(8*S*,9*R*,11*R*)-9-Methoxy-9-methoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1*H*,8*H*,11*H*-2,7b,11a-triazadibenzo[*a*,*g*]cycloocta[*cde*]trinden-1-one (3). To a suspension of **7** (76.5 g, 128 mmol) in EtOH (1530 mL) was added 2 mol/L HCl (153 mL), and the mixture was stirred at 75 °C for 2 h. The mixture was then stirred under ice cooling for 1 h. The precipitated crystals were filtered, washed with cold aqueous EtOH, and dried under vacuum to afford **3** as a pale yellow solid: 57.1 g (92%); mp 252−257 °C dec; ^{1}H NMR (DMSO-d_6) δ = 2.20 (dd, J = 13.6, 5.0 Hz, 1H), 2.30 (s, 3H), 3.15 (s, 3H), 3.64 (dd, J = 13.6, 7.2 Hz, 1H), 4.10 (s, 3H), 5.13 (s, 2H), 7.39 (m, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.2 Hz, 2H), 7.99 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), 8.79 (s 1H), 9.34 (d, J = 7.8 Hz, 1H); IR (KBr) ν = 1735, 1680, 1460, 1395, 1315, 1272 cm^{-1}; SIMS 482 $(M + H)^+$; HRFABMS calcd for $C_{28}H_{23}N_3O_5$ m/z 482.1716 $(M + H)^+$, found 482.1740.

(8*S*,9*R*,11*R*)-2,8-Dimethyl-9-hydroxy-9-methoxycarbonyl-2,3,9,10-tetrahydro-8,11-epoxy-1*H*,8*H*,11*H*-2,7b,11a-triazadibenzo[*a*,*g*]cycloocta[*cde*]trinden-1-one (4) and (8*S*,9*R*,11*R*)-2,8-Dimethyl-9-methoxy-9-methoxycarbonyl-2,3,9,10-tetrahydro-8,11-epoxy-1*H*,8*H*,11*H*-2,7b,11a-triazadibenzo[*a*,*g*]cycloocta[*cde*]trinden-1-one (5). To a solution of **1** (K252a, 1.00 g, 2.14 mmol) in DMF (30 mL) were added powdery NaOH (128 mg, 3.21 mmol) and MeI (0.400 mL, 6.42 mmol), and the mixture was stirred under ice cooling for 5 h. After quenching with 1 mol/L HCl (2.0 mL) and concentrating under reduced pressure, to the residual mixture was added H_2O (20 mL), and the solution was extracted with $CHCl_3$ (20 mL). The organic layer was dried over Na_2SO_4, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, 95:5 $CHCl_3$/acetone as an eluent) to afford **3** (760 mg, 1.58 mmol; 74%), **4** (10 mg, 0.02 mol; 1%) as a pale yellow solid and **5** (150 mg, 0.30 mol; 14%) as a pale yellow solid, and **1** (90 mg, 0.19 mol; 9%) was recovered.

Compound **4**: ^{1}H NMR (DMSO-d_6) δ = 1.94 (dd, J = 13.9, 4.7 Hz, 1H), 2.08 (s, 3H), 3.21 (s, 3H), 3.86 (s, 3H), 5.03 (s, 2H), 6.31 (s, 1H), 7.08 (dd, J = 6.9, 4.9 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.43 (dd, J = 6.9, 6.0 Hz, 2H), 7.84 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 8.25 (s 1H), 9.16 (d, J = 8.2 Hz, 1H); IR (KBr) ν = 1734, 1652, 1458, 1394, 1317, 1259 cm^{-1}; SIMS 482 $(M + H)^+$; HRFABMS calcd for $C_{28}H_{23}N_3O_5$ m/z 482.1716 $(M + H)^+$, found 482.1715.

Compound **5:** ^{1}H NMR (DMSO-d_6) δ = 2.06 (dd, J = 13.6, 5.0 Hz, 1H), 2.16 (s, 3H), 3.02 (s, 3H), 3.25 (s, 3H), 3.50 (dd, J = 13.8, 7.5 Hz, 1H), 3.97 (s, 3H), 5.09 (s, 2H), 7.24 (t, J = 7.1 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 8.30 (s 1H), 9.21 (d, J = 8.0 Hz, 1H); IR (KBr) ν = 1732, 1678, 1458, 1394, 1296, 1274 cm^{-1}; SIMS 496 $(M + H)^+$; HRFABMS calcd for $C_{29}H_{25}N_3O_5$ m/z 496.1872 $(M + H)^+$, found 496.1868.

(8*S*,9*S*,11*R*)-9-Hydroxymethyl-9-methoxy-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1*H*,8*H*,11*H*-2,7b,11a-triazadibenzo[*a*,*g*]cycloocta[*cde*]trinden-1-one (2, KT6587). To a solution of **3** (54.5 g, 113 mmol) in THF (812 mL) and MeOH (273 mL) was added $NaBH_4$ (4.75 g, 125 mmol) four times at 20-min intervals (total 19.0 g, 500 mmol) at 40 °C, and the mixture was stirred at 40 °C for 2 h. To this suspension was added the mixture (5 °C) of CH_2Cl_2 (1090 mL), 2 mol/L HCl (490 mL), and saturated brine (1640 mL), and the solution was stirred at room temperature for 5 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (164 mL). The combined organic layer was washed with saturated brine (1640 mL) and dried over Na_2SO_4. The mixture was passed through a pad of silica gel (164 g) and washed with a mixture of CH_2Cl_2 and acetone (2:1) to afford a fraction containing **2**. After removal of volatiles, the residue was recrystallized from the mixture of EtOAc (500 mL) and DMF (50 mL) and dried under vacuum to afford the mono DMF solvate of **2** as a slightly yellow solid (54.4 g). To the solvate was added H_2O (1090 mL), and the suspension was refluxed for 3 h. After ice-cooling of the suspension for 1 h, the precipitated crystals were filtered, washed with cold H_2O (545 mL), and dried under vacuum to afford **2** as a pale yellow solid: 46.7 g (91%); mp 230−243 °C dec; ^{1}H NMR (DMSO-d_6) δ = 2.02 (dd, J = 13.6, 5.0 Hz, 1H), 2.23 (s, 3H), 2.97 (s, 3H), 3.04 (dd, J = 13.7, 7.6 Hz, 1H), 3.95 (br s, 2H), 5.01 (s, 2H), 5.32 (s, 1H), 7.08 (dd, J = 7.5, 5.0 Hz, 1H), 7.30 (m, 2H), 7.47 (m, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 7.7 Hz, 1H), 8.62 (s 1H), 9.21 (d, J = 7.9 Hz, 1H); IR (KBr) ν = 3412, 3063, 2837, 1668, 1587, 1458, 1123 cm^{-1}; UV λ_{max} (CH_3OH) nm (ϵ) 291 (68 800); SIMS 454 $(M + H)^+$; HRFABMS calcd for $C_{27}H_{23}N_3O_4$ m/z 454.1767 $(M + H)^+$, found 454.1779.

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