Enantioselective Synthesis of the Diazatricyclic Core of Alkaloid TAN1251C via an Iodoaminocyclization Reaction†

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A concise enantioselective synthesis of the diazatricyclic core of alkaloid TAN1251C is reported. The method featured a stereoselective formation of the iodide intermediate **16b** (in 2∶1 ratio) from homoallylic amine **11b** by iodine-promoted iodoaminocyclization, a previously claimed to be unsuccessful reaction. The intermediate **16b** was converted to the tricyclic core of TAN1251C **28** in five steps. During this study, two unexpected products **22** and **25** were obtained, and compound **23**, derived from **11a** was shown to be unsuitable for the oxidative formation of the enamide of TAN1251C.

Keywords alkaloids, iodoaminocyclization, azaspirane, asymmetric synthesis

Introduction

The TAN1251 series of alkaloids including TAN1251A (**1**), TAN11251B (**2**), TAN1251C (**3**), and TAN1251D (**4**) were isolated from a *Penicillium thomii* RA89 fermentation broth at Takeda Industries[1] (Figure 1). TAN1251A and TAN1251B exhibit cholinergic activity and cause acetylcholine-induced contraction of Guinea-pig ileum.[2] TAN1251A is also known as a selective muscarinic M_1 subtype receptor antagonist.[3] The affinity of TAN1251B to a muscarinic acetylcholine receptor is stronger than that of atropine. Like its congeners, TAN1251C is a muscarinic antagonist of potential interest in the treatment of ulcer.[4]

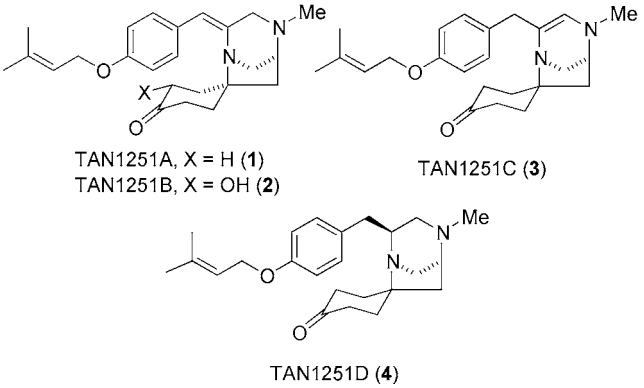

Figure 1 The structures of TAN1251 family.

The attractive biological activity of TAN1251 compounds and unique diazatricyclic structure have attracted significant attention from synthetic organic chemists, and several approaches for the synthesis of TAN1251 alkaloid have been published.[5-8] Most of them have been devoted to the synthesis of TAN1251A.[5] Comparatively, little attention was focused on the asymmetric synthesis of TAN1251C.[7] Most synthetic approaches to TAN1251 alkaloid involved initial formation of a 1-azaspiro[4,5]decane,[9] followed by a ring-closure reaction to form the tricyclic system.[10] Kawahara and co-workers[5b,5c,5g] used compound **5a** and **5b** to synthesize (−) and (+)-TAN1251A. Similarly, Wardrop's group synthesized (−)-TAN1251A using azaspiro compound **6**.[5e] Recently, Snider and Ciufolini reported the synthesis of TAN1251C via building block **7**[5f] and **8**[7b], respectively (Figure 2).

With the aim to develop an asymmetric approach to TAN1251C, optically active 1-azaspiro[4,5]decane derivative **9a** was selected as a common intermediate in our initial study (Scheme 1). Compound **9a** could be prepared from iodide **16a**. The later was envisioned to be synthesized from optically active homoallylic amine **11a** by iodine-promoted iodoaminocyclization reaction.[11]

Experimental

Optical rotations were recorded on a Perkin-Elmer 341 automatic polarimeter. ^{1}H NMR and ^{13}C NMR

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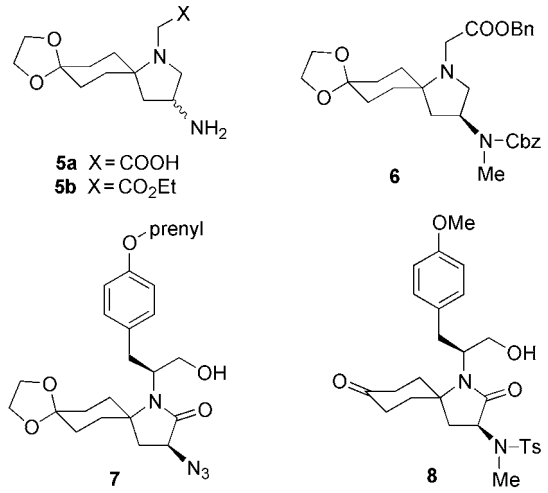
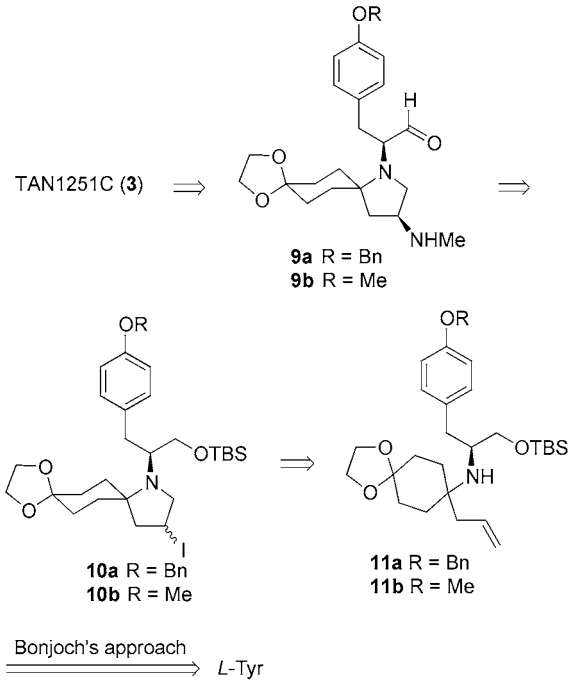


Figure 2 The structures of some azaspirane compounds.

Scheme 1 Retrosynthetic analysis of TAN1251C (**3**)



spectra were recorded on a Bruker 400 spectrometer. ^{1}H NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed relative to internal Me_4Si. IR spectra were recorded on a Nicolet Avatar 360 RT-IR spectrophotometer. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus and Finnigan Mat-LCQ (ESI direct injection). HRFABMS spectra were recorded on a Bruker APEX-FTMS apparatus. Elemental analyses were performed using a Vario RL analyzer. Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) was distilled prior to use from sodium benzophenone ketyl. Dichloromethane was distilled from phosphorus pentoxide. Dimethylformamide was distilled from calcium hydride. Silica gel from Yantai silica gel factory (China) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate (EtOAc)/petroleum ether (PE) (60—90 ℃) mixture.

Compounds **12a** and **12b** were prepared essentially according to the literature procedure,[11b] excepted that all the reactions were preformed at 0 ℃ or at room temperature.

(8-Allyl-1,4-dioxa-spiro[4.5]dec-8-yl)-[1-(4-benzyloxy-benzyl)-2-(*tert*-butyldimethylsilanyloxy)-ethyl]-amine (11a)

To a solution of 1,4-cyclohexanedione monoethylene acetal (126 mg, 0.8 mmol) in CH_2Cl_2 (2 mL) was added 4 Å molecular sieves (0.5 g) and a solution of compound **12a** (300 mg, 0.8 mmol) in CH_2Cl_2 (2 mL). After stirring at room temperature overnight, the suspension was filtered through a celite, and the filtrate was concentrated under reduced pressure to give the corresponding imine **13a**. To a solution of this imine in Et_2O (4 mL) was added dropwise allylmagnesium bromide (4.0 mL, 0.5 mol/L). The reaction was stirred at 0 ℃ for 2 h, then at r.t. for 2 h and the reaction was quenched with NH_4Cl (4 mL), H_2O (2 mL), and extracted with CH_2Cl_2 (4 mL×3). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with [*V*(PE)∶*V*(EtOAc)=10∶1] to give amine **11a** (279 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ −3.0 (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.03 (s, 6H), 0.90 (s, 9H), 1.40—1.80 (m, 8H), 2.10—2.20 (m, 2H), 2.65 (dd, *J*=5.8, 13.5 Hz, 1H), 2.77 (dd, *J*=7.2, 13.5 Hz, 1H), 2.85—2.92 (m, 1H), 3.32 (dd, *J*=6.0, 9.8 Hz, 1H), 3.45 (dd, *J*=4.4, 9.8 Hz, 1H), 3.91 (s, 4H), 4.98—5.05 (m, 4H), 5.70—5.85 (m, 1H), 6.88 (d, *J*=8.6 Hz, 2H), 7.10 (d, *J*=8.6 Hz, 2H), 7.30—7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: −5.4, −5.3, 18.3, 26.0, 30.6, 30.7, 33.2, 39.6, 53.6, 53.8, 64.1, 65.7, 70.1, 108.9, 114.7, 117.3, 127.4, 127.8, 128.5, 130.5, 132.1, 134.8, 137.3, 157.2; IR (film) *v*: 3067, 3030, 2928, 2856, 1610, 1510, 1470, 1247, 1103 cm^{-1}; MS (ESI) *m/z*: 552 ($M+H^+$). Anal. calcd for $C_{33}H_{49}NO_4Si$: C 71.82, H 8.95, N 2.54; found C 71.48, H 8.77, N 2.43.

2-[11-(Benzylmethylamino)-1,4-dioxa-9-azadispiro-[4.2.4.2]tetradec-9-yl]-3-(4-benzyloxyphenyl)-propan-1-ol (18a) and 2-[11-(benzylmethylamino)-1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-9-yl]-3-(4-benzyloxy-phenyl)-propan-1-ol (19a)

A solution of iodine (50 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a mixture of amine **11a** (50 mg, 0.09 mmol) in CH_2Cl_2 (0.36 mL) and 5% aqueous $NaHCO_3$ (1 mL). After stirring for 4 h at room temperature, a 10% aqueous $Na_2S_2O_3$ (5 mL) was added. The mixture was extracted with CH_2Cl_2 (5 mL×4). The combined organic phases were concentrated under reduced pressure to give a diastereomeric mixture of iodides **16a**, which was used in the next step without further purification.

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To a solution of the diastereomeric mixture of iodides **16a** (0.09 mmol) in CH_3CN (0.2 mL) were added benzylmethylamine (32 mg, 0.27 mmol) and K_2CO_3 (37 mg, 0.27 mmol). After stirring at 40 ℃ overnight, the suspension was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel [*V*(PE)∶*V*(EtOAc)=10∶1] to afford diamine **17a** (26 mg, 44% from **11a**) as a diastereomeric mixture. **17a** was used in the next step without further purification.

To a solution of the diastereomeric mixture of **17a** (20 mg, 0.03 mmol) in THF (0.06 mL) was added a solution of tetrabutylammonium fluoride (TBAF) (1 mol/L in THF, 0.1 mL). After stirring for 12 h at room temperature, the reaction was quenched with water and extracted with EtOAc (3 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with [*V*(PE)∶*V*(EtOAc)=1∶1] to afford alcohols **18a** (10 mg, 60%) as a colorless oil and **19a** (5 mg, 30%) as a colorless oil. **18a**: $[\alpha]_D^{20}$ −40.3 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.24—1.33 (m, 2H), 1.65—1.84 (m, 6H), 1.85—1.98 (m, 2H), 2.12 (s, 3H), 2.22 (dd, *J*=7.4, 12.7 Hz, 1H), 2.45 (dd, *J*=10.2, 13.2 Hz, 1H), 2.80—2.91 (m, 2H), 2.98 (dd, *J*=1.0, 12.1 Hz, 1H), 3.10—3.20 (m, 3H), 3.29 (dd, *J*=10.9, 16.0 Hz, 1H), 3.45 (d, *J*=12.9 Hz, 1H), 3.56 (d, *J*=12.9 Hz, 1H), 3.92—3.97 (m, 4H), 5.03 (s, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 7.07 (d, *J*=8.6 Hz, 2H), 7.24—7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 31.8, 32.1, 33.0, 35.6, 36.3, 40.3, 40.8, 48.0, 56.0, 60.3, 60.8, 62.4, 62.5, 64.2, 64.3, 70.0, 108.0, 115.0, 127.0, 127.4, 127.8, 128.2, 128.5, 129.1, 129.7, 131.1, 137.0, 138.5, 157.2; IR (film) *v*: 3404, 2946, 2857, 1510, 1453, 1369, 1240, 1106, 1028 cm^{-1}; MS (ESI) *m/z*: 557 ($M+H^+$). Anal. calcd for $C_{35}H_{44}N_2O_4$: C 75.51, H 7.97, N 5.03; found C 75.13, H 7.55, N 4.96.

19a: $[\alpha]_D^{20}$ −8.2 (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.30—1.40 (m, 1H), 1.52—1.82 (m, 7H), 2.02 (td, *J*=4.0, 13.5 Hz, 1H), 2.15 (s, 3H), 2.31 (dd, *J*=7.4, 12.5 Hz, 1H), 2.53 (dd, *J*=10.4, 13.4 Hz, 1H), 2.82 (dd, *J*=3.2, 13.4 Hz, 1H), 3.03 (dd, *J*=3.5, 8.5 Hz, 1H), 3.09—3.27 (m, 4H), 3.35 (dd, *J*=4.8, 10.1 Hz, 1H), 3.51 (d, *J*=13.1 Hz, 1H), 3.54 (d, *J*=13.1 Hz, 1H), 3.90—3.40 (m, 4H), 5.05 (s, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H), 7.25—7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 29.2, 29.7, 32.9, 35.2, 36.0, 38.0, 38.9, 45.9, 49.0, 56.2, 59.8, 60.9, 63.6, 64.2, 64.3, 70.0, 108.1, 114.9, 127.0, 127.4, 127.9, 128.3, 128.5, 129.0, 129.8, 131.6, 137.1, 138.8, 157.2; IR (film) *v*: 3396, 2926, 2859, 2786, 1719, 1649, 1513, 1431, 1377, 1237 cm^{-1}; MS (ESI) *m/z*: 557 ($M+H^+$). Anal. calcd for $C_{35}H_{44}N_2O_4$: C 75.51, H 7.97, N 5.03; found C 75.16, H 7.64, N 4.95.

(8-Allyl-1,4-dioxaspiro[4.5]dec-8-yl)-[2-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxybenzyl)-ethyl]-amine (11b)

To a solution of 1,4-cyclohexanedione monoethylene acetal (126 mg, 0.8 mmol) in CH_2Cl_2 (2 mL) were added 4 Å molecular sieves (0.5 g) and a solution of compound **12b** (240 mg, 0.8 mmol) in CH_2Cl_2 (2 mL). After stirring at room temperature overnight, the suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure to give the corresponding imine **13b**. To a solution of this imine in Et_2O (4 mL) was added dropwise allylmagnesium bromide (4.0 mL, 0.5 mol/L). The reaction was stirred at 0 ℃ for 2 h, then at r.t. for 2 h and the reaction was quenched with NH_4Cl (4 mL), H_2O (2 mL), and extracted with CH_2Cl_2 (4 mL×3). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with [*V*(PE)∶*V*(EtOAc)=10∶1] to give amine **11b** (310 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ −2.8 (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 0.03 (s, 6H), 0.91 (s, 9H), 1.40—1.60 (m, 6H), 1.60—1.81 (m, 2H), 2.09—2.21 (m, 2H), 2.65 (dd, *J*=5.8, 13.5 Hz, 1H), 2.75 (dd, *J*=7.2, 13.5 Hz, 1H), 2.87—2.95 (m, 1H), 3.31 (dd, *J*=6.0, 9.8 Hz, 1H), 3.45 (dd, *J*=4.4, 9.8 Hz, 1H), 3.79 (s, 3H), 3.91 (s, 4H), 4.98—5.05 (m, 2H), 5.70—5.82 (m, 1H), 6.80 (d, *J*=8.6 Hz, 2H), 7.10 (d, *J*=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: −5.3, −5.4, 18.3, 25.9, 30.6, 30.7, 33.2, 39.5, 42.8, 53.6, 53.8, 55.3, 64.1, 65.6, 108.9, 113.7, 117.2, 130.5, 131.8, 134.8, 158.0; IR (film) *v*: 2952, 2929, 2857, 1611, 1512, 1247, 1108 cm^{-1}; MS (ESI) *m/z*: 476 ($M+H^+$). Anal. calcd for $C_{27}H_{45}NO_4Si$: C 68.17, H 9.53, N 2.94; found C 68.47, H 9.84, N 3.09.

2-[11-(Benzylmethylamino)-1,4-dioxa-9-azadispiro-[4.2.4.2]tetradec-9-yl]-3-(4-methoxyphenyl)-propan-1-ol (18b) and 2-[11-(benzylmethylamino)-1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-9-yl]-3-(4-methoxyphenyl)-propan-1-ol (19b)

A solution of I_2 (40 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a mixture of amine **11b** (50 mg, 0.105 mmol) in CH_2Cl_2 (0.4 mL) and 5% aqueous $NaHCO_3$ (1 mL). After stirring for 4 h at room temperature, a 10% aqueous $Na_2S_2O_3$ (3 mL) was added. The mixture was extracted with CH_2Cl_2 (5 mL×4), The combined organic phases were concentrated under reduced pressure to give a diastereomeric mixture of iodides **16b**, which was used in the next step without further purification.

To a solution of the diastereomeric mixture of iodides **16b** (0.1 mmol) in CH_3CN (0.2 mL) were added benzylmethylamine (32 mg, 0.27 mmol) and K_2CO_3 (37 mg, 0.27 mmol). The mixture was stirred at 40 ℃ overnight, the suspension was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica

gel [*V*(PE)∶*V*(EtOAc)=10∶1] to afford diamine **17b** (19 mg, 30% from **11b**) as a diastereomeric mixture.

To a solution of the diastereomeric mixture of **17b** (400 mg, 0.67 mmol) in THF (0.2 mL) was added a solution of TBAF (1 mol/L in THF, 2 mL). After stirring for 12 h at room temperature, the reaction was quenched with water and extracted with EtOAc (3 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with [*V*(PE)∶*V*(EtOAc)=1∶1] to afford alcohols **18b** (192 mg, 60%) and **19b** (96 mg, 30%) as colorless oils. **18b**: $[\alpha]_D^{20}$ −8.2 (*c* 0.8, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.20—1.30 (m, 2H), 1.65—1.85 (m, 6H), 1.87—1.96 (m, 2H), 2.12 (s, 3H), 2.22 (dd, *J*=7.4, 12.3 Hz, 1H), 2.45 (dd, *J*=10.1, 12.1 Hz, 1H), 2.80—2.91 (m, 2H), 2.98 (dd, *J*=1.0, 12.1 Hz, 1H), 3.10—3.19 (m, 3H), 3.29 (dd, *J*=10.9, 16.0 Hz, 1H), 3.47 (d, *J*=12.9 Hz, 1H), 3.57 (d, *J*=12.9 Hz, 1H), 3.79 (s, 3H), 3.92—3.97 (m, 4H), 6.83 (d, *J*=8.6 Hz, 2H), 7.09 (d, *J*=8.6 Hz, 2H), 7.25—7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 31.8, 32.2, 33.1, 35.6, 36.3, 40.3, 40.8, 48.1, 55.3, 56.1, 60.4, 60.9, 62.6, 64.2, 64.3, 108.0, 114.0, 127.1, 128.3, 129.2, 129.8, 130.9, 158.1; IR (film) *v*: 3420, 2935, 2847, 1611, 1511, 1247, 1106, 1034 cm^{-1}; MS (ESI) *m/z*: 481 (M+H$^+$); HRMS (ESI) calcd for [$C_{29}H_{40}N_2O_4$+H$^+$] 481.3066, found 481.3077.

19b: $[\alpha]_D^{20}$ −35.6 (*c* 0.4, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.30—1.37 (m, 1H), 1.51—1.80 (m, 7H), 2.00 (td, *J*=3.9, 13.3 Hz, 1H), 2.15 (s, 3H), 2.31 (dd, *J*=7.5, 13.3 Hz, 1H), 2.53 (dd, *J*=10.4, 13.4 Hz, 1H), 2.82 (dd, *J*=3.2, 13.4 Hz, 1H), 3.03 (dd, *J*=3.6, 8.7 Hz, 1H), 3.09—3.27 (m, 4H), 3.35 (dd, *J*=4.8, 10.1 Hz, 1H), 3.51 (d, *J*=13.2 Hz, 1H), 3.54 (d, *J*=13.2 Hz, 1H), 3.78 (s, 3H), 3.90—4.00 (m, 4H), 6.81 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 29.2, 29.7, 32.9, 33.0, 35.3, 36.0, 38.0, 38.9, 46.0, 55.3, 56.3, 59.8, 61.0, 63.6, 64.2, 64.3, 108.2, 113.9, 127.1, 128.3, 129.1, 129.8, 131.3, 158.1; IR (film) *v*: 3389, 2933, 1681, 1512, 1442, 1247, 1178, 1106, 1034 cm^{-1}; MS (ESI) *m/z*: 481 (M+H$^+$); HRMS (ESI) calcd for [$C_{29}H_{40}N_2O_4$+H$^+$] 481.3066, found 481.3076.

3-(4-Methoxyphenyl)-2-(11-methylamino-1,4-dioxa-9-azadispiro[4.2.4.2]tetradec-9-yl)-propan-1-ol (26)

To a degassed methanolic solution (5 mL) of compound **18b** (100 mg, 0.21 mmol) was added 20% $Pd(OH)_2$/C (50 mg). The mixture was stirred at room temperature under 101.3 kPa hydrogen pressure for 4 h. After filtration through Celite, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with [*V*(CH_2Cl_2)∶*V*(MeOH)∶*V*(Et_3N)=10∶1∶0.1] to afford compound **26** (49 mg, 60%) as a colourless oil. $[\alpha]_D^{20}$ −12.0 (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.22—1.28 (m, 1H), 1.53 (dd, *J*=7.6, 12.5 Hz, 1H), 1.61—1.80 (m, 5H), 1.84—1.93 (m, 2H), 2.21 (dd, *J*=8.2, 12.5 Hz, 1H), 2.43 (s, 3H), 2.45 (dd, *J*=10.4, 13.1 Hz, 1H), 2.65 (dd, *J*=8.2, 7.2 Hz, 1H), 2.92 (dd, *J*=2.9, 13.1 Hz, 1H), 3.10—3.21 (m, 4H), 3.30 (dd, *J*=3.9, 8.9 Hz, 1H), 3.79 (s, 3H), 3.90—4.00 (m, 4H), 6.81 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 31.6, 32.3, 33.0, 35.2, 35.3, 36.3, 42.1, 49.4, 55.2, 56.0, 57.5, 60.6, 62.3, 64.2, 64.3, 108.0, 113.9, 129.7, 131.0, 158.1; IR (film) *v*: 3393, 2932, 1606, 1511, 1246, 1104, 1033 cm^{-1}; MS (ESI) *m/z*: 391 (M+H$^+$); HRMS (ESI) calcd for [$C_{22}H_{34}N_2O_4$+H$^+$] 391.2597, found 391.2607.

(5*S*)-4-Methyl-2-[(4-methoxyphenyl)methyl]-dispiro-[1,4-diazabicyclo[3.2.1]oct[2]en-7,1'-cyclohexane-4', 2"-[1,3]dioxepane] (28)

Trifluoroacetic anhydride (0.04 mL, 0.298 mmol) was added to a solution of DMSO (0.05 mL, 0.662 mmol) in 0.8 mL of CH_2Cl_2 at −78 ℃ and the resulting mixture was stirred at −78 ℃ for 20 min. To the resulting mixture was added a solution of **26** (17 mg, 0.044 mmol) in 0.8 mL of CH_2Cl_2, and the mixture was stirred for 30 min. Then Et_3N (0.07 mL, 0.53 mmol) was added and the mixture was allowed to warm to 0 ℃, stirred for 30 min and was taken up with 5 mL of CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). After filtration, the solvent was concentrated under reduced pressure to give the crude aldehyde **27** as a mixture of diastereomers, which was used in the next step without further purification.

To a solution of **27** in 2 mL of MeOH were added 0.8 mL of water and K_2CO_3 (100 mg, 0.72 mmol). The reaction was stirred at 25 ℃ for 2 h and concentrated under reduced pressure. The residue was taken up with 5 mL of CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). After filtration, the solvent was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with [*V*(CH_2Cl_2)∶*V*(MeOH)=60∶1] to give **28** (9.8 mg, 60%) as a colorless oil. $[\alpha]_D^{20}$ +10.5 (*c* 0.6, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.45—1.52 (m, 1H), 1.59—1.80 (m, 6H), 1.85—1.91 (m, 1H), 2.00—2.10 (m, 2H), 2.45 (s, 3H), 2.71 (dd, *J*=1.0, 11.4 Hz, 1H), 3.16 (dd, *J*=2.2, 11.4 Hz, 1H), 3.22 (s, 2H), 3.28—3.32 (m, 1H), 3.78 (s, 3H), 3.90—4.00 (m, 4H), 5.11 (s, 1H), 6.81 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 29.7, 31.7, 32.5, 33.5, 34.9, 40.4, 41.4, 42.4, 51.6, 55.2, 59.1, 64.3, 72.1, 108.5, 113.6, 114.6, 127.3, 130.1, 132.2, 157.8; IR (film) *v*: 2879, 2851, 2929, 1586, 1510, 1245, 1106, 1036 cm^{-1}; MS (ESI) *m/z*: 393 ($C_{22}H_{30}N_2O_3$+Na$^+$); HRMS (ESI) calcd for [$C_{22}H_{30}N_2O_3$+Na$^+$] 393.2154, found 393.2140.

Results and discussion

Our synthesis commenced with the preparation of the *O*-TBS (*O*-*tert*-butyldimethylsilyl) protected *β*-amino alcohols **12a** and **12b**. The building blocks **12a** and **12b** were prepared from *L*-tyrosine by a known

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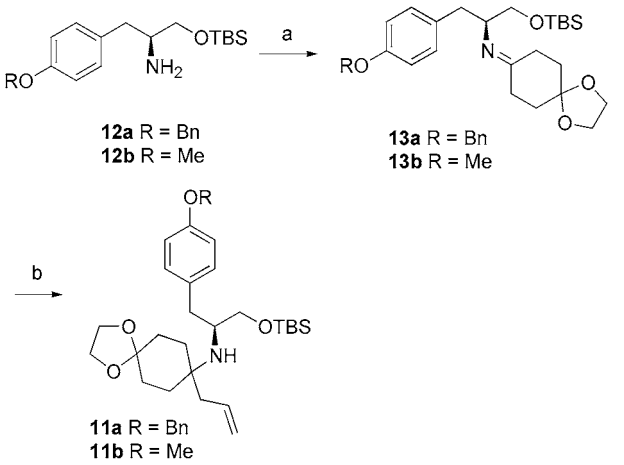
procedure[11b] with minor modification. The key element resided in running all reactions at 0 ℃ or room temperature to avoid any possible racemization. Thus the total yield was improved to 40% (for **12a**) and 49% (for **12b**), respectively.

The requisite homoallylamine **11a** was prepared by the Bonjoch's one-pot procedure[11b] with modifications. Thus, in the presence of 4 Å MS, 1,4-cyclohexanedione monoethylene acetal reacted with protected amino alcohol **12a** (CH_2Cl_2, r.t., overnight) to yield the corresponding imine **13a**, which was treated with allylmagnesium bromide (Et_2O, 0 ℃, 2 h) to give the addition product **11a** in an overall yield of 82%[12] (Scheme 2). Following the same procedure, homoallylamine **11b** was prepared from protected amino alcohol **12b** in 83% yield.

Scheme 2 Synthesis of homoallylamines **11a** and **11b**

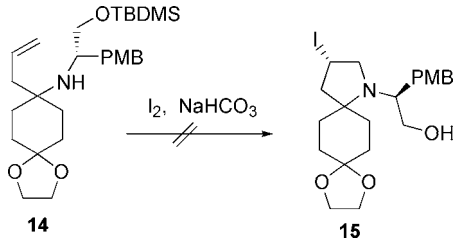


Reagents and conditions: (a) 1,4-Cyclohexanedione monoethylene acetal, 4 Å MS, CH_2Cl_2, r.t., overnight; (b) allylmagnesium bromide, Et_2O, 0 ℃, 2 h, 82% yield (for **11a**) and 83% yield (for **11b**) over two steps

With the homoallylamine **11a** in hand, we proceeded to investigate the key iodoaminocyclization reaction. When amino-olefin **11a** was treated with iodine in alkaline medium, an iodoaminocyclization proceeded smoothly to provide the 3-iodopyrrolidine **16a**. Iodine-promoted iodoaminocyclization process has been employed to form some *N*-containing ring systems.[11] However, Bonjoch and co-workers[11b] reported that attempt to prepare **15** from homoallylamine **14** by iodoaminocyclization procedure was unsuccessful due to the steric hindrance (Scheme 3).

Initial attempts to isolate the iodo-amine product **16a** by silica gel chromatography met with failure, which was attributed to the lability of the iodo-amine during the column chromatography. To tackle this problem, work-up procedure was modified. Thus, after the reaction and work-up, without purification of the resultant iodo-amine **16a**, the mixture was treated with K_2CO_3 in CH_3CN and allowed to react with methyl benzylamine

Scheme 3 Unsuccessful iodoaminocyclization reaction of compound **14**



at 40 ℃ overnight to afford the corresponding amine **17a** in 44% yield from **11a**. It is noteworthy that in order to improve the yield of iodide **16a**, iodine solution in dichloromethane should be slowly added to a sodium bicarbonate solution of homoallylamine **11a**. As indicated by the ^{1}H NMR spectral, azaspirane **17a** is a mixture of two diastereomers, and is inseparable by column chromatography on silica gel. To our satisfaction, when the *tert*-butyldimethylsilyl (TBS) group in **17a** was cleaved with TBAF in dichloromethane, alcohols **18a** and **19a** were obtained in a ratio of 2∶1 (determined by ^{1}H NMR, combined 90% yield), which are separable by flash chromatography on silica gel.

To determine the stereochemistries of diastereomers **18a** and **19a**, their NOESY spectra were recorded. However, due to both the overlap of signals at δ 3.15 and the free rotation of the C—N bond, we were unable to determine the stereochemistry of **18a**. In contrast, a correlation between the proton at C-3 (δ 3.20) and one of the benzylic protons at C-6 (δ 2.53) was observed for **19a** (Figure 3). Because C-6 is not in the ring, the observed resonance signals at this carbon reflected an average result. On the basis of this result, the configuration of C-3 was tentatively assigned as *R*. To confirm this reasoning, quantum chemical calculations were performed. In the optimized stable conformation of **19a** (Figure 4), the nearest distance between the proton at C-3 and one of the benzylic proton at C-6 was 2.501 Å, which is within the range of observable NOEs. Furthermore, in the optimized stable conformation of **18a**, the nearest distance between the proton at C-3 and one of the benzylic protons at C-6 was 4.587 Å, which is at the marginal to observe NOEs between the two

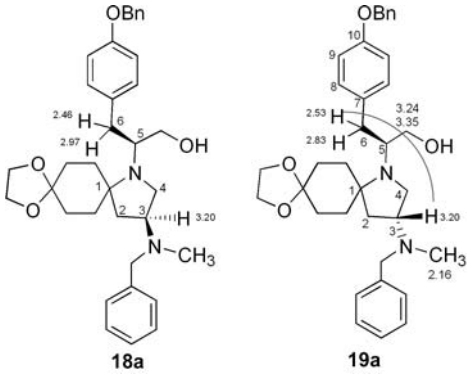


Figure 3 Selected NOESY correlation for compounds **18a** and **19a**.

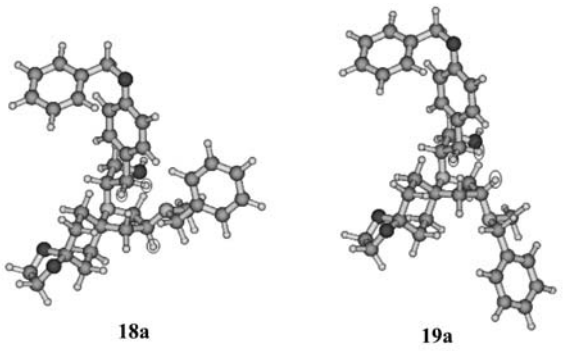
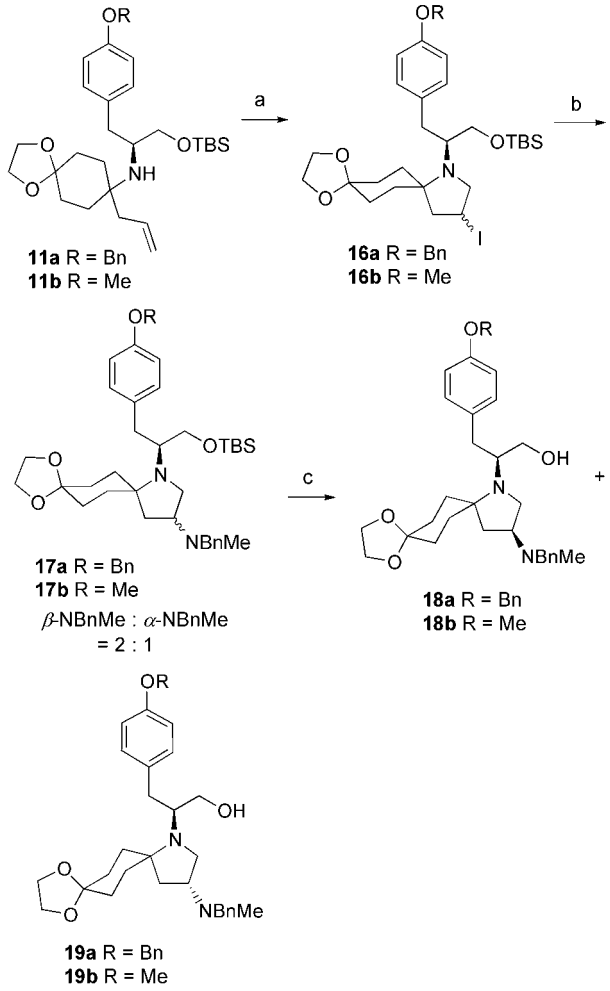


Figure 4 B3LYP/6-31G*-optimized structures for compounds **18a** and **19a**.

protons. Thus, the stereochemistries of diastereomers **18a** and **19a** were determined to be those shown in Figure 3. Because the *N*-substitution of the system in analog to **16** has been shown to proceed with inversion of configuration,[13] the stereochemistries of the diastereomeric **16a** were determined as those shown in Scheme 4.

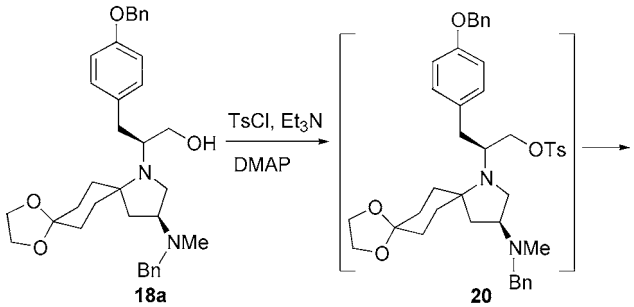
Scheme 4 Synthesis of 1-azaspiroanes **18** and **19**.



Reagents and conditions: (a) I_2, sat. $NaHCO_3$, CH_2Cl_2, r.t., 4 h; (b) BnNHMe, CH_3CN, K_2CO_3, 40 ℃, overnight, yields over two steps 44% for **17a**; 30% for **17b**; (c) TBAF, THF, r.t., 12 h, 90% (R=Bn) and 80% (R=Me)

With the azaspiranes in hand, their cyclizations to form the tricyclic systems were investigated. To this end, *O*-tosylation of **18a** was first attempted (*p*-TsCl, DMAP, Et_3N) (Scheme 5). However, instead of the desired tosylation product **20**, an unexpected chloride (**22**) was obtained in 80% yield, which was presumed to be formed via the aziridinium intermediate **21**.[14] The structure of the chloride **22** was determined by HMBC technique (Figure 5). The stereochemistry of the newly formed stereogenic center was not determined.

Scheme 5 Reaction of compound **18a** with TsCl



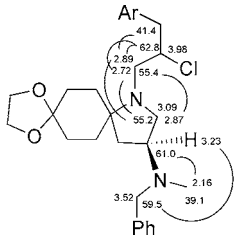


Figure 5 Part correlations shown in HMBC spectrum of compound **22**.

To overcome this difficulty, a debenzylation-cyclization procedure was designed (Scheme 6). Unfortunately, although the concomitant *N*,*O*-didebenzylation under hydrogenolytic conditions gave compound **23** in 60% yield, its cyclization under Ciufolini's conditions failed.[7c] Alternatively, compound **23** was subjected to oxidation with TFAA-DMSO-Et_3N system,[15] and the presumed resultant aldehyde was treated with K_2CO_3 in MeOH/H_2O, which afforded an unexpected TAN1251C derivative **25** in a yield of 20%. Presumably, compound **25** was resulted from a rearrangement of the sulfur ylide formed during the reaction course.[16]

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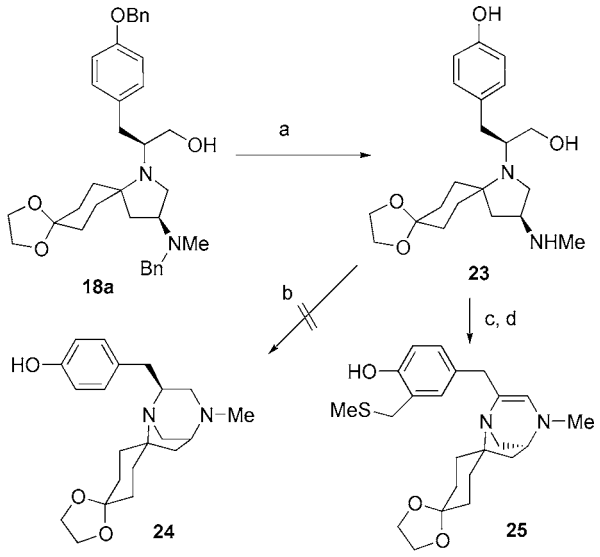
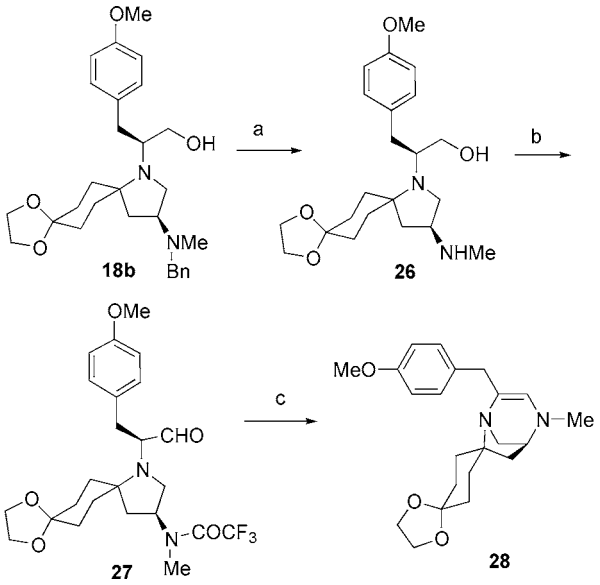
Scheme 6 The formation of compound **25**



Reagents and conditions: (a) 20% $Pd(OH)_2/C$, H_2, MeOH, r.t., 4 h, 60%; (b) PPh_3, CCl_4, Et_3N; (c) TFAA, DMSO, Et_3N, CH_2Cl_2, −78 ℃ to 0 ℃, 2 h; (d) K_2CO_3, MeOH/H_2O, r.t., 2 h, 20% from **23**

Now it was clear that the free phenol hydroxyl group in intermediate **23** is unsuitable for the construction of the desired tricyclic system. We then turned our attention to investigate the analog of **18a**, namely, methyl aryl ether **18b**. Compound **18b** was prepared as outlined in Schemes 3 and 4, and then subjected to hydrogenolysis (101.3 kPa H_2, 20% $Pd(OH)_2/C$, MeOH, r.t., 4 h) to generate the desired secondary amine **26** in 60% yield (Scheme 7). Compound **26** was oxidized with TFAA/DMSO to yield the aldehyde intermediate **27**, which without further purification, was subjected to hydrolytic conditions (K_2CO_3, MeOH/H_2O, r.t., 2 h) to give, via the presumed intermediate **9b**, the tricyclic core of TAN1251C (**28**) in an overall yield of 60%.

Scheme 7 Synthesis of the core structure of TAN1251C (**28**)



Reagents and conditions: (a) $Pd(OH)_2/C$, H_2, MeOH, r.t., 4 h, 60%; (b) TFAA, DMSO, Et_3N, CH_2Cl_2, −78 ℃, 50 min then 0 ℃ 30 min; (c) K_2CO_3, MeOH/H_2O, r.t., 2 h, 60% from **26**

Conclusion

In summary, a new and concise synthetic protocol has been established for the construction of the diazatricyclic core of alkaloid TAN1251C. In contrast to a literature report, the key I_2-promoted intramolecular iodoaminocyclizations of **11a** and **11b** preceded smoothly to give the 1-azaspiro[4,5]decane cores **16a** and **16b**, respectively. The formation of the diazatricyclic core **28** was accomplished by oxidation of compound **26** with TFAA/DMSO, followed by treatment with K_2CO_3 in MeOH/H_2O. Attempted tosylation of **18a** led to an unexpected product **22**, which was presumed to be formed via an aziridinium ion intermediate. Oxidation of compound **23** with TFAA-DMSO-Et_3N system led to the formation of an unexpected TAN1251C derivative **25** in 20% yield.

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