Enantiospecific Total Synthesis of TAN1251C and TAN1251D

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Abstract: An enantiospecific total synthesis of TAN1251C and TAN1251D has been achieved. An aromatic oxidation reaction of a secondary amine, which is prepared from two molecules of L-tyrosine derivatives, with hypervalent iodine reagent gave a spirocyclic product as a key intermediate for the synthesis of TAN1251C and D.

Key words: TAN1251 alkaloid, total synthesis, aromatic oxidations, hypervalent iodine, spiro cyclization

TAN1251A (**1**), B (**2**), C (**3**) and D (**4**), isolated from a *Penicillium thomii* RA-89 by researchers at Takeda Chemical Industries Ltd.,[1] have unique structural features with a 1,4-diazabicyclo[3.2.1]octane ring system and a spirocyclic cyclohexanone. TAN1251A and B exhibit cholinergic activity and inhibit the acetylcholine-induced contraction of Guinea-pig ileum. TAN1251A is also known as a selective muscarinic M_1 subtype receptor antagonist (Figure 1).[2]

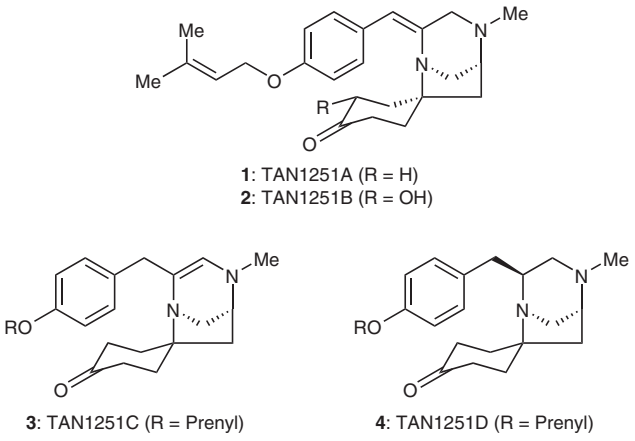
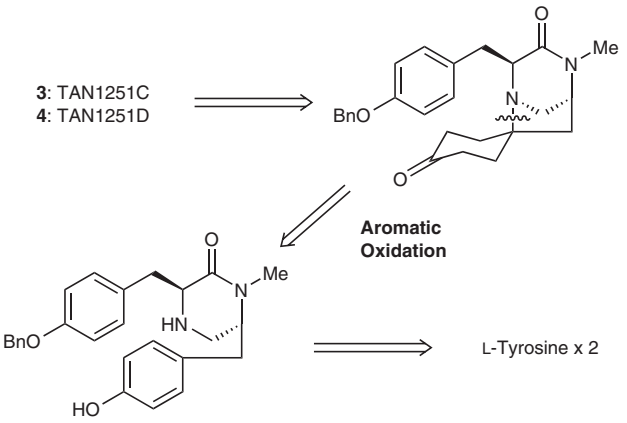


Figure 1 Family of TAN1251 alkaloid

Due to the attractive biological activity and also intriguing structural feature, a number of total synthesis of TAN1251A have been published to date.[3,4] However, little attention was focused on the chiral synthesis of TAN1251C and TAN1251D compared to the synthesis of TAN1251A, and two total syntheses have so far been reported by Snider[4] and Ciufolini,[5] respectively, in which the problematic spirocyclic carbon-nitrogen bond was constructed by a 1,3-dipolar cycloaddition reaction of the chiral nitrone derived from L-tyrosine, and also by an aromatic oxidation of the oxazoline derivative, as a key step, in each synthesis. Although an aromatic oxidation with hypervalent iodine reagent was widely utilized to construct a carbon-nitrogen bond of the target compounds,[6] rare example of its application to a secondary amine has been reported. Recently, we have succeeded in the chiral synthesis of TAN1251A starting from L-tyrosine and glycine, where the aromatic oxidation of the secondary amine with hypervalent iodine reagent was successfully employed, as the key reaction, to construct the desired spirocyclic carbon-nitrogen bond.[7] In this synthesis, however, the benzylidene side chain at the α-position of piperazinone ring was introduced at the later stage of its synthesis. Thus, we investigated to develop more effective synthetic path to those alkaloids, especially to TAN1251C and TAN1251D.

In searching the structures of **3** and **4** for retrosynthetic disconnections, we focused our attention on the formation of the spirocyclic carbon-nitrogen bond by an aromatic oxidation of the dimeric L-tyrosine derivative having a desired benzyl side chain in its molecule, as depicted in Scheme 1.



Scheme 1 Retrosynthetic route for TAN1251C and TAN1251D

Thus, the requisite starting material was prepared as follows. The carbamate **5**[7] was converted into its MPM ether **6**, in a usual manner, which, on reduction with lithium aluminum hydride afforded the primary alcohol **7** in 79% yield from **5**. Reaction of **7** with $(Boc)_2O$, followed by Swern oxidation of the resulting *N*-Boc derivative **8** gave the corresponding aldehyde **9** in quantitative yield. The desired dimeric tyrosine derivative **10** was synthesized by

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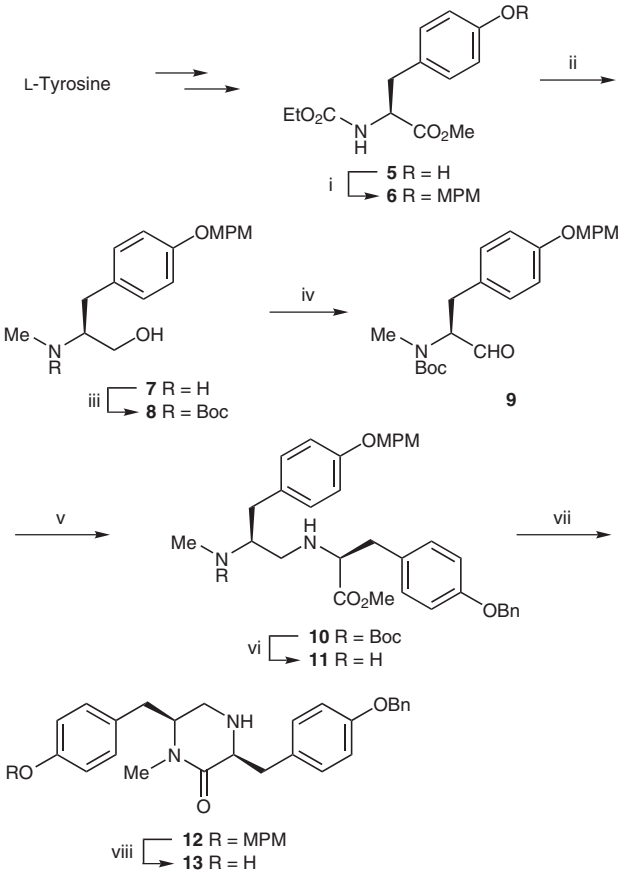
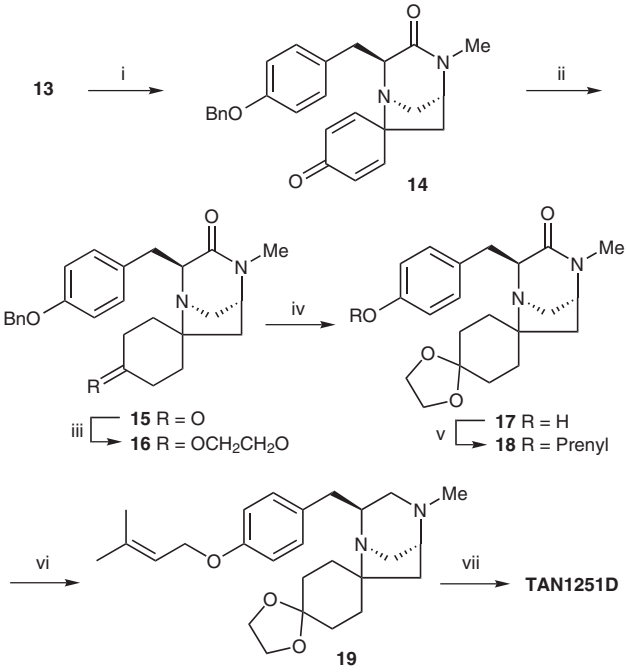
condensation of the aldehyde with *O*-benzyl-L-tyrosine under the reductive amination conditions in the presence of sodium cyanoborohydride[8] in 90% yield. After selective deprotection of the *N*-Boc group with zinc bromide, the resulting amine **11** was cyclized with sodium methoxide to provide the piperazinone derivative **12**, which, on further treatment with trifluoroacetic acid gave the key precursor **13** for an aromatic oxidation in 58% yield from **10** (Scheme 2).



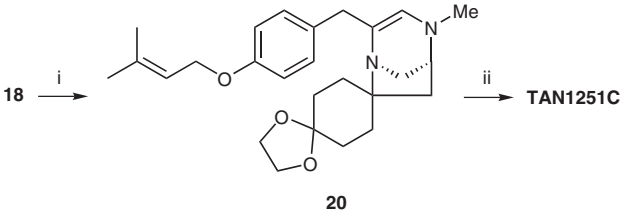
Scheme 2 *Reagents and conditions*: (i) MPMCl, K_2CO_3, DMF, r.t. (96%); (ii) LAH, THF, reflux (82%); (iii) $(Boc)_2O$, K_2CO_3, THF–H_2O (1:1), 0 °C (99%); (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C (99%); (v) *O*-benzyl-L-tyrosine methyl ester, $NaBH_3CN$, DMF, 0 °C (90%); (vi) $ZnBr_2$, CH_2Cl_2, 0 °C (99%); (vii) MeONa, THF, 0 °C (85%); (viii) CF_3CO_2H, CH_2Cl_2, 0 °C (92%).

The mono-phenolic compound **13** was subjected to an aromatic oxidation with $PhI(OAc)_2$ or PIFA under various reaction conditions. Among them, it was found that treatment of **13** with $PhI(OAc)_2$ in hexafluoroisopropanol as the solvent afforded the desired dienone **14**[9] in the best yield (49%).[10] 1,4-Reduction of the dienone with copper hydride[11] to the corresponding cyclohexanone **15**[12] was achieved, in 65% yield, by using the same reaction conditions as for the synthesis of TAN1251A.[7] After protection of the carbonyl group of **15**, the benzyl group of the resulting amide was removed with palladium hydroxide under the hydrogenolysis conditions to give the phenolic compound **17**. O-Alkylation of **17** with prenyl bromide in the presence of sodium hydride in THF gave the prenyl ether **18**, which, on reduction with lithium aluminum hydride afforded the amine **19**. Finally, deprotection of the ketal group under the acidic conditions furnished TAN1251D,[13] whose spectroscopic data including specific optical rotation {$[\alpha]_D$ +24.7 (*c* 0.20, MeOH); lit.,[1] $[\alpha]_D$ +24 (*c* 0.47, MeOH); lit.,[4] $[\alpha]_D$ +22 (*c* 0.10, MeOH)} were identical with those reported. Thus, we were able to establish the facile synthesis of TAN1251D by using an aromatic oxidation of the secondary amine as the key reaction (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) $PhI(OAc)_2$, $(CF_3)_2CHOH$, 0 °C (49%); (ii) CuCl, dppf, Et_3SiH, *t*-BuONa, CH_2Cl_2, 0 °C (65%); (iii) ethylene glycol, PPTS, benzene, reflux (99%); (iv) H_2, $Pd(OH)_2$, EtOH, r.t. (99%); (v) prenyl bromide, NaH, THF, 0 °C (73%); (vi) LAH, $AlCl_3$, Et_2O, 0 °C (83%); (vii) 1 M HCl aq, acetone, r.t. (67%).

To accomplish the synthesis of TAN1251C, introduction of the double bond in the piperazine ring would be required. Fortunately, we could find that DIBALH reduction of the amide in Et_2O provided the desired enamine **20**, in 70% yield, in one step. At this reduction step, the over reduction providing the corresponding amine **19**, as the major product, was observed under the other solvent system, such as methylene chloride, THF or toluene (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) DIBALH, Et_2O, –78 °C (70%); (ii) 1 M HCl aq, acetone, r.t. (70%).

Again, deprotection of the ketal group under the acidic conditions afforded TAN1251C.[14] The spectroscopic data including specific optical rotation {$[\alpha]_D$ +23 (*c* 0.76, MeOH); lit.[1] $[\alpha]_D$ +24 (*c* 0.44, MeOH); lit.[4] $[\alpha]_D$ +23 (*c* 0.45, MeOH)} were identical with those reported.

In summary, we disclosed herein the facile synthesis of TAN1251C and D in optically pure forms starting from the dimeric tyrosine derivative. This synthesis demonstrated that an aromatic oxidation with hypervalent reagent was applicable to the secondary amines to construct a problematic carbon-nitrogen bond.

Acknowledgment

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References

(1) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. PCT Int. Appl., WO 9113887, **1991**; *Chem. Abstr.* **1992**, *116*, 39780h.

(2) Widzowski, D.; Helander, H. F.; Wu, E. S. C. *Drug Discov. Today* **1997**, *2*, 341.

(3) (a) Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493. (b) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (c) Nagumo, S.; Nishida, A.; Yamazaki, C.; Matoba, A.; Murashige, K.; Kawahara, N. *Tetrahedron* **2002**, *58*, 4917. (d) Nagumo, S.; Matoba, A.; Ishii, Y.; Yamaguchi, S.; Akutsu, N.; Nishijima, H.; Nishida, A.; Kawahara, N. *Tetrahedron* **2002**, *58*, 9871. (e) Auty, J. M. A.; Churcher, I.; Hayes, C. J. *Synlett* **2004**, 1443.

(4) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643.

(5) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534.

(6) For reviews, see: (a) Ochiai, M. *Rev. Heteroatom Chem.* **1989**, *2*, 92. (b) Moriarty, R. M. *Synthesis* **1990**, 431. (c) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365. (d) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers Inc.: New York, **1992**. (e) Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem.* **1992**, *3*, 113. (f) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (g) Varvogolis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, **1997**. (h) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409.

(7) (a) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411. (b) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Heterocycles* **2004**, *62*, 343.

(8) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(9) Spectroscopic data of compound **14**: white solid; mp 129–130 °C; $[\alpha]_D$ –163.6 (*c* 1.40, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 2.01 (1 H, dd, *J* = 3.8, 13.5 Hz), 2.28 (1 H, dd, *J* = 2.8, 13.5 Hz), 2.71 (1 H, dd, *J* = 8.9, 14.7 Hz), 2.99 (3 H, s), 3.18 (1 H, d, *J* = 12.2 Hz), 3.41–3.50 (2 H, m), 3.85–3.90 (2 H, m), 5.01 (2 H, s), 6.19 (1 H, dd, *J* = 1.8, 10.1 Hz), 6.31 (1 H, dd, *J* = 1.8, 10.1 Hz), 6.75 (1 H, dd, *J* = 3.1, 10.1 Hz), 6.85 (2 H, d, *J* = 8.6 Hz), 6.90 (1 H, dd, *J* = 3.1, 10.1 Hz), 7.06 (2 H, d, *J* = 8.6 Hz), 7.31–7.43 (5 H, m). ^{13}C NMR ($CDCl_3$): δ = 33.5, 35.9, 44.9, 59.3, 61.6, 63.2, 69.7, 70.4, 114.4, 124.4, 126.7, 127.2, 127.7, 128.3, 129.9, 132.4, 136.9, 149.0, 150.8, 157.0, 169.7, 185.1. IR (KBr): 2970, 1668, 1650, 1510, 1452, 1396, 1310, 1235, 1178, 1095, 1005, 864 cm^{-1}. HRMS: *m/z* calcd for $C_{26}H_{26}N_2O_3$: 414.1943; found: 414.1940. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.37; H, 6.48; N, 6.71.

(10) In the aromatic oxidation, PIFA instead of $PhI(OAc)_2$ gave the dienone **14** in only 15% yield.

(11) (a) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (c) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573.

(12) Spectroscopic data of compound **15**: white solid; mp 134–135 °C; $[\alpha]_D$ –52.6 (*c* 1.23, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.91 (1 H, dd, *J* = 4.3, 12.9 Hz), 1.98–2.01 (3 H, m), 2.21 (1 H, dd, *J* = 2.3, 12.9 Hz), 2.26–2.55 (5 H, m), 2.81 (1 H, dd, *J* = 5.4, 14.2 Hz), 2.92 (3 H, s), 3.19 (1 H, d, *J* = 10.7 Hz), 3.39–3.50 (2 H, m), 3.77 (1 H, br m), 3.99 (1 H, t, *J* = 6.3 Hz), 5.03 (2 H, s), 6.89 (2 H, d, *J* = 8.7 Hz), 7.32 (2 H, d, *J* = 8.7 Hz), 7.29–7.44 (5H, m). ^{13}C NMR ($CDCl_3$): δ = 29.5, 33.1, 35.9, 37.4, 38.3, 39.0, 39.7, 42.0, 59.5, 61.8, 66.0, 69.8, 70.4, 114.4, 127.3, 127.7, 128.3, 129.9, 133.5, 137.0, 156.9, 170.5, 209.5. IR (KBr): 2955, 2868, 1715, 1650, 1510, 1456, 1392, 1310, 1235, 1176, 1024, 826 cm^{-1}. HRMS: *m/z* calcd for $C_{26}H_{30}N_2O_3$: 418.2256; found: 418.2245. Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.22; N, 6.69. Found: C, 74.64; H, 7.24; N, 6.64.

(13) Spectroscopic data of TAN1251D: colorless oil; $[\alpha]_D$ +24.7 (*c* 0.20, MeOH). ^1H NMR ($CDCl_3$): δ = 1.67 (1 H, dd, *J* = 5.8, 13.7 Hz), 1.73 (3 H, s), 1.79 (3 H, s), 1.86 (1 H, d, *J* = 13.7 Hz), 1.98–2.03 (2 H, m), 2.14 (3 H, s), 2.18–2.27 (2 H, m), 2.33–2.59 (5 H, m), 2.63–2.68 (2 H, m), 2.98–3.05 (2 H, m), 3.18–3.35 (3 H, m), 4.47 (2 H, d, *J* = 6.6 Hz), 5.46–5.51 (1 H, m), 6.82 (2 H, d, *J* = 8.6 Hz), 7.07 (2 H, d, *J* = 8.6 Hz). ^{13}C NMR ($CDCl_3$): δ = 18.2, 25.8, 33.0, 33.2, 37.9, 39.2, 39.5, 41.3, 42.4, 52.2, 61.2, 61.8, 64.7, 65.0, 65.7, 114.6, 119.7, 129.7, 131.8, 138.0, 157.4, 210.8. IR (thin film): 2925, 2853, 1719, 1611, 1520, 1458, 1377, 1297, 1238, 1010, 772 cm^{-1}. HRMS: *m/z* calcd for $C_{24}H_{34}N_2O_2$: 382.2620; found: 382.2648.

(14) Spectroscopic data of TAN1251C: colorless oil; $[\alpha]_D$ +23.0 (*c* 0.76, MeOH). ^1H NMR ($CDCl_3$): δ = 1.74 (3 H, s), 1.79 (3 H, s), 1.81–1.84 (1 H, m), 1.88 (1 H, dd, *J* = 5.1, 13.0 Hz), 1.98 (1 H, ddd, *J* = 4.6, 10.2, 13.0 Hz), 2.51 (3 H, s), 2.16–2.64 (7 H, m), 2.79 (1 H, dd, *J* = 1.3, 11.5 Hz), 3.20 (1 H, dd, *J* = 3.0, 11.5 Hz), 3.21 (2 H, s), 3.39–3.44 (1 H, m), 4.48 (2 H, d, *J* = 6.8 Hz), 5.24 (1 H, s), 5.47–5.52 (1 H, m), 6.83 (2 H, d, *J* = 8.6 Hz), 7.08 (2 H, d, *J* = 8.6 Hz). ^{13}C NMR ($CDCl_3$): δ = 18.2, 25.8, 34.6, 37.3, 37.8, 39.5, 40.3, 41.4, 42.9, 52.2, 59.0, 64.7, 71.4, 114.4, 119.9, 127.8, 128.2, 129.8, 131.9, 138.0, 157.1, 211.6. IR (thin film): 3415, 2928, 2865, 1716, 1678, 1642, 1610, 1508, 1445, 1376, 1298, 1234, 1174, 1112, 1057 cm^{-1}. HRMS: *m/z* calcd for $C_{24}H_{32}N_2O_2$: 380.2464; found: 380.2453.