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# Biomimetic Total Syntheses of (−)-TAN1251A, (+)-TAN1251B, (+)-TAN1251C, and (+)-TAN1251D

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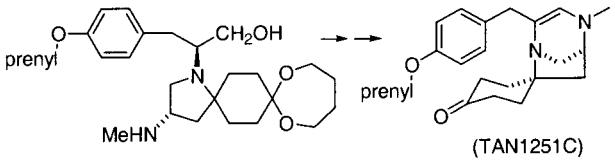
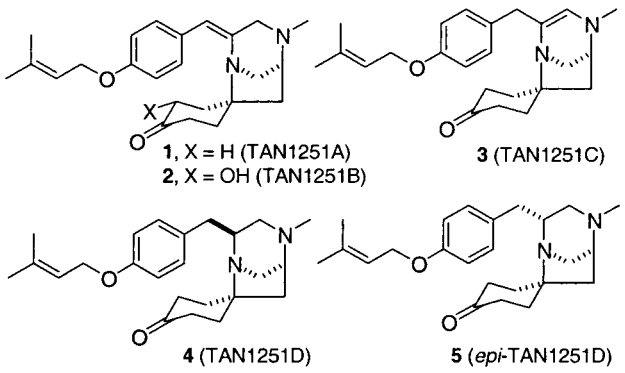
## ABSTRACT




**The muscarinic antagonists (−)-TAN1251A (1), (+)-TAN1251B (2), (+)-TAN1251C (3), and (+)-TAN1251D (4) have been synthesized biomimetically by enamine formation from an amino aldehyde to give TAN1251C ketal 18. Oxidation and reduction lead to TAN1251A (1), which has been hydroxylated to give TAN1251B (2). Stereospecific reduction of TAN1251C ketal 18 leads to TAN1251D (4).**

TAN1251A (**1**), TAN1251B (**2**), TAN1251C (**3**), and TAN1251D (**4**) were isolated from a *Penicillium thomii* RA-89 fermentation broth at Takeda Industries.[1] TAN1251A (**1**) and TAN1251B (**2**) are muscarinic antagonists of value as mydriatic or antispasmodic/antiulcer agents that inhibit the acetylcholine-induced contraction of Guinea pig ileum with $ED_{50}$ values of 8.0 and 10.0 nM, respectively. The relative stereochemistry of TAN1251B (**2**) was determined by X-ray crystallographic analysis, and the absolute stereochemistry was established by analysis of the CD of the dibenzoate of the diol obtained by reduction of the α-hydroxy ketone moiety.[2] Since TAN1251A (**1**) is converted to **2** by *Penicillium thomii* RA-89, it has the same absolute stereochemistry. The absolute stereochemistry of TAN1251C (**3**) and the absolute and relative stereochemistry of TAN1251D (**4** or **5**) were not known and have been assigned on the basis of the syntheses reported herein. Kawahara and co-workers recently reported the first total synthesis of racemic TAN1251A (**1**).[3]




The TAN1251 series of compounds have a novel tricyclic skeleton containing a 1,4-diazabicyclo[3.2.1]octane and a spiro-fused cyclohexanone. We believe that they are biosynthetically related to the potent immunosuppressant FR901483 (**8**),[4] which is probably biosynthesized from modified tyrosine dimer **6** by oxidative coupling to close the pyrrolidine ring and further elaboration to provide keto aldehyde **7** (see Scheme 1). An intramolecular aldol reaction of the keto aldehyde will lead to the tricyclic skeleton of

(1) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. *PCT Int. Appl.* **1991**, WO 91 13,887; *Chem Abstr.* **1992**, *116*, 39780t.
(2) Personal communication from Dr. Tsuneaki Hida, Research Head, Takeda Chemical Industries, Ltd., May 6, 1999.
(3) Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493−4496.
(4) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44.

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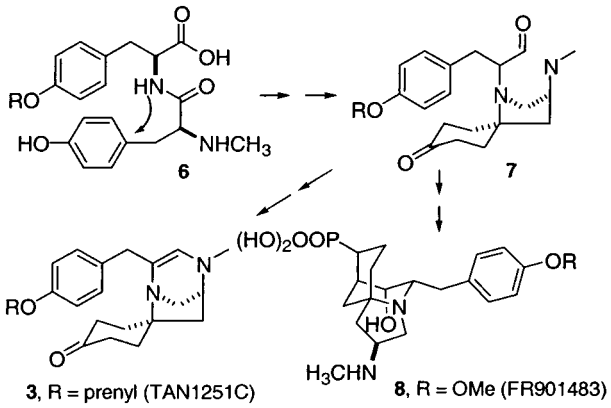
FR901483 (**8**), while dienamine formation from the secondary amine and aldehyde will provide TAN1251C (**3**), which can be isomerized to TAN1251A (**1**) or reduced to TAN1251D (**4**).

**Scheme 1.** Possible Biosynthesis of TAN1251A-D and FR901483

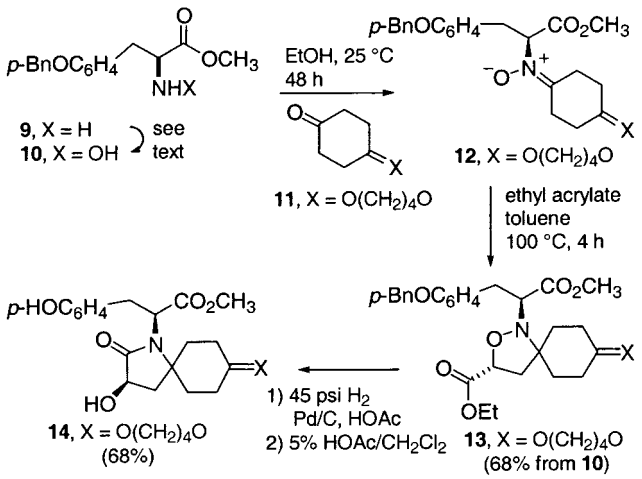



We have recently completed the first synthesis of (−)-FR901483 (**8**), which proceeds along biomimetic lines through an intermediate that is a protected analogue of keto aldehyde **7**, R = OMe, which was prepared efficiently in optically active form by a 1,3-dipolar cycloaddition product of a nitrone and ethyl acrylate.[5]

Adaptation of this route to the synthesis of the TAN1251 series will require the preparation of the protected amino aldehyde with a prenyl rather than a methyl aryl ether and condensation to form the dienamine. Since the prenyl group is not compatible with the conditions required for the preparation of the hydroxylamine or hydrogenation of the isoxazolidine, tyrosine was protected as the benzyl ether. *N*-BOC-tyrosine methyl ester was treated with benzyl bromide and cesium carbonate in acetone at 50 °C to provide the benzyl aryl ether, which was deprotected with 25% TFA in $CH_2Cl_2$ to give *O*-benzyltyrosine methyl ester (**9**) in quantitative yield. Hydroxylamine **10** was made by Grundke's procedure in 53% overall yield.[6] Condensation of **9** with anisaldehyde in MeOH at 25 °C for 6 h afforded the imine, which was oxidized to the oxaziridine with *m*-CPBA. Reaction of the oxaziridine with hydroxylamine hydrochloride afforded **10** (see Scheme 2).

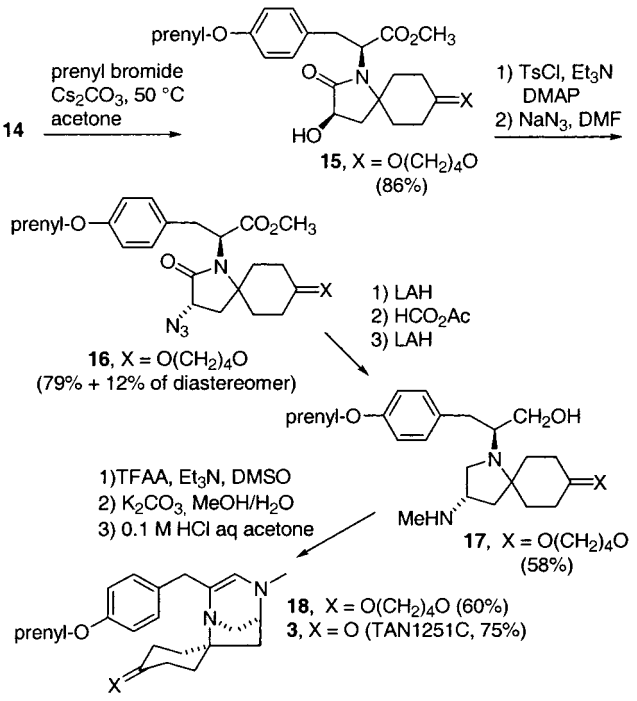
Condensation of hydroxylamine **10** with monoketal **11**[7−9] in EtOH for 48 h gave nitrone **12**, which was treated with ethyl acrylate in toluene at reflux to afford 68% of a 6:1 mixture of diastereomers rich in desired isomer **13**. Hydrogenolysis of the N−O bond under 45 psi of $H_2$ in HOAc for 6 h, followed by acid-catalyzed lactam formation with a catalytic amount of HOAc in $CH_2Cl_2$ for 12 h, provided 68% of an inseparable 6:1 mixture of **14** and the diastereomer and 17% of the phenol corresponding to **13**, which was recycled.

**Scheme 2**




Alkylation of **14** and the diastereomer with 1-bromo-3-methyl-2-butene and cesium carbonate in acetone at 50 °C provided 86% of a 6:1 mixture of **15** and the diastereomer, which was tosylated with TsCl, $Et_3N$, and DMAP (see Scheme 3). Reaction of the crude tosylates with sodium azide in DMF at 25 °C for 6 h provided 79% of pure azide **16** and 12% of the diastereomer, which were easily separated.

**Scheme 3.** Synthesis of TAN1251C (**3**)




(5) (a) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442−6443. (b) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786.

(6) Grundke, G.; Keese, W.; Rimpler, M. *Synthesis* **1987**, 1115−1116.

(7) Hyatt, J. A. *J. Org. Chem.* **1983**, *48*, 129−131.

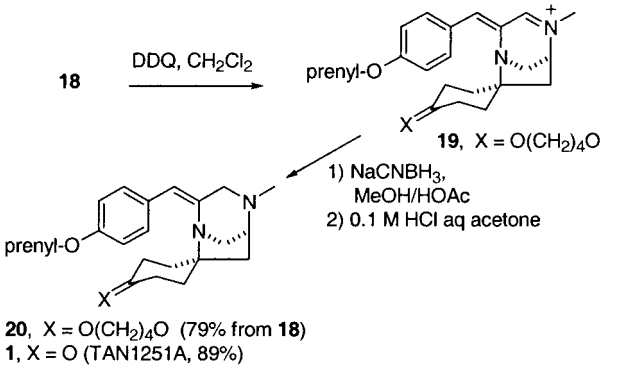
(8) This sequence was originally carried out with the mono dioxolane ketal used in the FR901483 synthesis. This ketal can be cleaved from the TAN1251A precursor **20**, X = $O(CH_2)_2O$, but not from the TAN1251C and TAN1251D precursors **18**, X = $O(CH_2)_2O$, and **23**, X = $O(CH_2)_2O$.

Reduction of the azide, lactam, and ester was accomplished with LAH in THF at reflux. The resulting primary alcohol and amine were formylated with formic acetic anhydride generated in situ.[10] Reduction of the crude formamide with LAH provided 58% of *N*-methylamine **17** from azide **16**.

Swern oxidation of amino alcohol **17** with trifluoroacetic anhydride and $Et_3N$ in DMSO[11] afforded the trifluoroacetamido aldehyde. Hydrolysis of the trifluoroacetamide with $K_2CO_3$ in aqueous MeOH provided 60% of **18**, the ketal of TAN1251C. Acidic hydrolysis of the ketal with 0.1 M HCl in aqueous acetone proceeded smoothly in 3 h to give TAN1251C (**3**) in 75% yield. The $^1H$ and $^{13}C$ NMR spectral data of synthetic TAN1251C are identical to those of the natural product.[1] The optical rotation for our synthetic material, $[\alpha]_D$ +23°, corresponds well with the reported value of +24°, confirming that TAN1251C has the *S* configuration as do TAN1251A and TAN1251B.

Oxidation of ketal **18** with DDQ (slow addition)[12] in dry $CH_2Cl_2$ provided eniminium salt **19** which was reduced with $NaCNBH_3$ in acidic MeOH to yield 79% of **20**, the ketal of TAN1251A (see Scheme 4). Hydrolysis with 0.1 M HCl in

**Scheme 4.** Synthesis of TAN1251A (**1**)

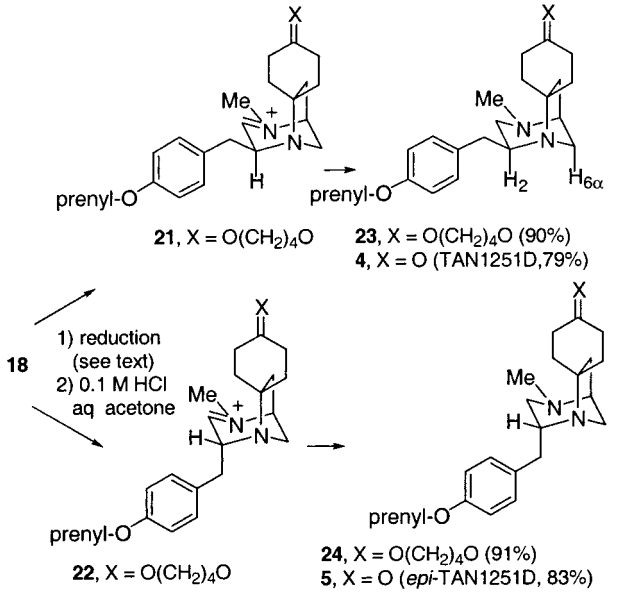



aqueous acetone gave TAN1251A (**1**) in 89% yield. The $^1H$ and $^{13}C$ NMR of synthetic TAN1251A are identical to those of the natural product.[13]

TAN1251D (**4**) is probably biosynthesized by reduction of the iminium salt formed by protonation of TAN1251C and should be available chemically by a similar protocol.

Reduction of **18** with $NaBH(OAc)_3$ in HOAc afforded 90% of a 1:9 mixture of ketals of **23** and **24**. Acidic hydrolysis of the major ketal **24** with 0.1 M HCl in aqueous acetone gave 83% of *epi*-TAN1251D (**5**) whose spectral data are quite different than those of TAN1251D (**4**) (see Scheme 5).

**Scheme 5.** Synthesis of TAN1251D (**4**)




Reduction of **18** with $NaCNBH_3$ in acidic MeOH (HOAc was added dropwise to keep the reaction mixture at pH 4) afforded a 2:1 mixture of ketals **23** and **24**. We were pleased to find that the a similar reduction of **18** with $NaCNBH_3$ in $CF_3CH_2OH$ provided a 6:1 mixture of ketals **23** and **24**, while use of the even more polar solvent $(CF_3)_2CHOH$ afforded 90% of a >25:1 mixture of **23** and **24**. Acidic hydrolysis of the major ketal **23** with 0.1 M HCl in aqueous acetone afforded 79% of TAN1251D (**4**), whose $^1H$ and $^{13}C$ NMR spectral data matched those of the natural product and whose optical rotation, $[\alpha]_D$ +22°, corresponds well with the reported value, +24°, confirming that the absolute configuration of TAN1251D (**4**) is also *S*.

Since the relative stereochemistry of TAN1251D had not been established, the stereochemistry of ketones **4** and **5** and ketals **23** and **24** was established by NMR experiments. The stereochemistry of **23** was established by NOE experiments on the formate salt. $H_2$ absorbs at $\delta$ 3.92 as a broad triplet, $J$ = 12 Hz, indicating that $H_2$ has a large axial−axial coupling constant and a large coupling constant to one of the benzylic methylene protons. The stereochemistry was confirmed by a strong NOE between $H_2$ and $H_{6\alpha}$ at $\delta$ 3.56. NOE experiments did not provide useful information about the stereochemistry of **4**, **5**, or **24** due to overlapping peaks. Fortunately, the stereochemical assignments of **4** and **5** could be confirmed by analysis of the $^{13}C$ NMR shifts, which were assigned by HSQC experiments. The axial benzyl substituent of *epi*-TAN1251D (**5**) shifts the benzylic carbon and the one-carbon bridge upfield to $\delta$ 39.7 and 52.4, respectively, from

(9) The dioxepane ketal **11** was chosen since these ketals are known be more easily cleaved than the analogous dioxolanes or dioxanes: (a) Oshima, T.; Ueno, S.-Y.; Nagai, T. *Heterocycles* **1995**, *40*, 607−617. (b) Conan, par J.-Y.; Natat, A.; Priolet, D. *Bull. Soc. Chim. Fr.* **1976**, 1935−1940. (c) Smith, S. W.; Newman, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 1249−1253. (d) Smith, S. W.; Newman, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 1253−1257.

(10) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315−3318.

(11) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425−4431.

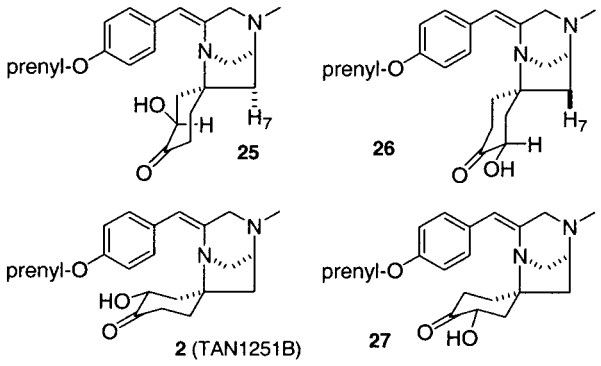
(12) An inseparable 7:1 mixture of **20** and the *E*-isomer was formed if DDQ was added too fast. The alkene hydrogen of the *E*-iosmer at $\delta$ 6.46 is deshielded by the syn nitrogen as compared to that of **20** at $\delta$ 5.91. The ortho aromatic protons of **20** at $\delta$ 7.76 are deshielded by the syn nitrogen as compared to those of the *E*-isomer at $\delta$ 7.05. These assignments were confirmed by NOE studies.

(13) Mp 112−114 °C (lit.[1] mp 118.5−120 °C); $[\alpha]_D$ −9.1° (*c* 0.40, MeOH) (lit.[1] −8.1° (*c* 0.42, MeOH)).

$\delta$ 41.4 and 61.9 observed in TAN1251D (**4**) because of the *gauche* butane effect.

The stereochemical control in the reduction of ketal enamine **18** occurs in the protonation step, which gives a mixture of iminium salts **21** and **22**, rather than in the reduction of the iminium salts to ketal amines **23** and **24**. Kinetic protonation should occur from the less hindered axial face to give iminium salt **21** with an equatorial benzyl group. However, MM2 calculations suggest that **21** is less stable than **22** by 3 kcal/mol because the steric hindrance between the equatorial benzyl group of **21** and the spiro cyclohexane ring is much greater than the steric hindrance due to the axial benzyl group of **22**. Therefore, if reduction of the iminium salt is slow and protonation is reversible, ketal amine **24** should be the major product as is observed with the weak reducing agent $NaBH(OAc)_3$. With the stronger reducing agent $NaBH_3CN$, reduction of kinetic iminium salt **21** to give amine ketal **23** is the major process. As the polarity of the solvent increases, the ionic iminium salt is stabilized relative to the enamine so that equilibration of the iminium salts is slower. Therefore, the ratio of diastereomers **23** to **24** increases from 2:1 in MeOH to 6:1 in $CF_3CH2OH$ and to >25:1 in $(CF_3)_2CHOH$ with increasing solvent polarity.[14]

The hydroxylation[15] of TAN1251A (**1**) to give TAN1251B (**2**) is a very challenging problem since four α-hydroxy ketones can be formed from **1** and the choice of oxidants is limited by the presence of readily oxidizable amines and double bonds. For instance, *m*-CPBA in $CH_2Cl_2$ at 0 °C oxidized the *N*-methylamine of the trimethylsilyl enol ether prepared from **1** to the amine oxide. TAN1251A (**1**) was treated with NaHMDS to form the enolate, which was oxidized with (1*S*)-10-(camphorsulfonyl)oxaziridine[16] to give 50% of an inseparable 2:3 mixture of **25** and **26** and 50% of recovered **1**.




The structure of **25** was tentatively assigned on the basis of the NOE between the C*H*OH peak at $\delta$ 4.07 (dd, $J$ = 10.8, 5.2) and $H_7$ at $\delta$ 1.74. Since this $H_7$ absorbs as a br dd, $J$ = 14, 5 Hz, it is the hydrogen indicated in the structure which should have a dihedral angle of 30° with the bridgehead hydrogen. Similarly, the structure of **26** was tentatively assigned on the basis of the NOE between the C*H*OH peak at $\delta$ 4.23 (dd, $J$ = 12.8, 6.0) and $H_7$ at $\delta$ 2.05. Since this $H_7$ absorbs as a br d, $J$ = 14 Hz, it is the hydrogen indicated in the structure which has a dihedral angle of almost 90° with the bridgehead. Hydroxylation of the enolate of **1** with (1*R*)-10-(camphorsulfonyl)oxaziridine gave about 40% of a 2:1 mixture of **25** and **26**. The successful hydroxylation leading to **25** and **26** without oxidation of the double bonds or amines was encouraging, but these oxaziridines hydroxylated the wrong face of the enolates of TAN1251A (**1**).

We therefore investigated hydroxylation of the trimethylsilyl enol ethers of **1** with $OsO_4$. Treatment of **1** with LDA in THF at −78 to −40 °C gave a mixture of enolates, which was quenched with TMSCl. Reaction of the crude silyl enol ethers with 1 equiv of NMO and 20% $OsO_4$ in aqueous *t*-BuOH for 5 min at 0 °C gave 39% of a 2:1:8:4 mixture of **25**, **26**, TAN1251B (**2**), and **27**, 23% of triols resulting from hydroxylation of both the enol ether and the prenyl group, and 9% of recovered **1**. PTLC gave 25% of a 2:1 mixture of the major products **2** and **27**, which were inseparable even by normal and reverse phase HPLC. Fortunately, the isomers were readily separable on a Chiralpak AD column since the α-hydroxy ketone moieties have the opposite absolute stereochemistry. The $^1H$ and $^{13}C$ NMR spectral data of **2** are identical to those of natural TAN1251B. Hydroxylation with $OsO_4$ to give **2** and **27** is moderately selective for the desired face of the enol ether opposite the nitrogen. Unfortunately, initial attempts at improving enolization selectivity with the lithium base prepared from either (*R, R*)- or (*S, S*)-bis(α-methylbenzylamine) gave lower selectivity.

In summary, we have completed the first syntheses of TAN1251B (**2**), TAN1251C (**3**), and TAN1251D (**4**) enantiospecifically and the first synthesis of (−)-TAN1251A (**1**). These results confirm the absolute stereochemical assignments based on CD studies and establish the relative stereochemistry of TAN1251D.

**Acknowledgment.** We thank the NIH (GM-50151) for financial support and Dr. Tsuneaki Hida, Takeda Chemical Industries, for the $^1H$ and $^{13}C$ NMR spectra of TAN1251A-D.

**Supporting Information Available:** Full experimental procedures and spectral data for **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083−4085. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934.