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Facile synthesis of enantiopure (–)-TAN1251A

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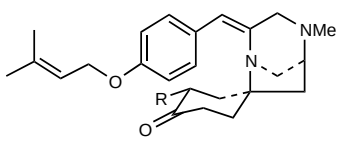
Abstract—Formal total synthesis of enantiopure (–)-TAN1251A, a muscarinic M_1 receptor antagonist, was achieved via a spirocyclic carbon–nitrogen bond formation by the use of aromatic oxidation with bis(acetoxy)iodobenzene as a key step.

TAN1251A **1** and B **2**, isolated from a culture of *Penicillium thomii* RA-89 by Takeda Industries, are a naturally occurring novel type of alkaloid, which contain unique structural features with a 1,4-diazabicyclo[3.2.1]octane ring system and a spirocyclic cyclohexanone (Fig. 1).[1]

These alkaloids exhibit cholinergic activity and inhibit the acetylcholine-induced contraction of guinea pig ileum with ED50 values of 8.0 and 10.0 nM, respectively.[2] TAN1251A is also known as a selective muscarinic M_1 subtype receptor antagonist.[2] Due to their attractive biological properties and structural novelty, the TAN1251 series of compounds have been the subject of extensive synthetic efforts which have culminated in several total syntheses involving one racemic[3] and two chiral syntheses,[4,5] in recent years. In the latter chiral syntheses, the problematic spirocyclic carbon–nitrogen bond was constructed by employing a 1,3-dipolar cycloaddition of the chiral nitron derived from tyrosine leading to the determination of their absolute configuration,[4] and by using an *N*-acylnitrenium ion intermediate as a reactive species,[5] respectively. We thought that a straightforward method for obtaining the key spirocyclic ring system would be the carbon–nitrogen bond formation of a secondary amine,[6] via aromatic oxidation with a hypervalent iodine reagent,[7] or via an aminylium ion intermediate, generated from the corresponding *N*-halogeno-compound.[8]



1 TAN1251A (R = H)
2 TAN1251B (R = OH)

Figure 1.

Based on our retrosynthetic scheme, L-tyrosine was chosen as the starting material with its chirality being transferred into the chiral center of TAN1251A. Moreover, the requisite secondary amine for aromatic oxidation will readily be obtained by condensation of a tyrosine derivative with glycine, as shown in Scheme 1.

Thus, a readily accessible tyrosine methyl ester hydrochloride **3** was converted into the carbamate **4** by treatment with ethyl chlorocarbonate in water in the presence of potassium carbonate, in 88% yield. After benzylation of **4** in the usual manner, the resulting benzyl ether **5** was subjected to lithium aluminum hydride reduction to give the alcohol **6**. The amino group of **6** was then protected as its Boc derivative **7**. Dess–Martin oxidation of **7** gave the aldehyde **8**, which was further condensed with glycine methyl ester in the presence of sodium cyanoborohydride[9] to provide the amine **9**. Deprotection of the Boc group of **9** gave the secondary amine **10**, which was treated with 25% ammonium hydroxide in ethanol to furnish the cyclized compound **11**, successfully (Scheme 2).

First, we attempted a carbon–nitrogen bond formation at this stage via an aminylium ion intermediate by chlorination of **11** with NCS, followed by treatment with silver oxide.[8] However, none of the desired product could be isolated. This bond formation was not effective for the formation of the desired product even

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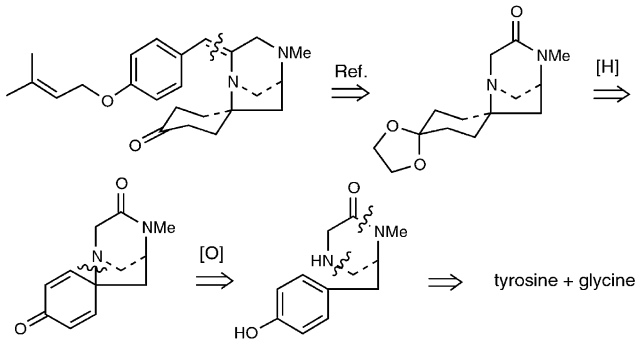
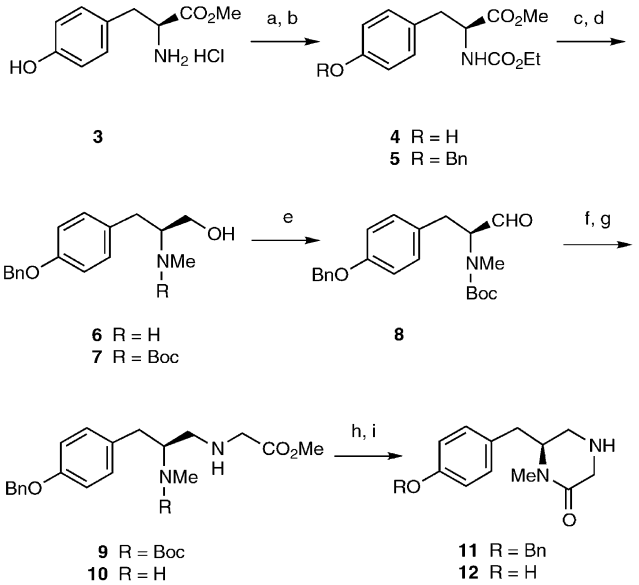


Scheme 1. Retrosynthetic route for TAN1251A.



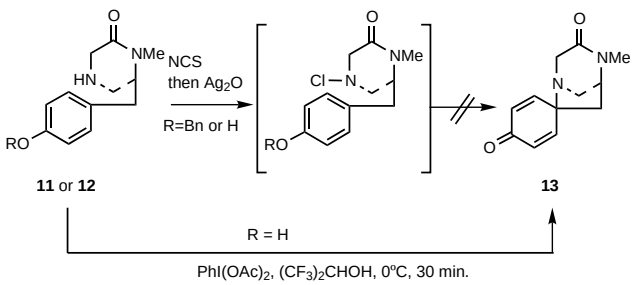
Scheme 2. (a) $ClCO_2Et$, K_2CO_3, H_2O, rt (88%); (b) BnBr, K_2CO_3, DMF, rt (88%); (c) $LiAlH_4$, THF, reflux, (92%); (d) $(Boc)_2O$, rt (92%); (e) Dess–Martin oxid. (86%); (f) glycine methyl ester, $NaB(CN)H_3$, MeOH, rt (87%); (g): CF_3CO_2H, CH_2Cl_2, rt (96%); (h) 25% NH_4OH, EtOH, rt (92%); (I) Pd–C, H_2, rt (96%).

with the use of a phenolic compound **12**, derived from **11** by debenzylation under catalytic hydrogenation over palladium on carbon. On the other hand, the aromatic oxidation of **12** with bis(acetoxy)iodobenzene in 2,2,2-trifluoroethanol afforded the desired spiro compound **13**[10] in 43% yield. When this oxidation was carried out in hexafluoroisopropanol as the solvent, the yield was increased to 69%. (Scheme 3) Since the basic skeleton of the target compound was thus constructed in relatively short steps, our attention was focused on reduction of the two carbon–carbon double bonds of the dienone **13**.

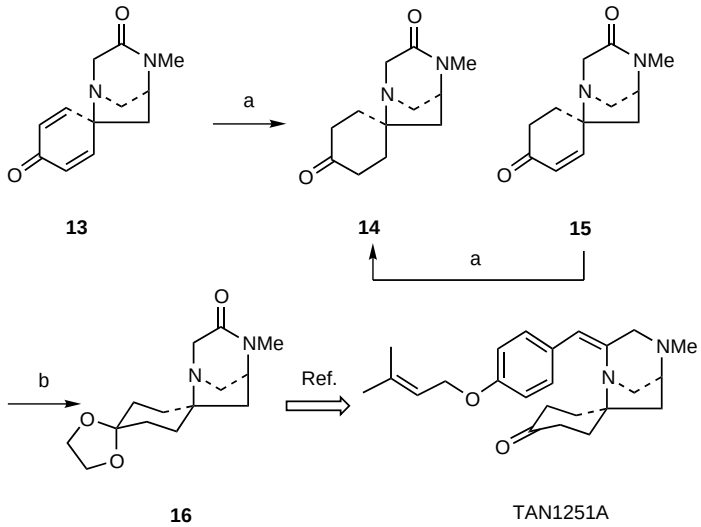
Although difficulties were initially encountered in obtaining the desired products by catalytic reduction under the various reaction conditions attempted, we found fortunately that the dienone could be converted to the ketone **14** by treatment with 2 equiv. of triethylsilane[11] in the presence of 20 mol% of copper(I) chloride and 20 mol% of dppf in dichloromethane at 0°C for 36 h in 30% yield, together with the partial reduction product **15** in 42% yield. The enone **15** could also be converted to the ketone **14** by further reduction under the same reduction conditions as above in 80% yield. When the reduction of **13** was carried out with 3 equiv. of Et_3SiH under similar reaction conditions at 0°C for 36 h, the ketone **14** was isolated in 60% yield together with the enone **15** in 9% yield (Scheme 4).

The structure of the enone **15** was determined based on the NMR study, where NOEs were observed between the methylene proton and the olefinic proton, as depicted in Fig. 2. Finally, ketalization of **14** with ethylene glycol in refluxing benzene in the presence of pyridinium *p*-toluenesufonate afforded the known key intermediate **16** for the synthesis of (–)-TAN1251A. The spectroscopic data of **16** including its optical rotation $\{[\alpha]_D$ +15.6 ($c=0.71$, $CHCl_3$); lit.,[5] $[\alpha]_D$ +15.2 ($CHCl_3$)$\}$ were identical with those reported.[5] Since this compound **16** has already been transformed into (–)-TAN1251A by Wardrop and co-worker,[5] this synthesis constitutes its formal total synthesis.

In summary, we have disclosed a facile formal synthesis of optically pure (–)-TAN1251A, in which aromatic oxidation of the secondary amine with bis(acetoxy)iodobenzene was employed as the key reaction. The synthetic strategy developed here would be applicable to the synthesis of other TAN series of compounds.



Scheme 3. Construction of the spiro-ring system.



Scheme 4. (a) Et_3SiH (3 equiv.), CuCl, dppf, CH_2Cl_2, 0°C, (60% for **14**; 9% for **15**); (b) $HO(CH_2)_2OH$, PPTS, benzene, reflux (66%).

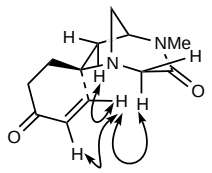


Figure 2. Observed NOEs are indicated by arrows for the enone **15**.

Acknowledgements

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10. Selected data for **13**: Mp 125–126°C. $[\alpha]_D^{20}=-23.5$ ($c=0.53$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.82–6.76 (m, 2H), 6.29 and 6.14 (each distorted d, $J=9.7$ Hz, each 1H), 3.93 (dd, $J=4.1$, 2.8 Hz, 1H), 3.75 (d, $J=18.5$ Hz, 1H), 3.58 (dd, $J=18.5$, 1.5 Hz, 1H), 3.46 (dd, $J=12.7$, 3.0 Hz, 1H), 3.20 (br d, $J=12.7$ Hz, 1H), 3.00 (s, 3H), 2.30 (dd, $J=13.8$, 2.8 Hz, 1H), 2.11 (dd, $J=13.8$, 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 184.8, 166.8, 149.9, 146.6, 129.3, 124.9, 63.4, 60.7, 58.1, 57.2, 45.1, 33.6; IR (KBr) 2970, 1668, 1630, 1488, 1432, 1405, 1318, 1262, 1213, 1100, 1005, 988, 969, 854 cm^{-1}; HRMS m/z found 218.1069 (calcd for $C_{12}H_{14}N_2O_2$, 218.1055). For **14**: Mp 92–93°C. $[\alpha]_D^{22}=+8.7$ ($c=0.90$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.70 (d, $J=18.5$ Hz, 1H), 3.69 (dd, $J=4.4$, 2.5 Hz, 1H), 3.33 (dd, $J=12.5$, 2.5 Hz, 1H), 3.14 (br d, $J=12.5$ Hz, 1H), 2.76 (ddd, $J=14.5$, 11.0, 5.4 Hz, 1H), 2.52–2.18 (m, 3H), 2.17–1.93 (m, 4H), 1.88–1.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 210.1, 167.5, 63.6, 59.7, 56.4, 55.1, 45.3, 38.6, 38.5, 38.1, 34.5, 33.2; IR (KBr) 2955, 2912, 2865, 1715, 1646, 1488, 1425, 1324, 1240, 1212, 1122, 1004, 958, 916 cm^{-1}; anal. calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.92; H, 8.20; N, 12.51%. For **15**: Mp 99–100°C. $[\alpha]_D^{20}=+96.0$ ($c=0.38$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.64 (dd, $J=10.1$, 2.0 Hz, 1H), 6.05 (dd, $J=10.1$, 1.0 Hz, 1H), 3.79 (dd, $J=4.3$, 2.6 Hz, 1H), 3.62 (d, $J=18.5$ Hz, 1H), 3.47

(dd, $J=18.5$, 1.6 Hz, 1H), 3.33 (dd, $J=12.4$, 2.6 Hz, 1H), 3.05 (m, 1H), 2.97 (s, 3H), 2.90 (ddd, $J=16.8$, 13.0, 4.9 Hz, 1H), 2.41–2.32 (m, 1H), 2.27 (dd, $J=13.7$, 2.6 Hz, 1H), 2.10–2.01 (m, 1H), 1.95 (dd, $J=13.0$, 3.8 Hz, 1H), 1.85 (dd, $J=13.7$, 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 198.9, 167.2, 150.9, 130.9, 63.4, 61.0, 57.1, 56.6, 48.3, 36.1, 35.4, 33.4; IR (KBr) 2960, 2862, 1678, 1646, 1485, 1443, 1398, 1323, 1236, 1157, 1052, 1000, 978, 965, 894 cm^{-1}; HRMS m/z found 220.1204 (calcd for $C_{12}H_{16}N_2O_2$, 220.1212). For **16**: A colorless oil. $[\alpha]_D^{20}=+15.6$ ($c=0.71$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.88 (br s, 4H), 3.55–3.49 (m, 2H), 3.41 (d, $J=18.6$ Hz, 1H), 3.18 (dd, $J=12.2$, 2.6 Hz, 1H), 2.98 (d, $J=12.2$ Hz, 1H), 2.83 (s, 3H), 1.86–1.62 (m, 7H), 1.60–1.42 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 168.2, 107.9, 64.2, 64.2, 64.1, 59.9, 56.3, 55.0, 45.0, 36.4, 33.3, 32.7, 32.5, 31.8; IR (thin film) 2950, 2930, 2890, 1644, 1488, 1439, 1398, 1320, 1285, 1212, 1154, 1075, 1008, 954, 922, 900 cm^{-1}; HRMS m/z found 266.1623 (calcd for $C_{14}H_{22}N_2O_3$, 266.1630).

11. We used the following asymmetric reduction conditions with slight modifications: Moritani, Y.; Appella, D. H.; Jurkauska, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798.