Pergamon

TOTAL SYNTHESIS OF (±)-TAN1251A

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Abstract: The first synthesis of novel type alkaloid (±)-TAN1251A possessing an antimuscarinic
activity was achieved. © 1998 Elsevier Science Ltd. All rights reserved.

Novel-type alkaloids, TAN1251 A and B, were isolated from a culture of *Penicillium thomii* RA-89 by the research group of Takeda Chemical Industries Ltd.[2] The structures involve a unique tricyclic skeleton which consists of a 1,4-diazabicyclo[3,2,1]octane ring and a cyclohexanone ring through a spiro bond. The skeleton is linked to a long side chain through a Z-double bond. The compounds have been found to show cholinergic activity on the basis of the radio ligand receptor binding assay by using ^{3}H-quinuclidinyl benzilate (QNB) and microsomal fractions of rat cerebral cortex. Especially, the affinity of TAN1251B to a muscarinic acetylcholine receptor is stronger than that of atropine. TAN1251A was selective to the M_1 subtype of muscarinic receptor. Scatchard plots of data revealed that both compounds were competitive to the muscarinic receptor. Furthermore, both compounds inhibited the acetylcholine-induced contraction of Guinea-pig ileum (ED_{50}; 8.0 and 10.0 nM, respectively). Such structural complexity and interesting biological activity provided us the stimulus for elaborating the synthetic study of TAN1251 derivatives. We wish to report here the first total synthesis of racemic TAN1251A.
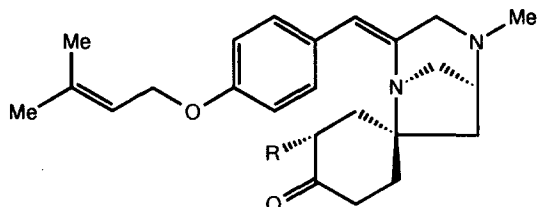

TAN1251A (R = H)
TAN1251B (R = OH)

Scheme 1 shows the retrosynthetic analysis of TAN1251A. The target molecule should be obtainable from amide (16) by a sequence of aldol reaction with aromatic aldehyde and a few steps of functional group interconversion. Excision of the lactam ring from 16 in a retrosynthetic sense leads to amino acid (14), which might be easily prepared from compound (10) via installation of an acetic acid unit. Disconnection of the pyrrolidine ring in the compound 10 leads to cyclohexylamine benzyl carbamate (3). Carboxylic acid (1) was considered to be a good precursor of 3 because Miller *et al.* have reported the efficient conversion of cyclohexylcarboxylic acid into cyclohexylamine methylcarbamate through a sequence of alkylation by the corresponding dianion and Curtius rearrangement.[3] The preparation of 1 has been already carried out.[4]
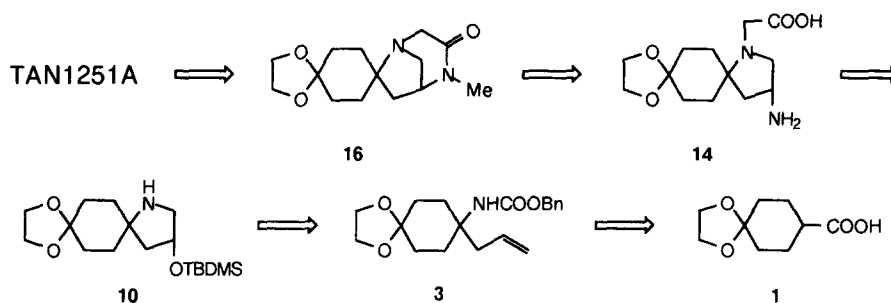
Scheme 1

The dianion which was generated from carboxylate 1 and 2 equivalents of LDA reacted with allyl bromide in THF to form carboxylic acid (2)[5] in 78% yield. Curtius rearrangement of 2 showed a satisfactory result in the case of using diphenylphosphoryl azide (DPPA).[6] Treatment of 2 with DPPA in refluxing benzene followed by addition of benzyl alcohol gave benzyl carbamate 3 in 65% yield. Dihydroxylation of 3 with a catalytic amount of osmium tetroxide and an equivalent of N-methylmorpholine N-oxide (NMO) as oxidants proceeded for 5 h to provide diol (4) in 94% yield. Selective tosylation of the primary hydroxy group of 4 with p-toluenesulfonyl chloride and a catalytic amount of 4-dimethylaminopyridine in pyridine gave tosylate (5) in 86% yield. The next step was the construction of the pyrrolidine ring. Our initial plan led us to attempt the ring formation of epoxide (6). Conversion of 5 into 6 was achieved by treatment with potassium carbonate in methanol in good yield. However, contrary to our expectation, ring formation of 6 turned out not to be efficient. As the best method, 6 was exposed to a solution of potassium *tert*-butoxide in THF and DMSO to afford cyclic compound (7) in 38% yield. The result might be attributed to the poor nucleophilicity of nitrogen in the carbamate group and the disadvantageous cyclization mode in view of Baldwin's rule.[7] In order to avoid these problems, conversion of 5 into amine (9) and the cyclization of the resulting product were carried out. Protection of 5 with *tert*-butyldimethylsilylchloride and imidazole in DMF afforded silylether (8) in 90% yield. Removal of the benzyloxycarbonyl group from 8 was carried out by using 5% Pd-C in MeOH under H_2 atmosphere to yield crude 9. Cyclization of 9 in the presence of 1,8-diazabicycloundec-7-ene in refluxing benzene proceeded smoothly to form azaspiro compound (10). Without purification, 10 was reacted with ethyl bromoacetate in the presence of potassium carbonate followed by deprotection with tetrabutylammonium fluoride to give alcohol (11) in 83% overall yield from 8. Treatment of 11 under Mitsunobu's conditions[8] in THF provided azide (12) in 82% yield. Catalytic hydrogenation of 12 with 5% Pd-C in MeOH gave primary

amine (13) in 75% yield. Hydrolysis of 13 with lithium hydroxide followed by cyclization with DPPA and Et₃N in DMF afforded amide (15) in 50% overall yield.[9] Treatment of 15 with methyl iodide in the presence of sodium hydride provided methylated compound (16) in 56% yield.
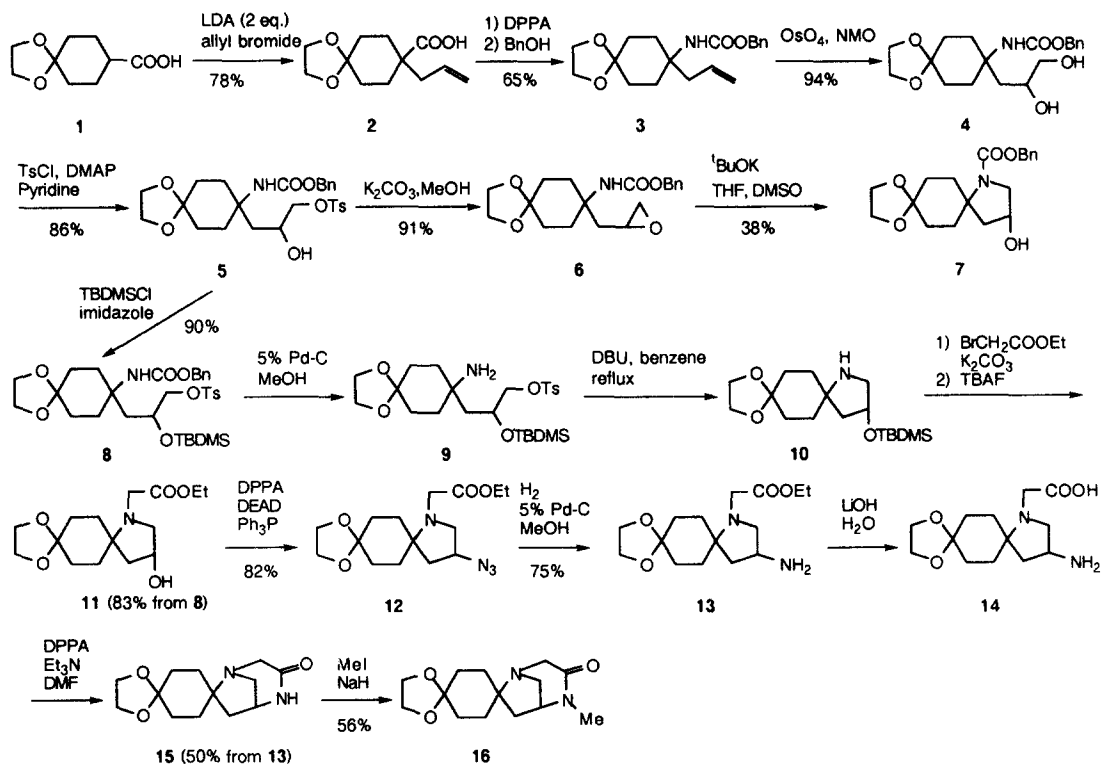
Scheme 2

The anion which was generated from amide 16 and LDA reacted with aldehyde (17) in THF at -78°C to form two separable aldol adducts (18A (less polar)) (36%) and (18B (more polar)) (49%). These compounds were determined to be epimeric at the benzylic position with each other on the basis of the spectroscopic data. The ^{1}H NMR of 18A showed the benzylic proton peak at 4.96 ppm (d, $J = 7.8$ Hz) and two bridgehead methylene proton peaks at 3.12 ppm (d, $J = 12.5$ Hz) and 2.76 ppm (d, $J = 12.5$ Hz) while that of 18B exhibited the benzylic proton peak at 4.77 ppm (d, $J = 7.3$ Hz) and two bridgehead methylene proton peaks at 3.29 ppm (d, $J = 12.0$ Hz) and 2.82 ppm (d, $J = 12.0$ Hz). Their configurations at the α position of the amide group were assigned by observation of NOEs between the bridgehead proton peak and the benzylic proton peak. It was found that the attack of aldehyde 17 took place from only the bridgehead side. However, the respective configuration at the benzylic position was not determined. Interestingly, mesylation of 18A and 18B followed by treatment with ^{t}BuOK gave enone (19) in 82% and 64% yield, respectively. These elimination steps might proceed in E_1 manner. Reduction of 19 with AlH₃ prepared from LiAlH₄ and AlCl₃ provided enamine (20) in 52% yield.[11] Finally, deprotection of 20 with HCl in acetone afforded (±)-TAN-1251A in 75% yield. Spectroscopic data of the synthetic material were in good agreement with those of natural product.

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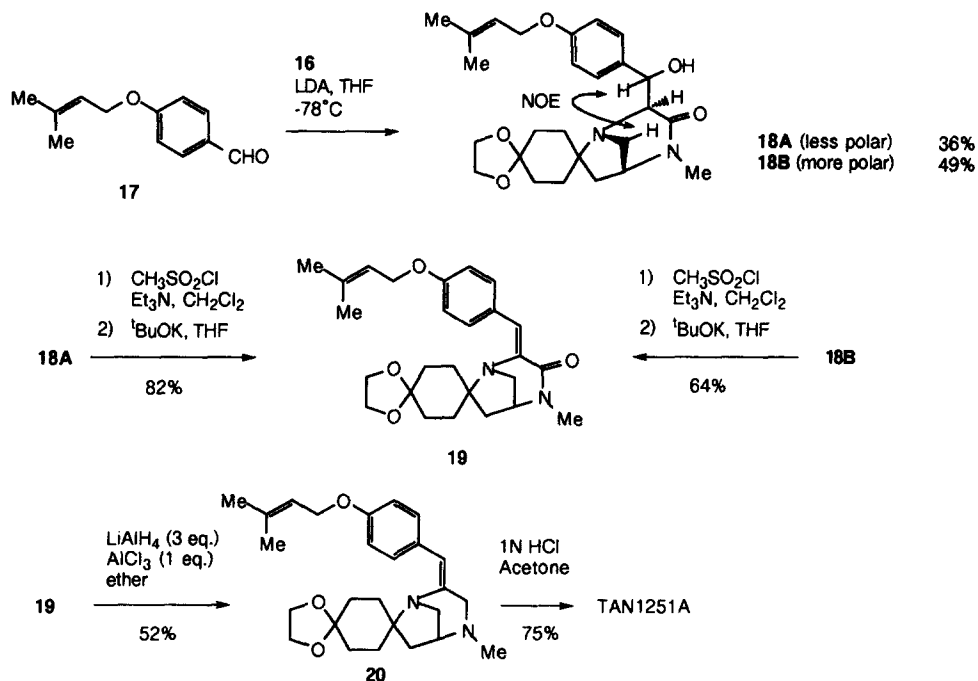
Scheme 3

Acknowledgment

Reference and Notes

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2.   Shirafuji, H.; Tuboya, S.; Ishimaru, T.; Harada, S. *Jpn. Kokai Tokkyo Koho* 94-501916.
        Tuboya, S.; Kimura, K.; Kita, Y.; Takamoto, M.; Shirafuji, H.; Harada, S. The Lecture Text in the Pharmaceutical Society of Japan, **1992**, 112, 225 (Vol. 2)

3.   Miller, R. D.; Goelitz, P. *J. Org. Chem.*, **1981**, 46, 1616.

4.   Nitz, T. J.; Volkots, D. L.; Aldous, D. J.; Oglesby, C. O. *J. Org. Chem.*, **1994**, 59, 5828.

5.   All purified compounds obtained gave satisfactory spectroscopic data.

6.   Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.*, **1972**, 94, 6203.

7.   Baldwin, J. E. *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

8.   Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.*, **1977**, 1977.

9.   Qian, L.; Sun, Z.; Deffo, T.; Mertes, K. B. *Tetrahedron Lett.*, **1990**, 31, 6469.

10.   Chari, V. M.; Aumhammer, G.; Wagner, H. *Tetrahedron Lett.*, **1970**, 3079.

11.   Tsuda, Y.; Nakai, A.; Ito, K.; Suzuki, F.; Haruma, M. *Heterocycles*, **1984**, 22, 1817.