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N-Methoxy-*N*-acylnitrenium Ions: Application to the Formal Synthesis of (−)-TAN1251A

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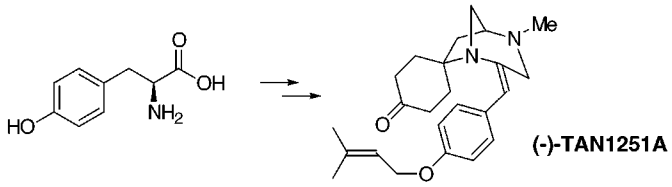
ABSTRACT



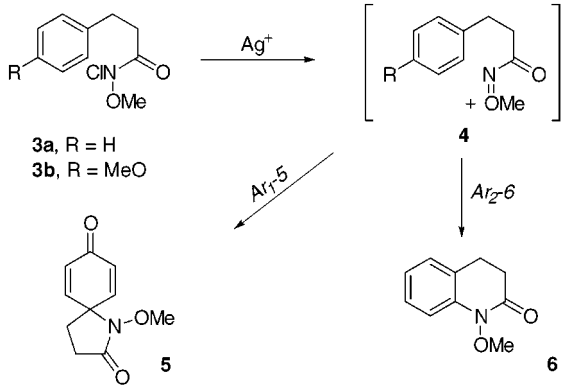
A formal synthesis of the muscarinic M_1 receptor antagonist (−)-TAN1251A (7) from L-tyrosine is described. Central to this venture has been the construction of the 1-azaspiro[4.5]decane skeleton present in the natural product by an *N*-methoxy-*N*-acylnitrenium ion-induced spirocyclization. The dienone generated in this transformation, 10, was converted to (−)-TAN1251A via tricycle 9, an intermediate in Kawahara's recent synthesis of racemic 7.

Nitrenium ions **1** remain a focus of attention three decades after the publication of Gassman's seminal review article,[1] not only because of their suspected role as the reactive metabolites[2] of mutagenic nitro and aminoaromatic compounds but also because of their utility in organic synthesis.[1,3]

1 **2**

Among the most easily formed and useful members of this class are *N*-alkoxy-*N*-acylnitrenium ions **2**. First reported independently by Kikugawa and Glover in 1984, these powerful electrophiles readily undergo inter- and intramolecular substitution reactions with a range of aromatic ring systems.[4] They can be generated by the treatment of *N*-alkoxy-*N*-chloroamides with a variety of Lewis acids, typically silver[4a−d] or zinc ions[4f] or, more conveniently, by direct oxidation of *N*-methoxyamides with bis(trifluoroacetoxy)iodobenzene.[4e,5] As illustrated in Scheme 1, the outcome

Scheme 1. Cyclization of *N*-Alkoxy-*N*-acylnitrenium Ions



(1) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26−33.

(2) (a) Garner, R. C.; Martin, C. N.; Clayson, D. B. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; ACS Monograph 182; American Chemical Society: Washington, DC, 1984; Vol. 1, pp 175−276. (b) Kennedy, S. A.; Novak, M.; Kolb, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 7654−7664. (c) Novak, M.; Xu, L.; Wolf, R. A. *J. Am. Chem. Soc.* **1998**, *120*, 1643−1644. (d) McClelland, R. A.; Ahmad, A.; Dicks, A. P.; Licence, V. E. *J. Am. Chem. Soc.* **1999**, *121*, 3303−3310.

(3) (a) Abramovitch, R. A.; Jeyaraman, R. In *Azides and Nitrenes*: *Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: Orlando, FL, 1984; pp 297−357. (b) Simonova, T. P.; Nefedov, V. D.; Toropova, M. A.; Kirillov, N. F. *Russ. Chem. Rev.* **1992**, *61*, 584−599. (c) McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823−6858.

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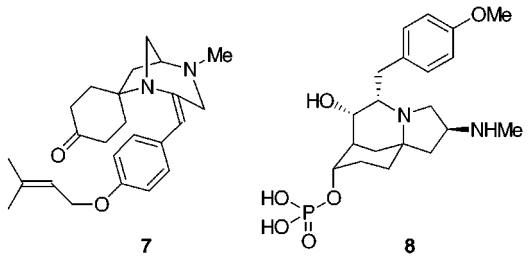
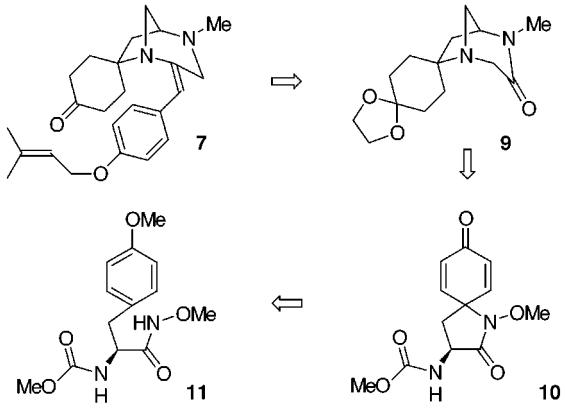
of the cyclization of nitrenium ions generated from *N*-chloro-*N*-methoxy-2-phenylacetamides (**3**) is highly dependent upon the substitution pattern of the aromatic ring. Unactivated systems such as **3a** cyclize via the Ar_2-6 pathway to form *N*-methoxybenzolactams **6** while substrates with a 4-methoxy substituent, such as **3b**, undergo spirocyclization (Ar_1-5) and loss of methanol to form dienones **5**.[4c] Glover has proposed that the ease with which **2** can be generated and the efficiency with which they undergo *N*-arylations is due to the fact that these ions are stabilized by the neighboring oxygen lone pair and are therefore sufficiently long-lived to undergo cyclization.[4d]

Although the pioneering studies of Kikugawa and Glover established methods for generating *N*-alkoxy-*N*-acylnitrenium ions and explored their reactivity, there have been surprisingly few applications of these intermediates in synthesis. Notable exceptions, which all involve Ar_2-5/6 cyclizations, include Kikugawa's total synthesis of eupolauramine,[6] preparation of an oxindole model of gelsemine by Fleming,[7] and, more recently, Romero's elegant use of consecutive nitrenium ion cyclizations in the preparation of the dopamine D_2 receptor agonist PNU-95666E.[8] However, to date, as far as we are aware, there have been no reports of the successful application of the nitrenium ion-induced Ar_1-5 spirocyclization to the synthesis of a natural product.[9] Our interest in this area was stimulated by the isolation of several alkaloids, including TAN1251A (**7**),[10] the immunosuppresant FR901483 (**8**),[11] and the cylindricines[12] which all contain a 1-azaspiro-[4.5]decane skeleton that we believed could be readily accessed using this nitrenium ion chemistry. The successful realization of this strategy as applied to the synthesis of (−)-TAN1251A is the subject of this Letter.



TAN1251A (**7**) is a member of a family of alkaloids, recently isolated from *Penicillium thomii* RA-89 by Takeda industries, which contain the novel 1,4-diazabicyclo[3.2.1]-octane skeleton.[13] TAN1251A is a selective and highly potent muscarinic M_1 receptor antagonist which inhibits the acetylcholine-induced contraction of Guinea-pig ileum with an ED_{50} value of 8.0 nM. Since most currently available muscarinic antagonists are not selective for the numerous receptor subtypes, there is considerable interest in M_1 selective antagonists as they have therapeutic potential for gastrointestinal and respiratory indications.[14] TAN1251A's combination of potent biological activity and structural novelty has attracted the attention of a number of groups: racemic and asymmetric total syntheses of **7** have recently been reported by Kawahara[15] and Snider.[16] Our retrosynthetic analysis of TAN1251A is illustrated in Scheme 2. We

Scheme 2. Retrosynthetic Analysis of (−)-TAN1251A (**7**)



envisioned that azaspirocyclization of L-tyrosine derivative **11** using Kikugawa's[4f] method would provide dienone **10** which could then serve as a common platform from which to launch asymmetric syntheses of both **7** and **8**. Recognizing the importance of an amine protecting group capable of withstanding the oxidative cyclization conditions, we deemed methyl carbamate to be ideal since it both tolerates bis-(trifluoroacetoxy)iodobenzene and would serve as a latent *N*-methyl group.[17] For our initial foray into this area, we

(4) (a) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2255−2260. (b) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728−5729 (c) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394−3403. (d) Glover, S. A.; Scott, A. P. *Tetrahedron* **1989**, *45*, 1763−1776. (e) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581−582. (f) Kikugawa, Y.; Shimada, M.; Matsumoto, K. *Heterocycles* **1994**, *37*, 293−301.

(5) For recent reviews of hypervalent iodine(III) reagents, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123−1178. (b) Varvogolis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997. (c) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proc. Int.* **1997**, *29*, 409−458.

(6) Kawase, M.; Miyake, Y.; Sakamoto, T.; Shimada, M.; Kikugawa, Y. *Tetrahedron* **1989**, *45*, 1653−1660.

(7) Fleming, I.; Moses, R. C.; Tercel, M.; Ziv, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 617−626.

(8) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582−6587.

(9) While this work was in progress, Ciufolini and Sorenson independently reported complementary methods for preparing spirocyclic pyrrolidinones involving the oxidation of phenolic oxazolines, and amines, respectively. These transformations involve aryl oxidation and subsequent trapping rather than the formation of *N*-acylnitrenium ions: (a) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E. M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397−4408. (b) Scheffler, G.; Seike, H.; Sorenson, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593−4596.

(10) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. PCT Int. Appl. 1991, WO 91 13,887; *Chem. Abstr.* **1992**, *116*, 39780t.

(11) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44.

(12) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645−8656.

(13) Although unprecedented in Nature, 1,4-diazabicyclo[3.2.1]octanes have been the subject of previous synthetic studies: Hirschfield, A.; Taub, W. *Tetrahedron* **1972**, *28*, 1275−1287. Strum, P. A.; Cory, M.; Henry, D. W.; Ziegler, J. B.; McCall, J. W. *J. Med. Chem.* **1977**, *20*, 1333−1337.

(14) Widzowski, D.; Helander, H. F.; Wu, E. S. C. *Drug Discovery Today* **1997**, *2*, 341−350.

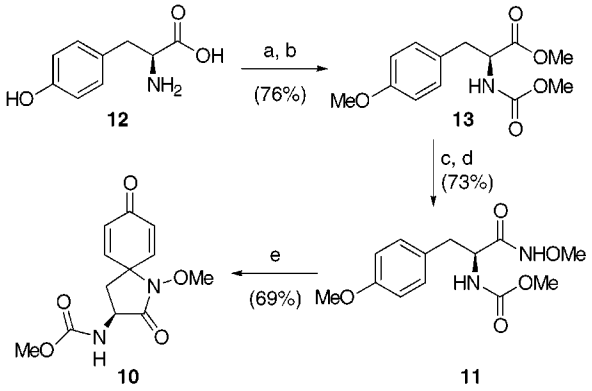
(15) Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493−4496.

(16) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643−646.

chose to merge our asymmetric route with Kawahara's[15] racemic synthesis at tricycle **9** and accordingly install the benzyl side chain employing the established protocol.

Our route to **7** commenced from L-tyrosine (**12**) which was converted to the corresponding *N*-methyl carbamate derivative under Schotten−Baumann conditions[18] (Scheme 3). Methylation of the remaining phenol and carboxylic acid

Scheme 3. Nitrenium Ion-Induced Spirocyclization[a]

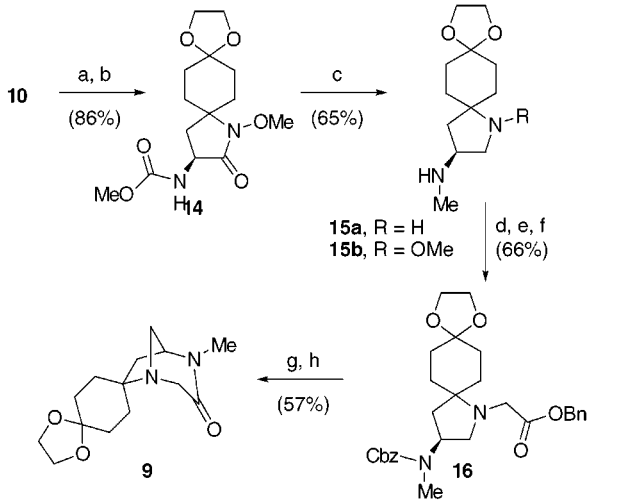


[a] Reagents and conditions: (a) i. MeOCOCl, NaOH, H_2O, 5 °C, 1.5 h; ii. NaOH, H_2O, 0 °C, 2 h; (b) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux, 3 h; (c) NaOH, H_2O, dioxane, 0 °C, 30 min; (d) $MeONH_2$·HCl, DCC, HOBT, NMM, DMF, CH_2Cl_2, rt, 24 h; (e) i. $PhI(OCOCF_3)_2$, CH_2Cl_2, MeOH, 0 °C, 10 min; ii. H_2O, 0 °C, 5 min.

using dimethyl sulfate and K_2CO_3 in acetone at reflux then gave **13** in 76% overall yield from **12**. This ester was saponified and the resulting acid then subjected to DCC/HOBt[19] coupling with methoxylamine to furnish *N*-methoxyamide **11** in 73% yield. Gratifyingly, reaction of **11** with bis(trifluoroacetoxy)iodobenzene (1.5 equiv) in CH_2Cl_2 and MeOH now resulted in the rapid formation of dienone **10** accompanied by varying amounts of the corresponding dimethyl acetal.[20] Although this mixture proved to be inseparable by flash chromatography, we found that addition of water to the reaction mixture after cyclization hydrolyzed the unstable acetal in situ. Using this procedure, **10** could be obtained without incident in 69% overall yield.

As shown in Scheme 4, hydrogenation (1 atm) of **10** now proceeded smoothly[21] with 10% Pd/C to furnish the saturated ketone which was then converted to the 1,2-dioxolane derivative **14** under standard conditions. While our original plan was to now exhaustively reduce **14** to *N*-methyldiamine **15a**, reaction with borane−dimethyl sulfide complex[8] in THF gave an intractable mixture of several products. We were

Scheme 4. 1,4-Diazabicyclo[3.2.1]octane Core[a]



[a] Reagents and conditions: (a) H_2, 10% Pd/C, EtOAc, rt, 6 h; (b) $(CH_2OH)_2$, PPTS, benzene, reflux, 3.5 h; (c) $LiAlH_4$, THF, reflux, 11 h; (d) BnOCOCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (e) Zn, AcOH, 75 °C, 5 h; (f) $BrCH_2CO_2Bn$, K_2CO_3, CH_3CN, 40 °C, 15 h; (g) H_2, Pd/C, MeOH, rt, 30 min; (h) DPPA, $NaHCO_3$, DMF, CH_2Cl_2, 0 °C to rt, 87 h.

encouraged to find, however, that reduction of **14** with $LiAlH_4$ in THF at reflux proceeded smoothly to furnish *N*-methoxylamine **15b** in 65% yield.[22] Capitalizing on this unexpected result, which conveniently differentiated the two secondary amines, we proceeded to protect the *N*-methylamine as the Cbz derivative and then unmask the pyrrolidine by reductive cleavage of the N−OMe bond with zinc powder in acetic acid.[23] Alkylation of the resulting amine with benzyl bromoacetate then furnished **16** in 66% yield from **15b**. The Cbz and benzyl protecting group were then simultaneously removed by hydrogenolysis (1 atm) with Pd/C and the resulting amino acid submitted directly to DPPA[24] coupling without purification. This cyclization, although slow, proceeded with reasonable efficiency to provide **9** in 57% yield from **16**.[25]

Having prepared the 1,4-diazabicyclo[3.2.1]octanone core of **7** in 13 steps, we now proceeded to install the benzyl side chain. Accordingly, generation of the enolate of **9** with LDA in THF and subsequent trapping with *p*-prenyloxybenzaldehyde (**17**)[26] (2 equiv) gave a 1.2:1 mixture of aldol products in a combined yield of 80%, as reported by Kawahara (Scheme 5).[15] Rather than separate this mixture,

(17) Romero and co-workers have previously reported the successful use of this protecting group strategy.[8]

(18) Determann, H.; Zipp, O.; Wieland, T. *Liebigs Ann. Chem.* **1962**, *651*, 172−184.

(19) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788−798.

(20) This acetal presumably arises from trapping of the intermediate oxonium cation by methanol. Use of CH_2Cl_2 alone led to lower yields of **10**.

(21) Interestingly, reductive aromatization, a complication in Ciufolini's[9a] work, was not observed with our spriocyclic system.

(22) For other examples of the reduction of *N*-methoxyamides to *N*-methoxyamines, see: (a) Godjoian, G.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 1717−1720. (b) Uneme, H.; Mitsudera, H.; Yamada, J.; Kamikado, T.; Kono, Y.; Manabe, Y.; Numata, M. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 1293−1299.

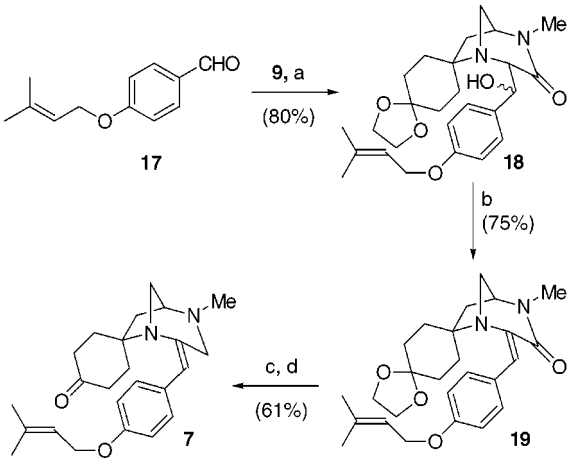
(23) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5513−5514.

(24) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205.

(25) For a discussion of the peptide coupling of secondary amines, see: Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243−2266.

(26) Prepared by the alkylation of *p*-hydroxybenzaldehyde with 1-bromo-3-methyl-2-butene: Chari, V. M.; Aurnhammer, G.; Wagner, H. *Tetrahedron Lett.* **1970**, *11*, 3079−3082.

Scheme 5. Synthesis of (−)-TAN1251A[a]



[a] Reagents and conditions: (a) i. **9**, LDA, THF, 0 °C, 30 min; ii. **17**, −78 °C, 90 min; (b) i. MsCl, Et_3N, CH_2Cl_2, 0 °C, 3 h; ii. ^{t}BuOK, THF, rt, 17 h; (c) AlH_3, Et_2O, 0 °C, 1 h; (d) 1 M HCl, acetone, rt, 12 h.

we found that reaction with MsCl/Et_3N and elimination of the resulting mixture of mesylates with ^{t}BuOK gave α,β-unsaturated amide **19** as a single stereoisomer in 75% overall yield. Reduction of **19** with AlH_3 in ether now gave an improved yield of the corresponding enamine which was finally deprotected by hydrolysis with aqueous HCl in acetone to provide (−)-TAN1251A. This material was found to be in close agreement with the reported spectral and physical data.[10,16,27]

In summary, we have completed a formal synthesis of (−)-TAN1251A and report the first application of an *N*-methoxy-*N*-acylnitrenium ion-induced spirocyclization to the synthesis of a natural product. Our progress toward the synthesis of FR901483 (**8**) will be reported in due course.

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Supporting Information Available: Full experimental procedures and spectral data for compounds **7**, **9**−**11**, and **13**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Mp 116−118 °C (lit.[9] mp 118.5−120°C); $[\alpha]_D$ −10.1° (*c* 0.41, MeOH) (lit.[9] −8.1° (*c* 0.42, MeOH)).