Total Synthesis of Tricyclic Azaspirane Derivatives of Tyrosine: FR901483 and TAN1251C

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Received April 17, 2001. Revised Manuscript Received June 7, 2001

Abstract: A solution to the long-standing problem presented by the oxidative cyclization of a phenolic 3-arylpropionamide to a spirolactam has been developed in this laboratory via oxazoline chemistry. This research was motivated by our interest in some novel tricyclic azaspirane natural products formally derived from tyrosine, such as FR901483 and TAN1251C. In this paper, we disclose full details of the total synthesis of these substances.

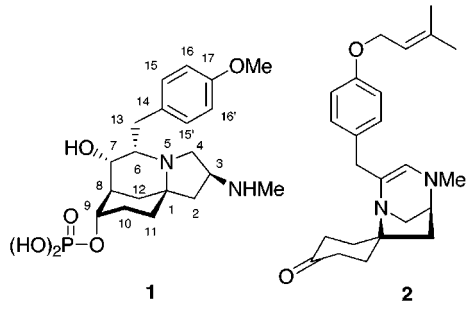
Introduction

FR901483, **1**, and the TAN1251 family, exemplified by TAN1251C, **2**, are architecturally interesting natural products that display a novel tricyclic azaspirane core (Scheme 1). The TAN1251 compounds are muscarinic antagonists of potential interest as antispasmodic or antiulcer agents, and were described in 1991 by researchers at Takeda Industries.[1] FR901483 is a powerful immunosuppressant that appears to act by inhibiting the biosynthesis of purines, especially adenine. The substance was reported in 1996 by a team of Fujisawa scientists.[2]

Natural products **1** and **2** appear to share a common biosynthetic antecedent in the form of a tyrosinyl tyrosine dipeptide, **3** (Scheme 2). A hypothetical oxidative cyclization of **3** may lead to spirolactam **4**, further biosynthetic elaboration of which could produce keto aldehyde **5**. This intermediate would advance to **1** or **2** via formation of a third ring incorporating the erstwhile carboxy carbon, **a** (Scheme 2). Thus, establishment of a C−C bond between atoms **a** and **b** leads to **1**, whereas formation of a C−N bond between atoms **a** and **c** would produce **2**.

Noteworthy bioactivity and structural novelty have elicited substantial interest in **1**−**2** at a synthetic chemical level;[3] to wit, four total syntheses of FR901483 and two of TAN1251 have been recorded to date. The first route to **1** was disclosed by Snider,[4] who also determined the absolute configuration of the molecule. Indeed, this important structural aspect had been left unresolved in the original Fujisawa communication. In rapid succession, Funk,[5] Sorensen,[6] and ourselves[7] announced alternative synthetic avenues to the target molecule. The synthesis of TAN1251 substances has been achieved by the groups of Kawahara (racemate)[8] and of Snider (enantiocontrolled).[9] Once again, the latter workers also determined the absolute configuration of these interesting molecules. A formal synthesis of TAN1251A has been described by Wardrop.[10]

Scheme 1



1 **2**

The biosynthetic hypothesis of Scheme 2 is central to the synthetic plan that we formulated for **1**−**2** at the beginning of the present effort. We felt that the synthesis of the target

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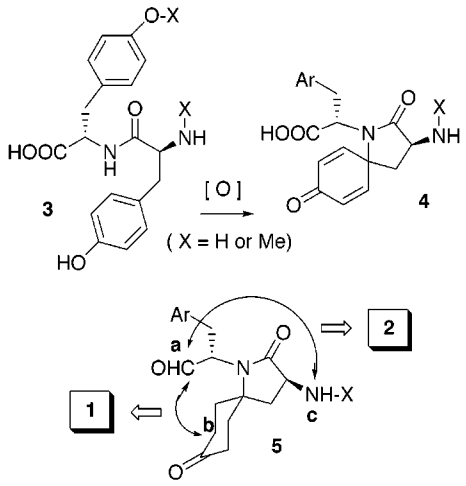
⊥ To whom inquiries regarding X-ray crystallographic studies should be addressed.

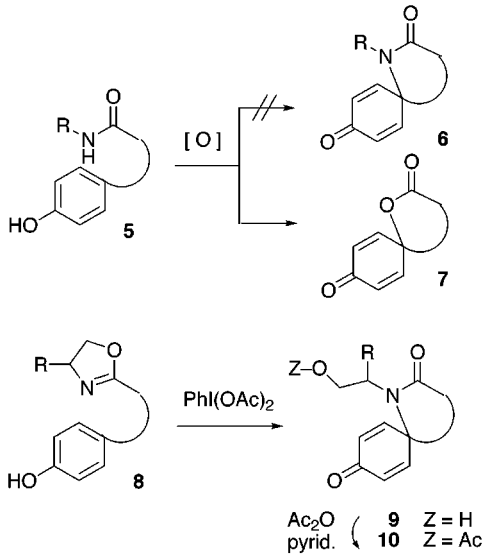
(1) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. International Patent PCT WO91/13887, 1999.
(2) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.
(3) FR901483: (a) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280 (synthetic studies). (b) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442 (synthesis of desmethylamino FR901483). (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaría, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891 (analogues). (d) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347 (synthetic studies). (e) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013 (synthetic studies).
(4) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778.
(5) (a) Funk, R. L.; Maeng, J.-H. *Abstracts of the 220th ACS National Meeting of the American Chemical Society, Washington, DC, August 20*−*24, 2000*; American Chemical Society: Washington, DC, 2000; Abs. ORGN 264. (b) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125.
(6) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4593.
(7) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765.
(8) Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493.
(9) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643.
(10) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053.

10.1021/ja016030z CCC: $20.00
Published on Web 07/13/2001

Scheme 2

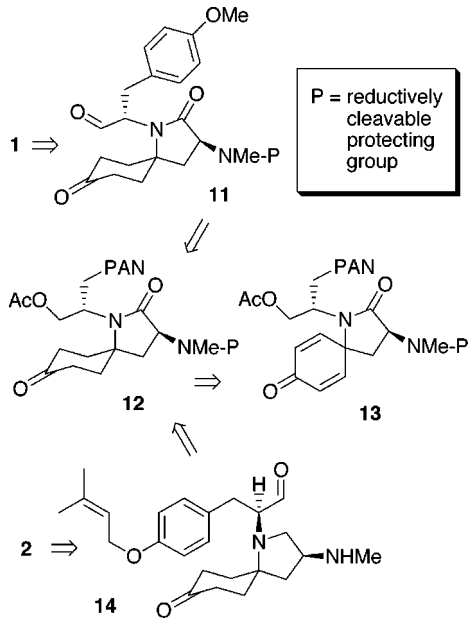


Scheme 3



alkaloids could be substantially simplified if it were possible to duplicate the oxidative conversion of their presumed forerunner **3** to spirolactam **4** by chemical means. A number of interesting applications of this unusual transformation could be envisioned well beyond the FR901483/TAN1251 problem. However, the oxidative conversion of a phenolic amide to a spirolactam was generally thought to belong to the realm of "impossible" reactions. As early as 1987, Kita and collaborators disclosed that oxidative treatment of generic substrates **5** does not yield lactams **6**, but rather lactones **7**.[11] These probably arise through capture of an electrophilic intermediate produced by activation of the phenol by the oxygen atom of the nucleophilically ambident carboxamide group, followed by hydrolysis of the emerging iminolactone upon workup (Scheme 3). Upon completion of extensive methodology studies, we disclosed in 1998 that the desired transformation may be achieved by oxidation of phenolic oxazolines **8** with iodobenzene diacetate ("DIB").[12,13] The free OH group in the resulting spirolactams **9** is subsequently acetylated to furnish **10**, so as to suppress facile Michael cyclization of **9**.[14]

Scheme 4



The ideas contained in Scheme 2 were clearly recognized also by Snider and by Sorensen. Thus, Snider formulated an analogous biosynthetic surmise in a landmark 1998 publication[3b] on the synthesis of desmethylamino FR901483, even though at a synthetic level he relied on chemical technology that does not involve the key C−N bond forming process of Scheme 3. On the other hand, Sorensen devised a particularly interesting variant of our chemistry, in which a free secondary amine, instead of an oxazoline, functions as the nucleophilic component of the reaction, and went on to incorporate this noteworthy transformation in his synthesis of **1**. The Sorensen contribution is significant because in our own work we were unable to devise conditions suitable for the oxidative cyclization of secondary amine substrates. Attempts in this sense resulted only in formation of octahydroquinoline-7-ones,[13,15] through Michael cyclization of an 4-(ω-aminoalkyl)dienone intermediate, in a fashion reminiscent of results obtained by Kita[16] and Wipf.[17]

A strategic plan for the synthesis of **1**−**2** was formulated on the basis of the foregoing chemical developments as shown in Scheme 4. Spirolactam **13** (PAN = *p*-anisyl) would be advanced to intermediate **12**, which represent the point of divergence of the syntheses of FR901483 and TAN 1251C. These would arise through intramolecular aldol cyclization of **11**, or intramolecular enamine formation from **14**, respectively. Details of how these plans were translated into practice are provided below.

Discussion

The construction of an oxazoline substrate suitable for the conduct of the synthesis required fragments of **16** and **17**, both of which may be made from L-tyrosine, **15**. A large quantity of **17** was secured in excellent chemical yield and stereochemical purity by a 1915 procedure by Fischer.[18] Conversely, the

(11) Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.

(12) (a) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. See also: (b) Braun, N. A.; Bray, J. D.; Ciufolini, M. A. *Tetrahedron Lett.* **1999**, *40*, 4985.

(13) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini M. A. *J. Org. Chem.* **2000**, 65, 4397.

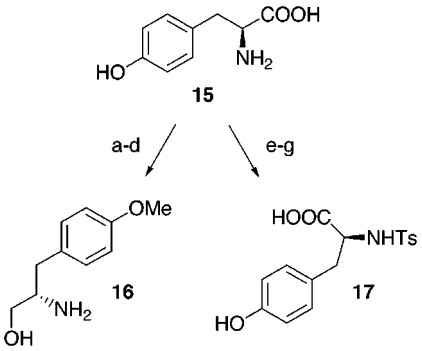
(14) The structure of a related Michael cyclization product was ascertained by X-ray diffractometry: Peters K.; Peters, E.-M.; Braun, N. A.; Ciufolini, M. A. *Z. Kristallogr. NCS* **1999**, *214*, 555.

(15) Structures ascertained by X-ray crystallography: Peters, K.; Peters, E.-M.; Braun, N. A.; Ciufolini, M. A. *Z. Kristallogr. NCS* **1999**, *214*, 273.

(16) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435.

(17) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.

Scheme 5[a]



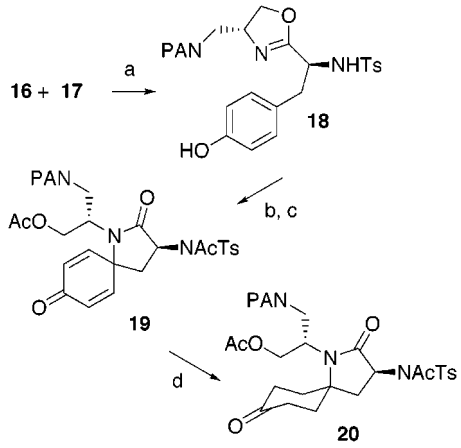
[a] Reagents: (a) MeOOCCl, $NaHCO_3$, H_2O/THF (1:1), 99%; (b) Me_2SO_4, K_2CO_3, acetone, 99%; (c) LAH, THF, 85%; (d) aqueous KOH, 86%; (e) EtOH, $HCl_{(g)}$, 100%; (f) TsCl, aqueous Na_2CO_3, $CHCl_3$, 98%; (g) aqueous NaOH, 98%.

preparation of **16** by literature methods[19] afforded material of mediocre optical purity. We thus devised an alternative route (Scheme 5), which proceeded efficiently and caused no erosion of stereochemical integrity. The optical quality of **16** was readily assessed by an ^1H NMR shift study using (+)-Eu(hfc)$_3$ as the chiral shift reagent.

The union of an amino alcohol and a carboxylic acid to form an oxazoline[20] may be achieved by various methods, among which the Wipf[21] and the Vorbrüggen[22] techniques are especially effective. In the present case, the Vorbrüggen protocol represents the method of choice, in that it leads to the desired heterocycle in one step and it tolerates an unprotected phenolic function in component **17**. Conversely, the Wipf procedure involves cyclization of a preformed *N*-hydroxyethyl amide with the Burgess reagent,[23] and it requires protection of the phenolic OH to suppress formation of sulfate esters. These are not readily converted back to the free phenol, to the detriment of overall yields.

Oxazoline **18** underwent DIB oxidation/acetylation to **19**. We note that the nature of the protecting group applied to the lateral amino group in **18** is crucial for the success of the cyclization step. In particular, a carbonyl-type blocking unit, e.g., BOC, is unsatisfactory because it competes effectively with the oxazoline for the electrophilic intermediate produced through DIB activation of the phenol. Products unrelated to the desired spirolactam are thus obtained.[12,13] The protecting group of choice here is a sulfonamide, as thoroughly detailed in our previous communications. The sulfonamide does not interfere with the cyclization step and it facilitates purification of the stereochemically labile oxazoline by a particularly mild acid−base extraction (cf. Experimental Section). Significantly, protection of the pendant amino group as a sulfonamide is also apparent in the Sorensen synthesis of **1**.[6] Our choice of a tosylamide, rather than a more

Scheme 6[a]



[a] Reagents: (a) CCl_4, PPh_3, NEt_3, MeCN/pyridine (1:1), 73%; (b) PhI(OAc)$_2$, CF_3CH_2OH, then solid $NaHCO_3$; (c) Ac_2O, pyridine, 41% (for b + c); (d) H_2, PtO_2, EtOAc, 96%. PAN = *p*-anisyl

readily cleavable Fukuyama-type nitrosulfonamide,[24] was motivated by our desire to retain the original *N*-protecting group during all transformation requiring reductants or nucleophiles. The free amine would be released during vigorous hydride reduction of the spirolactam segment to the corresponding pyrrolidine. Notice that acetylation of the primary product of oxidative cyclization results also in *N*-acylation of the tosylamide. This event is of no import, because both acetyl groups are removed simultaneously at a later stage of the synthesis.

Conversion of dienone **19** to the corresponding cyclohexanone was effected by hydrogenation in the presence of PtO_2 (Adams catalyst). Palladium or rhodium catalysts were unsatisfactory for the present application, due to their tendency to promote reductive aromatization of the substrate through C−N bond cleavage. This troublesome side reaction occurs to the extent of 50−60% when hydrogenation is attempted over supported Pd, but it constitutes the exclusive outcome when Rh catalysts are employed. It is also worthy of note that the use of supported platinum catalysts, e.g., Pt(C), resulted in formation of variable amounts of the cyclohexanol corresponding to **20**. No such problem was observed with the Adams catalyst. Saturation of dienones related to **19** may also be effected by hydrogenation over Raney nickel, but in this case the fully reduced cyclohexanol is obtained.[6]

A straightforward series of reactions advanced intermediate **20** to keto aldehyde **23** (Scheme 7), which constitutes the substrate for the crucial aldol cyclization leading to the obligatory intermediate **24.** The Snider synthesis of **1** employs an analogous aldol step, details of which were first disclosed in a preliminary communication[3b] that appeared while we were researching the same transformation. We were thus assisted in the optimization of our own reaction conditions by the important observations recorded by these workers, who ultimately chose *t*BuOK in *t*BuOH for the conduct of this step. We favor the use of sodium methoxide in 90% aqueous methanol to accomplish the same transformation.[25] Regio- and diastereoselectivity seem to be more satisfactory under these conditions.[26] Compound **24** was the major, but not the exclusive, product thus formed, and it was obtained in 44% yield after chromatographic purification. It should be noted that aldehyde **23** is fairly

(18) Fischer, E.; Lipschitz, W. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 360. It is noteworthy that direct tosylation of tyrosine gave only ditosylated tyrosine (conversion 50%) (McChesney, E. V.; Swann, Wm. K., Jr. *J. Am. Chem. Soc.* **1937**, *59*, 1116), whereas tyrosine ethyl ester gave clean monotosylated product.

(19) The preparation of **16** has been described byAbarbri et al. and Jung et al. (Abarbri, M.; Guignard, A.; Lamant, M. *Helv. Chim. Acta* 1995, *78*,-109. Jung, M. E.; Jachiet, D.; Rohloff, J. R. *Tetrahedron Lett.* 1989, *30*, 4211). Unfortunately, the product thus obtained is essentially racemic (cf. Supporting Information).

(20) Review: Gant, T. G.; Meyers A. I. *Tetrahedron* **1994**, *50*, 2297.

(21) (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett* **1992**, *33*, 907. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576.

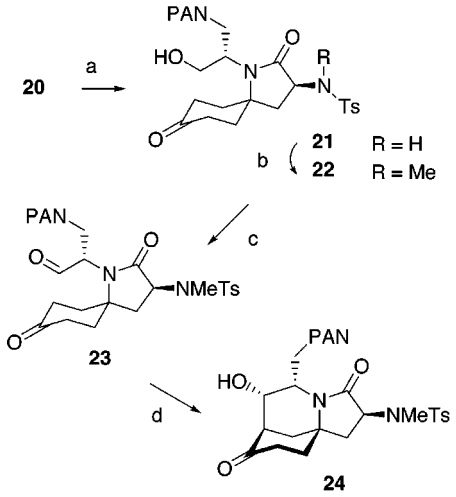
(22) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353.

(23) (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 788.

(24) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(25) The terminology "sodium methoxide in aqueous methanol" stands only to indicate the reagents utilized in this step, and it should not be interpreted as an inference regarding the precise nature of the basic species present in solution and/or responsible for the reaction.

Scheme 7[a]

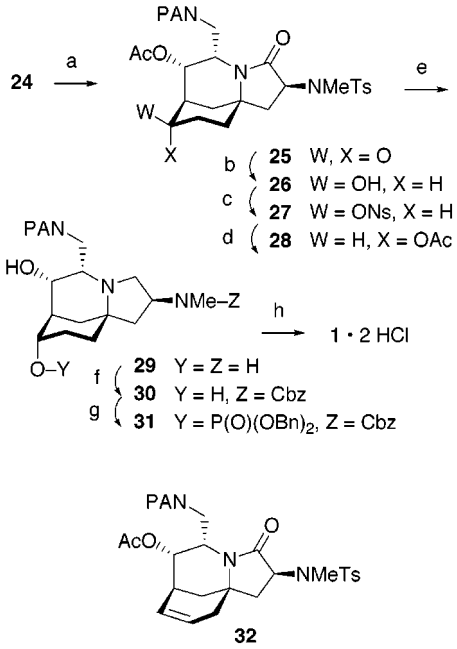


[a] Reagents: (a) K_2CO_3, MeOH, 79%; (b) MeI, K_2CO_3, acetone/DMF 97%; (c) catalyst TPAP, NMO, MS 4 Å, CH_2Cl_2, 77%; (d) NaOMe, 90% aqueous MeOH, 44%. PAN = *p*-anisyl

resistant to epimerization at C-6. This property, first recorded by Snider,[4] is consistent with recent observations by Myers[27] and earlier ones by Garner[28] concerning the configurational stability of amino acid-derived aldehydes. Stereochemical stability minimized the probability of formation of aldol isomers possessing the undesired C-6 (*R*)-configuration. Aldol products were best characterized as the corresponding acetates (cf. **25**), obtained in quantitative yield by the standard treatment with acetic anhydride in pyridine.

The final sequence that produced our first samples of fully synthetic FR901483 (Scheme 8) commenced with reduction of the ketone in **25** to the corresponding alcohol. The shape of the molecule disfavors the approach of reducing agents from the top (Re) face of the ketone, so that the desired C-9 axial carbinol is not directly available from **25**. This necessitates an ultimate inversion of configuration at C-9. In our case, reduction was effected by the use of L-Selectride, in the hope of obtaining at least some of the correct carbinol diastereomer,[29] but in fact the reaction occurred with complete diastereocontrol in favor of the equatorial alcohol **26** (within the limits of 500 MHz ^{1}H NMR spectroscopy). The structure of this intermediate was verified by X-ray crystallography.[30] Inversion of C-9 configuration was achieved by the method of Snider, via *p*-nitrobenzenesulfonate ester **27**. The resulting **28**, the structure of which was also ascertained by X-ray diffractometry,[31] was obtained in a satisfactory 73% yield, but olefin **32** was a significant byproduct (12%). Global deprotection/reduction of **28** was achieved in high yield by vigorous LAH treatment, and the secondary amino group in the emerging **29** was protected as a benzyl carbamate prior to selective phosphorylation of the C-9 carbinol. Notice that this step required no protection of the C-7 alcohol, which is rather hindered. Final hydrogenolysis of all benzyl groups in the presence of aqueous HCl provided the bis-hydrochloride salt of **1**, which was identical in all respects to material prepared from an authentic sample of FR901483, kindly provided by the Fujisawa Pharmaceutical Company.

Scheme 8[a]



[a] Reagents: (a) Ac_2O, pyridine, DMAP, CH_2Cl_2, 93%; (b) L-Selectride, THF, 95%; (c) NsCl, NEt_3, DMAP, CH_2Cl_2, 72%; (d) CsOAc, 18-cr-6, PhH, 73%; (e) LAH, THF; (f) Cbz-Cl, NEt_3, DMAP, CH_2Cl_2, 70% (for e + f); (g) *i*-$Pr_2NP(OBn)_2$, tetrazole, CH_2Cl_2, then *t*-BuOOH, decane, 29% + **30**; (h) H_2, Pd(C), aqueous HCl, MeOH, 94%. PAN = *p*-anisyl.

The Sorensen synthesis of **1** demonstrated the feasibility of a Mitsunobu-type inversion of configuration of the C-9 carbinol in substrates similar to **26**.[6] This observation allowed us to simplify our own synthesis as shown in Scheme 9. Thus, LAH reduction of compound **24** produced a 6:1 mixture of equatorial (compound **33**, major component) and axial (compound **29**, minor component) amino alcohols. This somewhat surprising stereochemical result is attributable to the greater reactivity, hence the lower selectivity, of LAH relative to other reducing agents. Separation of the two diastereomeric carbinols was difficult at this stage, due to their great polarity. Accordingly, the mixture was treated with excess dibenzyl phosphate, which presumably converted both secondary and tertiary amino groups to the corresponding salts, followed by DIAD and tris(4-chlorophenyl)phosphine. The emerging Mitsunobu products were again extremely polar and difficult to handle, necessitating conversion to *N*-Cbz derivatives prior to chromatography and characterization. The presumed major product, **34**, was thus retrieved as compound **31**. Separation of the minor diastereomer produced during LAH reduction was readily effected at this stage, providing us with a small sample of substance **35.** Overall yields were consistent with those described by Sorensen.[6] It thus seems that although the Mitsunobu step may be conducted in the presence of an unprotected methylamino substituent, technical difficulties rule in favor of protection of the secondary amine prior to inversion at C-9, just as described by the Scripps team.

(26) The beneficial effect of protic solvents on the diastereoselectivity of the aldol step in favor of **23** was first described by Snider (ref 4). We independently found that solvents of increasingly greater hydrogen bonding power afforded improved diastereoselectivity in favor of **23**. Conduct of the reaction in aqueous MeOH provided the best selectivity in the desired sense. A referee suggested the use of trifluoroethanol as the solvent for this reaction. However, fluorinated alcohols were not explored as possible aldol solvents.

(27) (a) Myers, A. G.; Kung, D. W.; Zhong B. *J. Am. Chem. Soc.* **2000**, *122*, 3236. (b) Myers, A. G.; Zhong, B.; Kung, D. W.; Movassaghi, M.; Lanman, B. A.; Kwon, S. *Org. Lett.* **2000**, *2*, 3337. (c) Myers, A. G.; Kung, D. W. *Org. Lett.* **2000**, *2*, 3019. (d) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828.

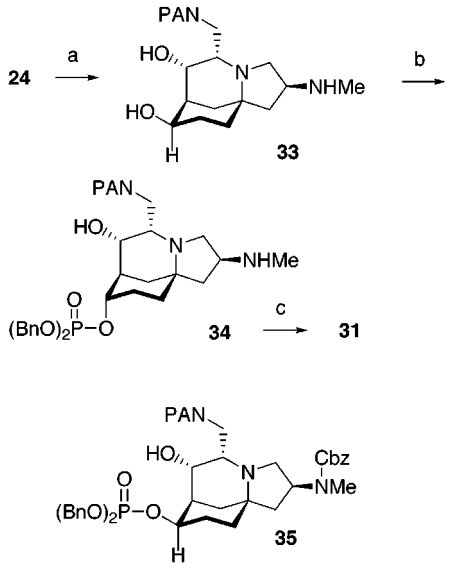
(28) (a) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855. Review: (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(29) The axial carbinol stereoisomer is normally the major product of reduction of cyclohexanones with Selectride reagents: Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(30) Ousmer, M.; Braun, N. A.; Ciufolini, M. A.; Perrin, M. *Z. Kristallogr. NCS* **2000**, *215*, 597.

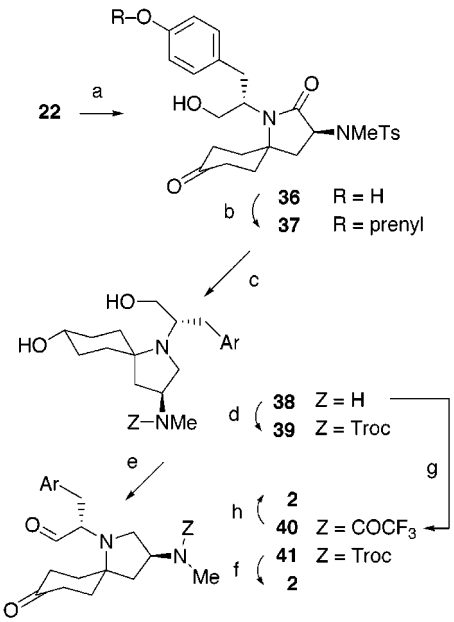
(31) Ousmer, M.; Braun, N. A.; Ciufolini, M. A.; Perrin, M.; Bavoux, C. *Z. Kristallogr. NCS* **2001**, in press.

Scheme 9[a]



[a] Reagents: (a) LAH, THF, reflux; (b) 6 equiv of $(BnO)_2P(O)OH$, THF, tris(4-chlorophenyl)phosphine, DIAD, then, NEt_3; (c) Cbz-Cl, $NaHCO_3$/THF, 26% for a−c.

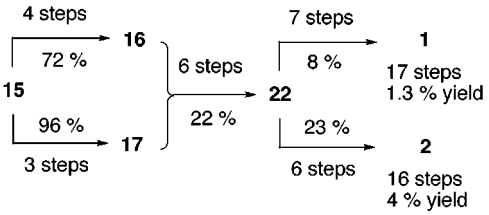
Scheme 10[a]



[a] Reagents: (a) BBr_3, CH_2Cl_2, −60 °C, 87%; (b) prenyl bromide, Cs_2CO_3, acetone, 98%; (c) LAH, THF; (d) Troc-Cl, $NaHCO_3$/THF, 60% (for c + d); (e) catalyst TPAP, NMO, MS 4 Å, CH_2Cl_2, 63%; (f) Cd/Pb couple, aqueous NH_4OAc/THF, 79%; (g) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C; (h) K_2CO_3, MeOH/H_2O, 10% (for g + h) + **40**.

We now turn to the total synthesis of TAN 1251C, **2**, which Snider has shown to represent the precursor to the entire TAN1251 family of compounds.[9] A synthesis of **2** thus amounts to a formal synthesis of all other TAN1251 substances. Our avenue to **2** (Scheme 10) evolved from spirolactam **22**, which was subjected to O-demethylation and prenylation of the intermediate phenol. Substance **37** thus obtained underwent stereoselective LAH reduction to aminodiol **38**. As reported by Snider for a similar system, this material may be oxidized to keto aldehyde **40** with DMSO/TFAA without prior protection of the secondary amine, because the latter apparently forms the corresponding trifluoroacetamide in situ under these conditions. Exposure of **40** to methanolic K_2CO_3 induced release of the trifluoroacetyl group and cyclization of the intermediate secondary amine (not observed) to fully synthetic TAN 1251C, **2**, whose properties were identical to those reported in the literature for the natural product**.** Whereas this step achieved the total synthesis, the overall yield of the final sequence was disappointing. We presume that the basic treatment required to liberate the secondary amine might have diverted a good portion of **40** into aldol manifolds. Considerable improvement in overall efficiency was observed upon protection of the amino group as a 2,2,2-trichloroethyl carbamate (Troc), followed by TPAP/NMO oxidation[32] of the resulting **39** to **41** and final Troc deprotection/cyclization by the use of the Cd/Pb couple.[33]

Scheme 11



A summary of our approach to **1** and **2** appears in Scheme 11. The longest linear sequence leading to FR901483 through a Snider-type inversion encompasses 20 steps from commercial L-tyrosine and it proceeds with an overall yield of 1%. The alternative synthesis involving a Sorensen-type Mitsunobu inversion is shorter (17 steps), and it affords identical overall yields (1.3%). This compares favorably with the other enantiocontrolled routes of **1**, both of which started with *N*-Boc-tyrosine and apparently proceeded in a total of 22[4] and 18[6] linear steps from this educt. Likewise, our synthesis of TAN1251C requires a maximum of 16 linear steps from L-tyrosine (4% overall yield). The alternative enantiocontrolled route to this natural product requires 18 steps from *N*-Boc-tyrosine (7.2% overall yield).[9]

In conclusion, our oxazoline-based avenue to spirolactams appears to be capable of sustaining synthetic efforts toward molecules of at least moderate complexity, such as **1** and **2**, and to simplify the synthetic problem posed by these structures to a significant extent. Further applications of oxidative cyclizations of oxazolines are currently under study and new developments in this area will be disclosed in due course.

Acknowledgment. We thank the MENRT (Fellowship to M. O.), the CNRS, the Région Rhône-Alpes, the NIH (CA-55268), the NSF (CHE 95-26183), and the R. A. Welch Foundation (C-1007) for support of our research. M.A.C. is a Fellow of the A. P. Sloan Foundation (1994−1998) and the recipient of a Merck & Co. Academic Development Award (2000, 2001). We are especially grateful to Dr. S. Goto and Mr. T. Sonoda, both from Fujisawa Pharmaceutical Co., for the sample of authentic FR901483. The authors also express their gratitude to Dr. Denis Bouchu and Laurence Rousset, of the mass spec facility of the LSMO, for measuring the mass spectra.

Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra of all compounds described herein (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

JA016030Z

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