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Synthesis of (−)-TAN-2483A. Revision of the Structures and Syntheses of (±)-FD-211 (Waol A) and (±)-FD-212 (Waol B)

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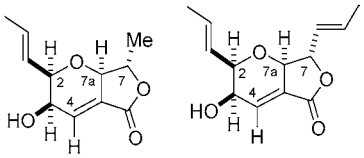
ABSTRACT



The structure of waol A has been revised from 1 to 6, the vinylogue of TAN-2483 A (5). Aldol reaction of 10b(c) with 2,4-hexadienal (11) affords 9b(c), which is subjected to iodoetherification with bis(*sym*-collidine)IPF$_6$ to provide 8b(c). Treatment with Et$_3$N in CH$_2$Cl$_2$ completes three-step syntheses of TAN-2483A (5) and waol A (6).

Mizoue and co-workers reported the isolation of waol A (FD-211, **1**), which has a broad spectrum of activity against cultured tumor cell lines, including adriamycin-resistant HL-60 cells, from the fermentation broth of *Myceliophthora lutea* TF-0409 (Figure 1).[1] More recently, they reported the isolation of waol B (FD-212, **2**), which has similar biological activity, from the same source.[2] Tadano has reported an approach to the synthesis of **1**.[3]

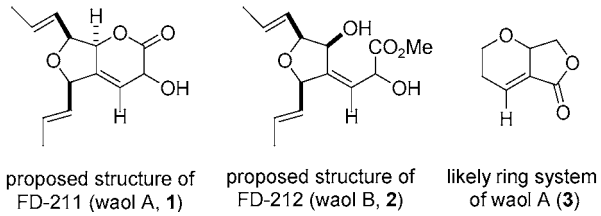


Figure 1. Proposed structures of waol A and waol B.

However, the carbonyl group of waol A absorbs at 1767 cm^{-1},[1] which is characteristic of a γ-lactone, rather than the δ-lactone of **1**. The alkene ring hydrogen of waol A absorbs at δ 6.90,[1] while that of **1** would be expected to absorb between δ 5 and 6. An absorbance at δ 6.90 is characteristic of CH═C−C═O. Taken together, these discrepancies suggest that waol A might be a substituted 2,3,7,7a-tetrahydro-5*H*-furo[3,4-*b*]pyran-5-one (**3**).

A literature search uncovered two compounds with this ring system, TAN-2483B (**4**) and TAN-2483A (**5**) (Figure 2), which show strong c-src kinase inhibitory action and inhibit PTH-induced bone resorption of a mouse femur.[4] The structure of **5** was assigned crystallographically, the absolute stereochemistry was assigned by the Mosher ester method, and the relative stereochemistry of **4** was determined by NOE

(1) Nozawa, O.; Okazaki, T.; Sakai, N.; Komurasaki, T.; Hanada, K.; Morimoto, S.; Chen, Z.-X.; He, B.-M.; Mizoue, K. *J. Antibiot.* **1995**, *48*, 113.
(2) Nazawa, O.; Okazaki, T.; Morimoto, S.; Chen, Z.-X.; He, B.-M.; Mizoue, K. *J. Antibiot.* **2000**, *53*, 1296.
(3) Suzuki, E.; Takao, K.-i.; Tadano, K.-i. *Heterocycles* **2000**, *52*, 519.
(4) Hayashi, K.; Takizawa, M.; Noguchi, K. Jpn. Patent 10287679, 1998; *Chem. Abstr.* **1999**, *130*, 3122e.

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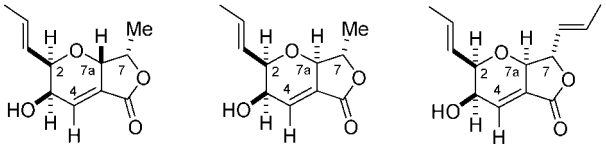
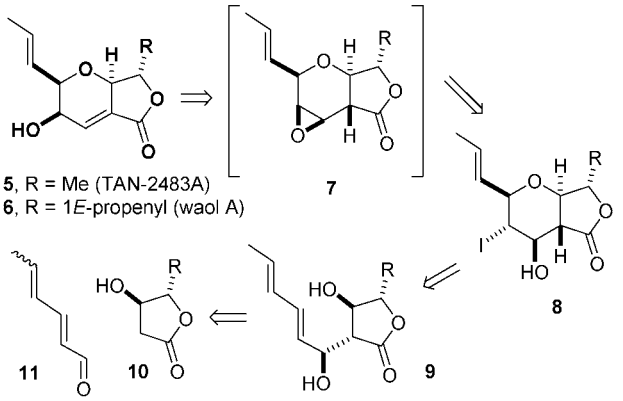


Figure 2. Structures of TAN-2483A and TAN-2483B and revised structure of waol A.

experiments.[5] The carbonyl groups of **4** and **5** absorb at 1760 cm^{-1}, and the alkene ring hydrogens absorb at δ 7.12 and 6.90, respectively. H_2 and H_3 of TAN-2483B (**4**) absorb at δ 4.35 and 4.45, and H_2 and H_3 of both TAN-2483A (**5**) and waol A absorb at δ 4.05 and 4.10, respectively. This suggests that waol A might be the vinylogue of TAN-2483A with structure **6**.

Retrosynthetic analysis (Scheme 1) suggested that TAN-2483A (**5**) and waol A (**6**) should be available from epoxy

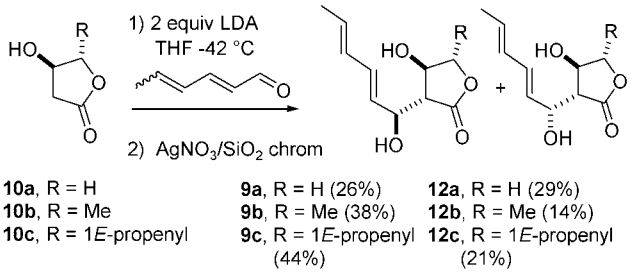
Scheme 1. Retrosynthetic Analysis



lactone **7**, which should be easily formed from iodohydrin **8**. Iodohydrin **8** should be accessible stereospecifically by iodoetherification of diene diol **9**, which can be prepared by an aldol reaction of the dianion of hydroxyfuranone **10** with 2,4-hexadienal (**11**). Aldol reactions of **10** occur stereospecifically from the face opposite the hydroxy group, but give mixtures of isomers at the hydroxy group on the side chain.[6]

A model study was carried out with commercially available (*S*)-dihydro-4-hydroxyfuranone (**10a**) and 2,4-hexadienal (**11**), which is a 4:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-isomers (Scheme 2). *Note that structures **10a**, **9a**, **12a**, **14**, and **16**−**21** are drawn for clarity with the same absolute stereochemistry as TAN-2483A, although they are the enantiomers.* Treatment of **10a** with 2 equiv of LDA in THF and addition of dienal **11** at −42 °C as described by Prestwich[6a] affords

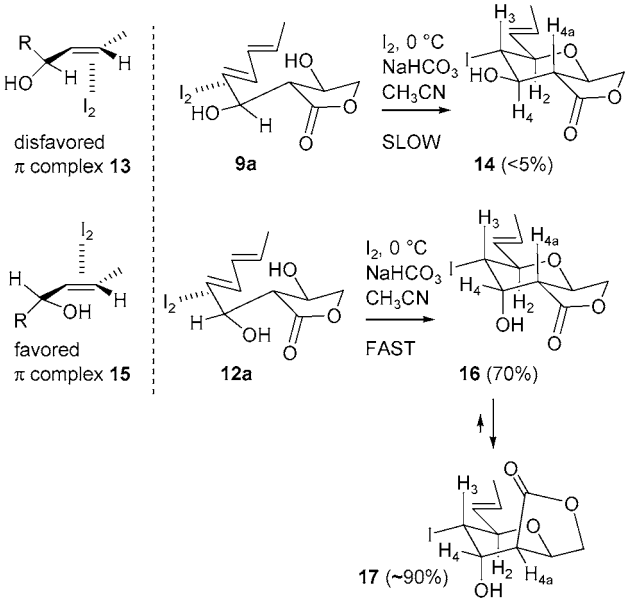
Scheme 2



a readily separable mixture of **9a** and **12a**, both as a 4:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-isomers. Flash chromatography on 20% $AgNO_3$ on silica gel gives pure **9a** (26%) and **12a** (29%). The stereochemistry of the side chain alcohol could not be determined by spectral analysis and was established from the spectra of iodohydrins **14** and **16** (see below).

Iodoetherification of the desired isomer **9a** under a wide variety of conditions provides <5% iodo alcohol **14**, while iodoetherification of the undesired isomer **12a** with I_2 and solid $NaHCO_3$ in CH_3CN affords 70% of iodo alcohol **16** (Scheme 3).[7] In **14**, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 9.8 Hz, $J_{4,4a}$ =

Scheme 3



10.4 Hz, and $J_{4a,7a}$ = 11.6 Hz, indicating that all of the hydrogens on the tetrahydropyran ring are axial and all of the substituents are equatorial. In **16**, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ < 1 Hz, $J_{4,4a}$ < 1 Hz, and $J_{4a,7a}$ = 11.6 Hz, indicating that the H_4 is equatorial and the hydroxy group is axial. Isomerization

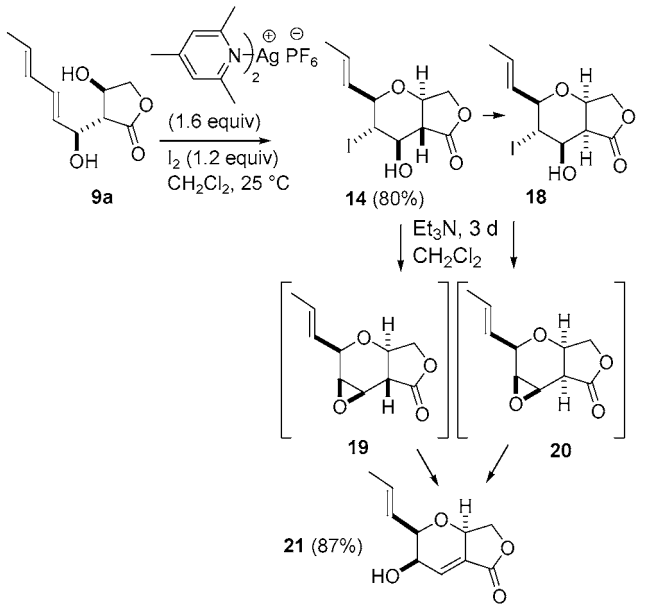
(5) Hayashi, K. Takeda Chemical Industries. Unpublished results.
(6) (a) Shieh, H.-M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319. (b) Chen, S. Y.; Joullie, M. *J. Org. Chem.* **1984**, *49*, 2168.
(7) (a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (b) Tamaru, Y.; Hojo, M.; Kawamura, S.-i.; Sawada, S.; Yoshida, Z.-i. *J. Org. Chem.* **1987**, *52*, 4062.

of **16** to the *cis*-fused isomer **17** occurs easily on heating in the presence of $NaHCO_3$ or on silica gel.

We were initially puzzled as to why **12a** undergoes facile iodoetherification to give **16**, while **9a** fails to give the more stable isomer **14** with an equatorial hydroxy group. Closer examination of the literature revealed that Chamberlin and Yoshida had made related observations[7] and that Chamberlin and Hehre had explained the origins of these effects.[8] Cyclizations in which the nucleophile is in the R group proceed slowly through the disfavored π complex **13** with the hydrogen eclipsed with the double bond and rapidly through the favored π complex **15** with the hydroxy group eclipsed with the double bond. The π complex formed from **9a** has the hydrogen eclipsed with the double bond and therefore cyclizes slowly to give **14**. The π complex formed from **12a** has the hydroxy group eclipsed with the double bond and therefore cyclizes rapidly to give **16**.

A more reactive iodinating agent is needed to convert **9a** to **14** in high yield. Bis(*sym*-collidine)IPF_6 is a very reactive but moisture-sensitive iodinating reagent that can easily be prepared in situ from bis(*sym*-collidine)$AgPF_6$ and iodine.[9] We were delighted to find that reaction of bis(*sym*-collidine)-$AgPF_6$ (1.6 equiv) and iodine (1.2 equiv) in CH_2Cl_2, addition of **9a**, and stirring for 1.5 h affords 80% of **14**, which can be purified by flash chromatography on water-deactivated silica gel (Scheme 4). Partial isomerization to the more stable

Scheme 4

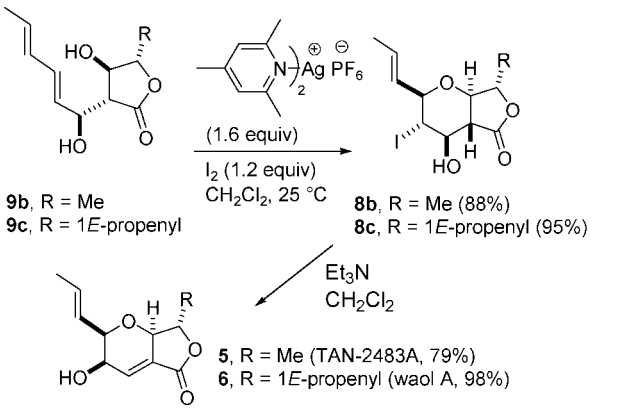


cis-fused isomer **18** occurs otherwise. Treatment of either **14** or **18** with Et_3N in CH_2Cl_2 for 3 d at 25 °C affords epoxides **19** or **20**, which react further to give 87% of **21**, with spectral data similar to those of TAN-2483A (**5**) and waol A (**6**). The iodide and hydroxy groups of **14** are in a diequatorial arrangement. Formation of the epoxide requires either that the pyran ring of **14** adopts a boat conformation with these groups anti-periplanar or that the flexible *cis*-fused isomer **18** adopts the chair conformation with the iodide and hydroxy groups anti-periplanar.

(−)-Dihydro-4-hydroxy-5-methyl-2-furanone (**10b**) was prepared by Hatakeyama's procedure in >90% ee.[10] Dihydroxylation of methyl 3*Z*-pentenoate[11] with OsO_4 and NMO and treatment of the resulting diol with acid gave (±)-**10b**. Treatment with Novozyme lipase, vinyl acetate, and 1,4,8,-11-tetrathiacyclotetradecane in diisopropyl ether gave (−)-**10b** and the enantiomeric acetate.

We were pleased to find that the selectivity for **9** in the aldol reaction improves with an alkyl substituent on the furanone. Treatment of the dianion of **10b** with **11** affords 38% of the desired adduct **9b** and only 14% of **12b** after $AgNO_3$ chromatography (Scheme 2). Iodoetherification of **9b** provides 88% of iodo alcohol **8b**, which gives 79% of TAN-2483A (**5**) on treatment with Et_3N in CH_2Cl_2 at 25 °C for 3 d (Scheme 5). The ^1H and ^{13}C NMR spectra of **5** are

Scheme 5



identical to those of the natural product. The optical rotation, $[\alpha]_D$ −236, has the same sign but is somewhat smaller than that reported, $[\alpha]_D$ −292, confirming the assignment of the absolute stereochemistry.

Propenyl lactone **9c** was made by modification of Griengl's procedure (Scheme 6).[12] Reaction of 2*E*-butenal with NaCN and HCl[13] and silylation[14] gives 34% (unoptimized) of **22**. Reaction of **22** with Zn, TMSCl, and $BrCH_2CO_2Me$[15] affords 86% of keto ester **23**, which is reduced with $NaBH_4$ in

(8) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.

(9) (a) Homsi, F.; Robin, S.; Rousseau, G. *Org. Synth.* **1999**, *77*, 206. (b) Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793. (c) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862.

(10) Nishiyama, T.; Nishioka, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Heterocycles* **2001**, *54*, 69.

(11) Krebs, E.-P. *Helv. Chim. Acta* **1981**, *64*, 1023.

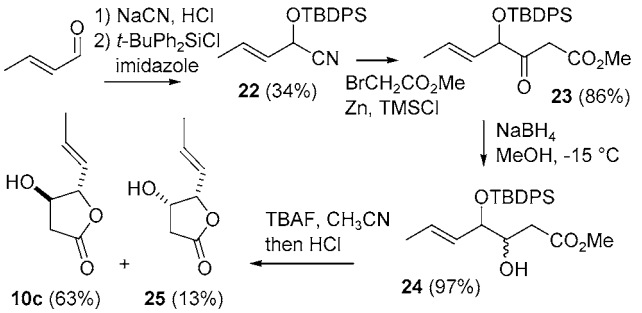
(12) Johnson, D. V.; Fischer, R.; Griengl, H. *Tetrahedron* **2000**, *56*, 9289.

(13) Anderson, J. R.; Edwards, R. L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 215.

(14) (a) Brussee, J.; Loos, W. T.; Kruse, C. G.; Van Der Gen, A. *Tetrahedron* **1990**, *46*, 979. (b) Warmerdam, E. G. J. C.; van den Nieuwendijk, A. M. C. H.; Kruse, C. G.; Brussee, J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 20.

(15) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.

Scheme 6

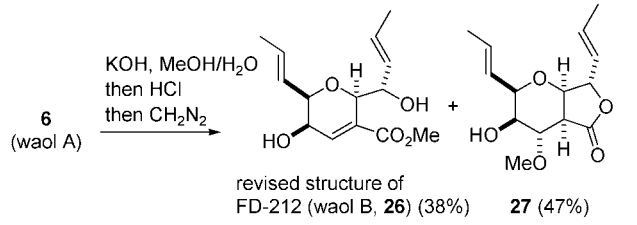


MeOH at −15 °C to give 97% of **24** as a 5:1 mixture of isomers. Deprotection with TBAF in CH_3CN and acid-catalyzed lactonization provides 63% of (±)-**10c** and 13% of (±)-**25**.[16]

Treatment of the dianion of **10c** with 2,4-hexadienal (**11**) affords 44% of the desired adduct **9c** and 21% of **12c** after $AgNO_3$ chromatography (Scheme 2). Iodoetherification of **9c** provides 95% of iodo alcohol **8c**, which gives 98% of **6** on treatment with Et_3N in CH_2Cl_2 at reflux overnight. The ^1H and ^{13}C NMR spectra of **6** are identical to those of FD-211 (waol A), indicating that the revised structure we proposed is correct.

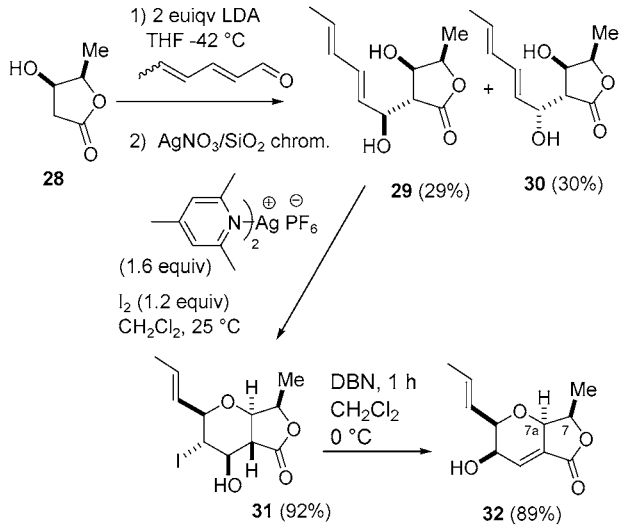
Hydrolysis of **6** with KOH in MeOH/H_2O, followed by acidification and immediate reaction with CH_2N_2, affords 38% of **26** with ^1H and ^{13}C NMR spectral data identical to those for FD-212 (waol B) and 47% of MeOH adduct **27** resulting from conjugate addition of methoxide and protonation to give the *cis*-fused ring system (Scheme 7).

Scheme 7



We prepared lactone **28** as a potential precursor to TAN-2483B by addition of OsO_4 and NMO to methyl 3*E*-pentenoate.[17] Addition of 2,4-hexadienal (**11**) to the dianion of **28** provides 29% of **29** and 30% of **30**. Iodoetherification of **29** affords 92% of **31** (Scheme 8). Treatment of **31** with

Scheme 8



Et_3N in CH_2Cl_2 at reflux for 3 d provides only 32% of **32** and 61% of recovered **31**. As expected, the spectral data of **32** are different from those of TAN-2483B (**4**), which is isomeric to TAN-2483A (**5**) at C_{7a} while **32** is isomeric at C_7. The formation of **32** from **31** is much slower than with the other iodohydrins, suggesting that the β-methyl group of **31** makes conformations with the iodide and hydroxy groups anti-periplanar more strained. Treatment of **31** with 5 equiv of the stronger base DBN in CH_2Cl_2 for 1 h at 0 °C gives 89% of **32**.

In conclusion, we have reassigned the structures of waols A and B as **6** and **26** and completed the first syntheses of these molecules and (−)-TAN-2483A (**5**) in three steps from lactones **9** by aldol reaction, iodoetherification, and elimination.

Acknowledgment. We thank the National Institutes of Health (GM-50151) for financial support. We thank Dr. Kozo Hayashi, Takeda Chemical Industries for information about the structures of and copies of the spectra of TAN-2483A and TAN-2483B and Dr. Kazutoshi Mizoue, Taisho Pharmaceutical Co. for copies of the spectra of waols A and B.

Supporting Information Available: Experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Attempted enzymatic resolution of **10c**, as successfully carried out for **10b**, gives the opposite enantiomer, (+)-**10c,** in 18% ee. Reduction of **23** with $NaBH_4$ and D-tartaric acid[14] and further elaboration yields 30% of (+)-**10c** (38% ee) and 45% of **25**.

(17) Harcken, C.; Brückner, R.; Rank, E. *Chem. Eur. J.* **1998**, *4*, 2342.