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Regioselective Oxidation of β-Hydroxyazo Compounds to β-Hydroxyazoxy Compounds and Its Application to Syntheses of Maniwamycins A and B

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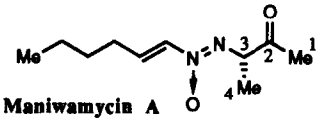
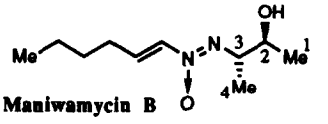
Abstract: A new preparation of β-hydroxyazo compounds and regioselectivities on their oxidation to β-hydroxyazoxy compounds have been described. A new synthesis of antifungal antibiotic maniwamycin A and the first synthesis of maniwamycin B by using this methodology have been also described.

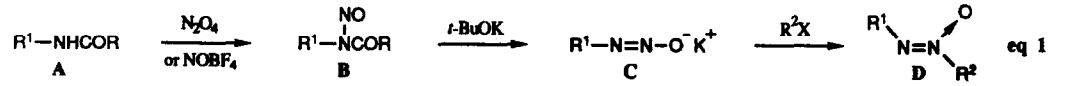
We have recently reported isolation[1] and structure determination[2] of novel antifungal antibiotics maniwamycins A (MMA) and B (MMB), and the synthesis of MMA.[3] The structural feature is an α,β-unsaturated azoxy system which has also been found in seven antibiotics, elaiomycin,[4] LL-BH 872α,[5] valanimycin,[6] jietacins A and B,[7] MH-071 and MH-072.[8] Among them, elaiomycin,[9] jietacin A,[10] and maniwamycin A[3] have been synthesized. The key sequence of these syntheses lies in constructing azoxy moiety (compounds **D** in eq 1) developed by Moss.[9,11] Namely, the alkylation of diazotates **C**, which are derived from amides (or carbamates) **A** by nitrosation with N_2O_4[12a] (or $NOBF_4$[12b]) followed by base treatment of the resulting nitrosoamides (or nitrosocarbamates) **B**, gives *Z*-azoxy compounds **D**. Although this sequence provides the desired stereo- and regioisomers **D** by selecting appropriate R^1 and R^2, the overall yield is not satisfactory (29 ~ 38%).[3,9,10] During the course of our investigations to explore more potent antifungal analogs of MMA and MMB, it was necessary to develop more practical and convenient procedure to make an α,β-unsaturated azoxy system. As shown in eq 2, we anticipated the "hydroxyl-directed" oxidation of β-hydroxyazo compounds **E** might give β-hydroxyazoxy compounds **F** regioselectively. It is known[3,9,10] that the latter **F** can be transformed to the desired **G** by dehydration. In this letter we describe the results of some investigations of new procedures involving preparation of β-hydroxyazo compounds **E** and their "hydroxyl-directed" regioselective oxidation. We also describe the application of this method to a new synthesis of MMA and the first synthesis of MMB in optically active form.



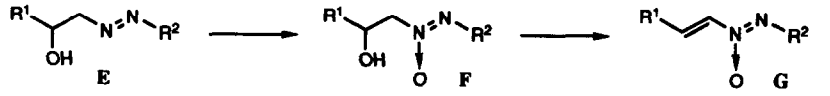
Maniwamycin A



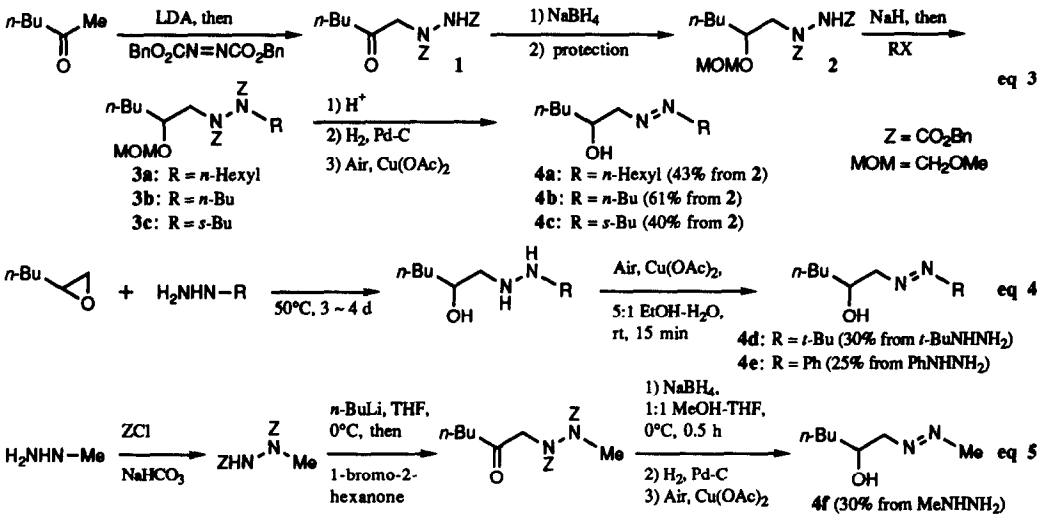
Maniwamycin B



eq 1



eq 2



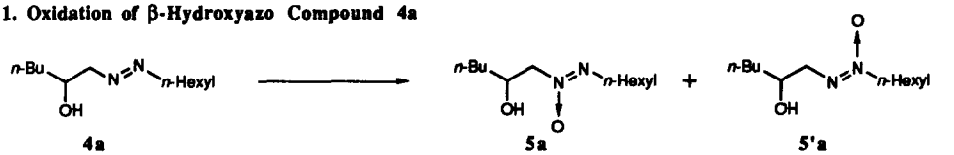
First, we investigated the preparation of the β-hydroxyazo compound as a model and developed a new procedure as shown in eq 3. 2-Hexanone was lithiated with LDA (THF, -78°C) and treated with dibenzyl azodicarboxylate to afford **1**[13] in 65% yield.[14] Reduction ($NaBH_4$/1:1 MeOH-THF, rt, 0.5 h) of **1** followed by protection [chloromethyl methyl ether (MOMCl)/*i*-$Pr_2EtN/CHCl_3$, 50°C, 6 h] gave **2**[13] in 70% yield. Deprotonation of **2** with NaH (DMF, 0°C) and alkylation with 1-iodohexane (0°C) provided **3a**[13] in 85% yield. Finally, deprotection (HCl-MeOH, rt, then H_2/Pd-C/AcOH-EtOH, rt) and oxidation (Air/10 mol% $Cu(OAc)_2$/AcOH-H_2O-EtOH, rt)[15] furnished **4a**[13] in 50% yield.[16]

The results of oxidation of **4a** to the azoxy compound **5a**[13] and its regioisomer **5'a**[13] are summarized in Table 1. Examination of Table 1 reveals that oxidation with 3.63M *t*-BuOOH in toluene[17] in the presence of 10 mol% $VO(acac)_2$[18] in CH_2Cl_2 (entry 7) gave the best selectivity.[19,20] Since the corresponding MOM-ether[13] of **4a** did not show any significant selectivity under the reaction conditions of entry 7 (rt, 18 h),[21] the hydroxyl group in **4a** is crucial.

We next examined the influence of the substituent on the azo group under the conditions of entry 7 in Table 1 (Table 2). **4b**[13,16] and **4c**[13,16] were prepared by the same sequence in eq 3. **4d**[13,16] and **4e**[13,16] were prepared by the sequence in eq 4.[22] **4f**[13,16] can be prepared by the sequence in eq 3, but it was prepared by the sequence in eq 5 only because of its simplicity. Examination of Table 2 reveals that **4a**, **4b**, **4c**, and **4f** underwent "hydroxyl-directed" oxidation (entries 1, 2, 3, and 6). In contrast, oxidation of **4d** afforded **5'd** as a major product in good selectivity (entry 4), whereas oxidation of **4e** proceeded in low selectivity (entry 5). Probably steric and electronic effects also play a key role in these reactions along with hydroxyl-direction.[23] Although precise reaction mechanism related to regioselectivities has not been clarified as yet, we believe that these procedures provide a new methodology for constructing β-hydroxyazoxy compounds.

Along this line, a new synthesis of MMA and the first synthesis of MMB have been achieved in optically active form (eq 6). Lithiation of **6**[13,24] with *n*-BuLi followed by addition of the cyclic sulfate **7**, which was prepared from (2*R*,3*R*)-(-)-2,3-butanediol,[25] afforded the 96% yield of adduct, which was then subjected to hydrolysis of the sulfate ester to give **8**[13] in 93% yield (based on the consumed starting material). The four-step conversion of **8** gave **9**[13,26] in 70% overall yield. Treatment of **9** with *t*-BuOOH in toluene and

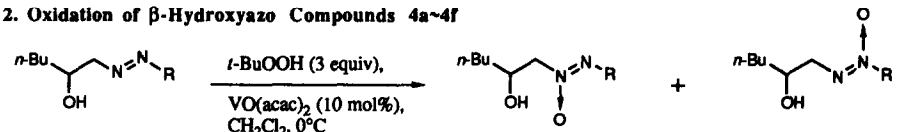
Table 1. Oxidation of β-Hydroxyazo Compound 4a



4a 5a 5'a

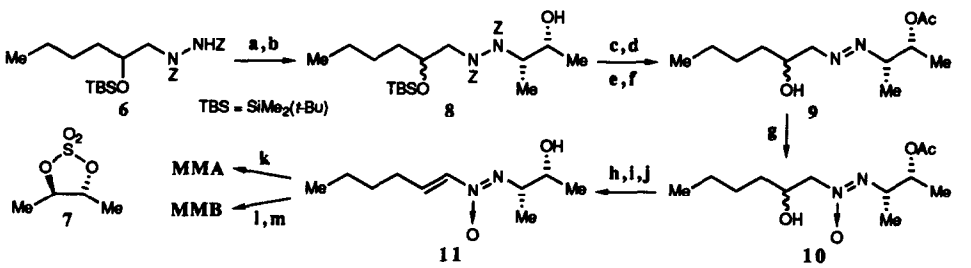
entry	conditions	ratio of 5a:5'a	yield (%) 5a	5'a
1	*m*-CPBA (1.5 equiv) / $Cl(CH_2)_2Cl$, 0°C, 5 min	1 : 1.1	47	53
2	*t*-BuOOH (3 equiv) / $Ti(Oi\text{-}Pr)_4$ (10 mol%) / $Cl(CH_2)_2Cl$, reflux, 45 min	1.1 : 1	52	47
3	*t*-BuOOH (3 equiv) / $Mo(CO)_6$ (10 mol%) / benzene, reflux, 20 min	1.9 : 1	66	34
4	*t*-BuOOH (3 equiv) / $VO(acac)_2$ (10 mol%) / CH_3CN, 0°C, 0.5 h, rt, 0.5 h	3.7 : 1	70	19
5	*t*-BuOOH (3 equiv) / $VO(acac)_2$ (10 mol%) / toluene, 0°C, 50 min	3.7 : 1	78	21
6	*t*-BuOOH (3 equiv) / $VO(acac)_2$ (10 mol%) / $Cl(CH_2)_2Cl$, 0°C, 50 min	4.9 : 1	74	15
7	*t*-BuOOH (3 equiv) / $VO(acac)_2$ (10 mol%) / CH_2Cl_2, 0°C, 0.5 h	9.7 : 1	87	9.0
8	cumene hydroperoxide (3 equiv) / $VO(acac)_2$ (10 mol%) / CH_2Cl_2, 0°C, 0.5 h	5.3 : 1	79	15
9	*t*-BuOOH (3 equiv) / CH_2Cl_2, rt, 20 min	——	no reaction	
10	80% aq *t*-BuOOH (3 equiv) / $VO(acac)_2$ (10 mol%) / CH_3CN, rt, 1 d	——	no reaction	

Table 2. Oxidation of β-Hydroxyazo Compounds 4a~4f



4a~4f 5a~5f 5'a~5'f

entry	R	time (h)	ratio of 5:5'	yield (%) 5	5'
1	*n*-Hexyl (4a)	0.5	9.7 : 1	87 (5a)	9.0 (5'a)
2	*n*-Bu (4b)	0.5	7.3 : 1	87 (5b)	12 (5'b)
3	*s*-Bu (4c)	0.5	5.9 : 1	71 (5c)	12 (5'c)
4	*t*-Bu (4d)	1.5	1 : 15.5	5.4 (5d)	84 (5'd)
5	Ph (4e)	2.5	1.6 : 1	56 (5e)	35 (5'e)
6	Me (4f)	0.25	6.5 : 1	56 (5f)	8.6 (5'f)



(a) *n*-BuLi/HMPA/THF, -78°C, 10 min, then 7/THF, rt, 2 d, 96%; (b) 5 mol% H_2SO_4 in dioxane, rt, 20 min, 93% (based on the consumed starting material); (c) Ac_2O/DMAP/Py, 40°C, 1 d; (d) 2%HCl-MeOH, rt, 0.5 h; (e) H_2/Pd-C/AcOH-EtOH, rt, 2 h; (f) Air/10 mol% $Cu(OAc)_2$/AcOH-H_2O-EtOH, rt, 40 min, 70% for 4 steps; (g) 3.63M *t*-BuOOH in toluene/40 mol% $VO(acac)_2$/CH_2Cl_2, 0°C, 20 min, 87%; (h) MsCl/Et_3N/CH_2Cl_2, 0°C, 15 min; (i) DBU/toluene, 40°C, 100 min; (j) K_2CO_3/MeOH, rt, 1 h, 85% for 3 steps; (k) DMSO/DCC/Py/TFA/ether, rt, 1.5 h, 98%; (l) PhCOOH/PPh_3/DEAD/THF, 0°C, 40 min, 70%; (m) K_2CO_3/MeOH, rt, 3.5 h, 50%.

40 mol% $VO(acac)_2$ in CH_2Cl_2 at 0°C for 20 min provided **10**[13] in 87% yield along with the 8% yield of its regioisomer.[27] Three-step transformation of **10** gave 2-*epi*-MMB **11**[13] in 85% overall yield. Oxidation of **11** afforded MMA in 98% yield. Finally, Mitsunobu reaction of **11**[28] followed by saponification provided MMB in 35% yield. The synthetic samples of MMA and MMB were identical with the natural ones[1,2,3] in all respects (^1H NMR, IR, UV, $[\alpha]_D$, and TLC mobilities).

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17. Anhydrous *t*-BuOOH in toluene used in all experiments was prepared by the literature procedure: Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607.
18. For example see: Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
19. Determination of the position of the N→O bond in **5** and **5'** was accomplished by ^1H NMR chemical-shift measurements: (a) Freeman, J. P. *J. Org. Chem.* **1963**, *28*, 2508. (b) Gillis, B. T.; Hagarty, J. D. *J. Org. Chem.* **1967**, *32*, 95. (c) Greene, F. D.; Hecht, S. S. *J. Org. Chem.* **1970**, *35*, 2482. (d) Swigert, J.; Taylor, K. G. *J. Am. Chem. Soc.* **1971**, *93*, 7337. (e) Taylor, K. G.; Riehl, T. *J. Am. Chem. Soc.* **1972**, *94*, 250.
20. The Z-stereochemistry of **5** and **5'** was supported by UV spectra. UV (EtOH) λ_{max} nm (ε): **5a**, 214.5 (18500); **5'a**, 213 (16900); **5b**, 217.5 (6600); **5'b**, 215.5 (7900); **5c**, 221.5 (6300); **5'c**, 217 (4700); **5d**, 220.5 (3800); **5'd**, 216 (4900); **5e**, 289 (12100), 223 (9400); **5'e**, 245.5 (2900), 206 (3200); **5f**, 211 (8300); **5'f**, 217 (7400). See ref. 11c, 19d, and 19e.
21. The corresponding MOM-ether of **5a** and **5'a** were obtained in 23% and 27% yields, respectively.
22. For example see: Schiessl, H. W. *Aldrichimica Acta* **1980**, *13*, 33.
23. Under the non-regioselective conditions using *m*-CPBA in CH_2Cl_2, oxidations of **4b** and **4c** proceeded in ratios of 1.1:1 (**5b**:**5'b**) and 1:1.1 (**5c**:**5'c**), respectively. In contrast, oxidation of **4d** under the same conditions afforded **5d** and **5'd** in an 1:15 ratio, still **5'd** dominated over **5d**.
24. **6** was prepared from **1** by $NaBH_4$ reduction and silylation (TBSOTf/Et_3N/CH_2Cl_2, 0°C, 40 min, 100%).
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26. At this stage, the *E*-stereochemistry of **9** was not ascertained.
27. Determination of the position of the N→O bond in **10** and its regioisomer was accomplished by ^1H NMR chemical-shift measurements (see ref 19) and by the completion of the synthesis.
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