Heteroaromatic Oxidation

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Formation of α-Hydroxy-β-diketones through Hydroxylation of Isoxazolium Salts: Stereoselective Approach to Angular *cis*-Diols in Polycyclic Systems**

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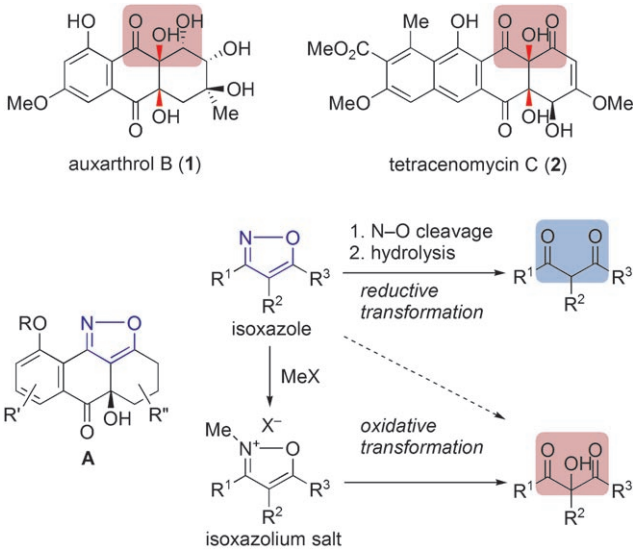
Among the natural products of the type-II polyketide biosynthesis,[1] highly oxidized polycyclic structures, such as auxarthrol B (**1**)[2] and tetracenomycin C (**2**),[3] are attractive for their biological relevance as well as for synthetic challenges (Scheme 1). In our continuing synthetic studies

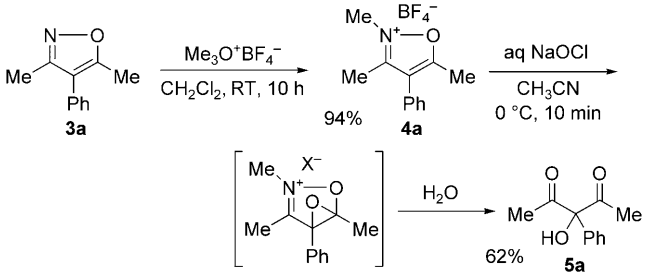


Scheme 1. Oxidative and reductive conversions of isoxazoles.

on the exploitation of isoxazole-based intermediates like **A**,[4] we have addressed the issue of installing the "angular *cis*-diols" that are characteristic of these compounds. We envisioned that, if viable, the oxidation of isoxazoles[5] to α-hydroxy-β-dicarbonyl structures would be ideally suited for this purpose. However, in contrast to the well-known reductive N–O bond fission and hydrolysis that made isoxazoles useful synthetic equivalents to β-dicarbonyl compounds,[6] the projected oxidation is unprecedented due to the resistance of this heterocycle toward various transformations.[7] Judging from the inherent reactivities, however, we expected that the corresponding isoxazolium salt would provide a potential solution by allowing elaborations including oxidation.[8]

Herein, we report the realization of this scenario through 1) the N-methylation of isoxazoles and 2) the oxidation of the resulting isoxazolium salts with sodium hypochlorite, followed by hydrolysis.[9] Whereas construction of α-hydroxy-β-dicarbonyl structures is not necessarily straightforward by α-hydroxylation of β-dicarbonyl compounds[10] or ketohydroxylation of α,β-unsaturated carbonyl compounds,[11] the present protocol provides an effective entry to such structures and also allows the construction of the angular *cis*-diol units embedded in many polycyclic natural products.

N-methylation of isoxazole **3a** by the Meerwein reagent (1.1 equiv) and precipitation (Et_2O) gave the model isoxazolium salt **4a** (Scheme 2). Although various potential oxidants



Scheme 2. Two-step hydroxylation. RT: room temperature.

failed to oxidize **4a**,[12] sodium hypochlorite[13] gave the desired product: Upon slow addition of aqueous NaOCl (ca. 4 equiv) to **4a**, α-hydroxy-β-diketone **5a** was obtained in 62% yield.

Table 1 shows the application of this two-step protocol to other isoxazoles, **3b–e**. The N-methylation gave isoxazolium salts **4b–e**, which underwent smooth oxidation under the above-stated conditions. The reaction of **4b** shows the applicability to a highly hindered substrate, with 73% yield of α-hydroxy-β-diketone **5b**. The reaction of **4c** is an example of a base-labile substrate that affords the corresponding

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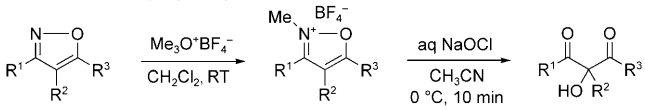
Table 1: Two-step hydroxylation of isoxazoles **3b–e**.[a]



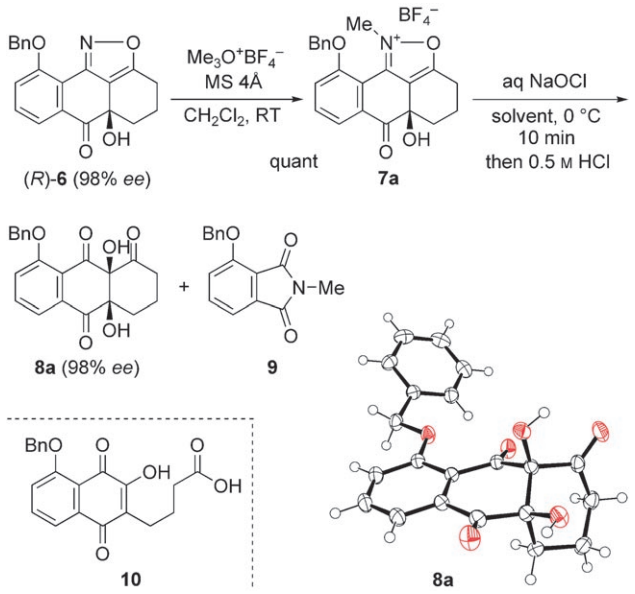
3b–e **4b–e** **5b–e**

Isoxazole	R^1	R^2	R^3	t [h]	Yield [%] (step 1)	Yield [%] (step 2)
3b	Ph	Me	Ph	18	97 (**4b**)	73 (**5b**)
3c	Ph	CO_2Et	Me	18	– (**4c**)	80 (**5c**)[b,c]
3d	*t*Bu	H	*t*Bu	24	76 (**4d**)	84 (**5d**)
3e	Ph	H	Ph	25[d]	95 (**4e**)	84 (**5e**)[b,e]

[a] Step 1: Meerwein reagent (1.05–1.1 equiv) in CH_2Cl_2 (0.5 M) at room temperature. Step 2: Unless otherwise noted, aq NaOCl (ca. 4 equiv) in MeCN (0.3 M) at 0 °C for 10 min. [b] Acidic workup with 0.5 M HCl. [c] Overall yield after two steps. [d] At 0.25 M in CH_2Cl_2. [e] In the presence of pyridine (4.0 equiv).

diketoester **5c** in 80% yield (over two steps from **3c**). Less-substituted isoxazolium salts **4d** and **4e** (where $R^2 = H$) also underwent smooth hydroxylation to give the secondary alcohols **5d** and **5e**. However, the latter case required that the reaction be performed in the presence of pyridine; otherwise, the yield of **5e** was substantially lower (ca. 42%) due to further oxidation to 1,3-diphenylpropan-1,2,3-trione (ca. 43%).[14]

After these promising results, the protocol was applied to more elaborate substrates, with attention to the stereochemical aspects. An enantiomerically enriched isoxazole (*R*)-**6** (98% *ee*) was used for the model study (Scheme 3). Table 2 shows several notable points. Firstly, the N-methylation should be carried out in the presence of an acid scavenger in order to preserve the enantiomeric purity. A preliminary attempt at the N-methylation by simple treatment of (*R*)-**6** with the Meerwein reagent led to a substantial decrease in the enantiomeric purity (65% *ee*),[15] presumably due to acidic impurities in the Meerwein reagent that caused the S_N1 ionization of the ketol next to the isoxazole unit.[16] 4 Å Molecular sieves proved to be effective for suppressing this racemization: Isoxazolium salt **7a**, prepared by the N-methylation of (*R*)-**6** in the presence of 4 Å molecular sieves, was treated with aqueous NaOCl, and acidic workup gave diol **8a** with full stereochemical integrity (98% *ee*; Table 2, entry 1). Also, importantly, diol **8a** had *cis* configuration (as determined by X-ray crystallography; see Scheme 3), which could be related to the attack of the oxidant from the convex face of the tetracyclic system in **7a**, as will be discussed below.



Scheme 3. Model system for the study of stereochemical aspects and ORTEP diagram of **8a** with the thermal ellipsoids at 50% probability. Bn = benzyl, MS = molecular sieves.

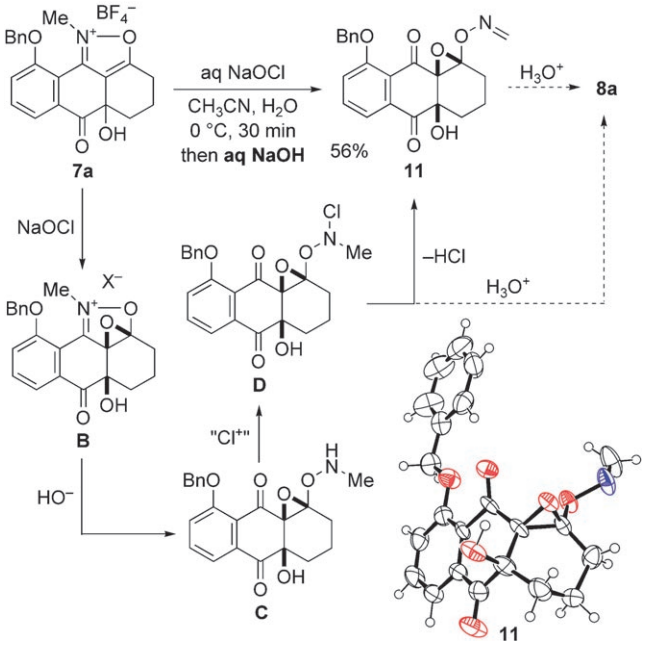
Table 2: Angular hydroxylation of isoxazolium **7a** (see Scheme 3).[a]

Entry	Solvent	pH value of NaOCl	Yield [%] **8a**	Yield [%] **9**
1	MeCN	ca. 12	48	37
2	MeOH	ca. 12	39	40
3	Me_2CO	ca. 12	11[b]	36
4	Me_2CO	8.6[c]	41	45
5	MeCN/H_2O (1:3)	ca. 12	64	16
6	MeCN/H_2O (1:3)	8.7[c]	71	13

[a] Aq NaOCl (ca. 8 equiv) in the indicated solvent (0.05 M) at 0 °C for 10 min. Acidic workup with 0.5 M HCl. [b] Acid **10** (see Scheme 3) was obtained (ca. 10% yield). [c] The pH value of the NaOCl solution (ca. 12) was adjusted with concentrated HCl (see the Supporting Information).

A remaining problem was the low yield of diol **8a**, and phthalimide **9** was identified as the major side product.[17] After considerable experimentation, the issue was improved by carefully choosing the solvent and pH value. The yield of **8a** decreased slightly with methanol (Table 2, entry 2), and substantially with acetone (Table 2, entry 3) as the solvent. The latter case, however, gave an interesting hint, in the formation of carboxylic acid **10** (ca. 10%; see Scheme 3), which could be ascribed to the base-induced retro-Claisen degradation of **8a** (the pH value of commercial NaOCl is ca. 12).[18] This recognition prompted us to adjust the pH value of the NaOCl solution.[19] Indeed, at pH 8–9, the yield of **8a** was even improved in acetone (Table 2, entry 4), although formation of phthalimide **9** remained serious. However, this issue was nicely solved by employing acetonitrile with an increased water content (Table 2, entry 5), and the optimal yield of **8a** was achieved with the pH adjustment (to 8.7; Table 2, entry 6).

With regard to the mechanistic insight, the intermediacy of epoxides was revealed by an interesting observation. Upon careful basic workup (aqueous NaOH), an unexpected product was obtained, which was proven by X-ray crystallography to be epoxide **11** with an unusual iminoxy moiety (Scheme 4).[20] Thus, the initial step is the epoxidation of **7a** to give epoxide **B**, which undergoes hydrolytic ring opening to give amino ether **C**. N-Chlorination gives chloride **D**, which undergoes elimination of HCl to afford epoxide **11**. While addition of aqueous NaOH facilitates this elimination, the acidic workup of the synthetic protocol allows ready hydrolysis of **D** and/or **11** en route to diol **8a**.[21]



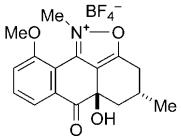
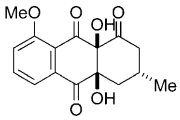
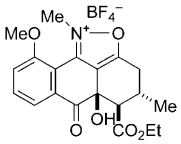
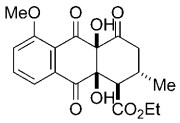
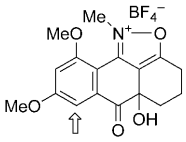
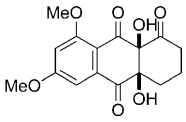
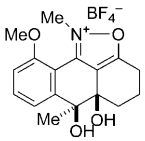
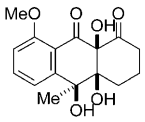
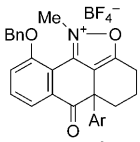
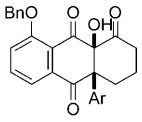
Scheme 4. Trapping of the intermediary epoxide **11**. Thermal ellipsoids in the X-ray crystal structure are at 50% probability.

The above-mentioned conditions furthermore proved to be applicable to various, more complex, polycyclic isoxazolium salts, **7b–f**, which were readily prepared by N-methylation of the corresponding isoxazoles (Table 3).[4] Pleasingly, the hydroxylation occurred smoothly to give the corresponding products, **8b–f**, in good to excellent yields and with rigorous diastereoselectivities. Isoxazolium salt **7b**, with a methyl group at the β position to the angular hydroxy moiety, afforded diol **8b** as a single isomer (Table 3, entry 1). Although substrate **7c** was potentially prone to side reactions (for example, elimination of the angular hydroxy group, ester hydrolysis, and retroaldolization), clean hydroxylation occurred to give diol **8c** in 67% yield as the sole product (Table 3, entry 2). The reaction of **7d** required a special precaution, because the electron-rich aromatic ring was prone to chlorination at the position indicated by the arrow (Table 3, entry 3).[22] However, the desired product **8d** was obtained in 62% yield by using commercial NaOCl as received (pH ≈ 12)[19] and setting a short reaction time (1 min). Isoxazolium salt **7e**, with a tertiary alcohol group next to the angular position, was converted into all-*cis* triol **8e** in high yield (Table 3, entry 4).[23] Furthermore, hydroxylation of **7f**, with an angular aryl group, occurred in a *cis*-selective manner to give alcohol **8f** in 87% yield (Table 3, entry 5).

It should be noted that the rigorous stereoselectivities could be rationalized by the convex/concave terms. Although the exclusive formation of the *cis*-di(tri)ol in the reactions of isoxazolium salts **7a–e** might suggest the involvement of hydrogen-bonding interactions, this possibility is excluded by the fact that even isoxazolium salt **7f**, lacking a hydroxy group, but with a bulky aryl group at the angular position, reacted in a *cis*-selective manner; this result strongly supports the convex/concave interpretation.

The above-described method to form α-hydroxy-β-diketones through the N-methylation/hydroxylation of isoxazoles enabled the construction of the angular *cis*-diol embedded in polyketide-derived polycyclic natural products **1** and **2** and provides a promising approach to access these compounds.

Table 3: Substrate scope.[a]

Entry	Isoxazolium salt	Yield [%] (step 1)	Product[b]	Yield [%] (step 2)
1	 **7b**	98	 **8b**	77
2	 **7c**	quant	 **8c**	67[c]
3[d]	 **7d**	95[e]	 **8d**	62[c, f, g]
4	 **7e**	95[h]	 **8e**	88[f, i]
5	 Ar = 4-Me-C_6H_4 **7f**	98	 **8f**	87[j]

[a] Step 1: Unless otherwise noted, Meerwein reagent (1.1 equiv) and 4 Å MS (1 g mmol^{-1}) in CH_2Cl_2 at room temperature. Step 2: Unless otherwise noted, the pH value of the NaOCl solution was adjusted to 8.5–8.7 and it was used (ca. 8 equiv) in MeCN/H_2O (1:3) at 0°C for 10 min. [b] X-ray analysis. [c] Yield of the corresponding phthalimide: entry 2: 23%; entry 3: 19%. [d] The arrow at the formula of **7d** represents the position of chlorination (see main text). [e] At 10°C. [f] The pH value of the NaOCl solution was ca. 12. [g] For 1 min. [h] Without 4 Å MS. [i] Acidic workup in dimethylsulfoxide (0.5 M HCl, 0°C, 10 min). [j] In MeCN/water (3:4) and with acidic workup in THF (0.5 M HCl, 0°C, 30 min).

Experimental Section

Typical procedure for the two-step conversion of isoxazole (*R*)-**6** to diol **8a**: $Me_3O^+BF_4^-$ (90%, 215 mg, 1.3 mmol) was added to a mixture of isoxazole (*R*)-**6** (413 mg, 1.19 mmol, 98% *ee*) and 4 Å MS (2.4 g) in CH_2Cl_2 (12 mL) at 0°C. After the reaction mixture had been stirred for 10 h at room temperature, MeOH was added. After filtration through a celite pad, the filtrates were concentrated in vacuo. Trituration of the residue (Et_2O) gave isoxazolium salt **7a** (531 mg, quant) as an off-white solid.

The pH value of commercial NaOCl (5% (w/v), pH ≈ 12) was adjusted to 8.7 by careful addition of concentrated HCl at 0°C.

NaOCl (pH 8.7, 2.9 mL, ≈2 mmol) was slowly added to a chilled solution (0 °C) of **7a** (108 mg, 0.241 mmol) in MeCN (1.2 mL) and water (3.6 mL). After 10 min, the products were extracted with EtOAc (three times). The combined organic extracts were washed with aq $Na_2S_2O_3$ (10 % w/v), 0.5 M HCl, and brine and then dried over Na_2SO_4. Concentration in vacuo followed by purification by silica gel column chromatography (EtOAc/hexane/CF_3COOH 1:2:0.001) gave diol **8a** (63.0 mg, 71 %) as a yellow solid.

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[12] Various oxidants (*t*BuOOH/NaOH, H_2O_2/NaOH, OsO_4, mCPBA, [VO(acac)$_2$]/*t*BuOOH, dimethyldioxirane) were tested. Although the ROOH/base system led to complete consumption of the substrates, no hydroxylated product **5a** was obtained.

[13] For nucleophilic epoxidation by NaOCl, see: a) S. Marmor, *J. Org. Chem.* **1963**, *28*, 250–251; b) A. A. Jakubowski, F. S. Guziec, Jr., M. Sugiura, C. C. Tam, M. Tishler, S. Omura, *J. Org. Chem.* **1982**, *47*, 1221–1228; c) T. Ohta, H. Tsuchiyama, S. Nozoe, *Heterocycles* **1986**, *24*, 1137–1143; d) T. E. Kedar, M. W. Miller, L. S. Hegedus, *J. Org. Chem.* **1996**, *61*, 6121–6126.

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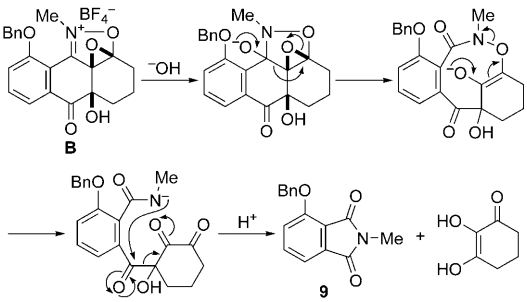
[15] Direct assessment of the *ee* value of isoxazolium salt **7a** was not possible. Instead, the *ee* value was assessed after oxidation to form **8a** and conversion of this product into the bis(trimethylsilyl) derivative (trimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, *N*,*N*-dimethylformamide (DMF), RT, 97 %). See the Supporting Information.

[16] α-Ketol (*R*)-**6** (98 % *ee*) underwent facile racemization upon exposure to 3 M H_2SO_4 (for example, 60 % *ee* in THF, 40 °C, 12 h). See reference [4e].

[17] The following scheme shows a possible mechanism for the formation of phthalimide **9**:



[18] Upon treatment with 1 M NaOH (1 equiv; 0.1 M THF, 0 °C), diol **8a** decomposed to give carboxylic acid **10** in 41 % yield.

[19] While the active species ($^-$OCl) is abundant at higher pH values, HOCl and Cl_2 begin to prevail at pH values below 10. Indeed, no hydroxylated product **8a** was obtained at pH 7.0 (data not shown). For the pH-dependent composition of aq NaOCl, see: a) J. C. Morris, *J. Phys. Chem.* **1966**, *70*, 3798–3805; b) J. M. Glavin, E. N. Jacobsen in *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 7* (Ed.: L. A. Paquette), Wiley, New York, **1995**, pp. 4580–4585; c) S. Banfi, F. Montanari, S. Quici, *J. Org. Chem.* **1989**, *54*, 1850–1859.

[20] Epoxide **11**, unstable on silica gel, was isolated by trituration in Et_2O.

[21] Upon acid treatment (0.5 M HCl, THF, 0 °C), epoxide **11** was smoothly hydrolyzed to give diol **8a**.

[22] The position of chlorination was confirmed by X-ray analysis of the chlorinated product. See the Supporting Information.

[23] Other solvents (THF, DMF, acetone) for the hydrolysis gave mixtures of **8e** and unidentified byproducts.

