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Synthesis of enantiomerically pure analogues of the *meta*-substituted aniline antibiotics

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Abstract—A practical route is described for the preparation of enantiomerically pure analogues of the *meta*-substituted aniline antibiotics. Starting with enantiomerically pure anilinide, photooxygenation, reduction and diastereoselective Weitz-Scheffer epoxidation protocols provide enantiomerically pure analogues of the *meta*-substituted aniline antibiotics in three steps.

1. Introduction

There are many natural products with antibiotic and antitumor activity whose common feature is an aminoepoxycyclohexenone (*m*-C_7N) unit with polyunsaturated side chains linked to C-4 and to the amine substituent, respectively.[1] Manumycin A **1**, isolated as the main metabolite of *Streptomyces parvulus*, is the most representative member of the *meta*-substituted aniline (*m*-C_7N) antibiotics.[2] The *meta*-substituted aniline unit is thought to originate from 3-amino-4-hydroxybenzoic acid through a biosynthetic pathway.[3]

A consequence of this synthetic pathway is the *syn*-orientation of the epoxide (relative to the hydroxyl group), a feature that is common to the *meta*-substituted aniline (*m*-C_7N) antibiotics. Manumycin A **1**, and related natural products such as asukamycin,[4] U62162,[5] U56407,[6] nisamycin,[7] alisamycin,[8] and colabomycin,[9] are known to exhibit antibiotic, antifungal, cytotoxic and elestase inhibitory activities. A significant discovery is that they act as selective inhibitors of *Ras* farnesyltransferase and might be of use in cancer chemotherapy. Their activity depends on *meta*-substituted aniline unit (*m*-C_7N); complex side chains are not essential, since a series of smaller *meta*-substituted aniline (*m*-C_7N) analogues without complex side chains such as MM 14201 **2**,[10] LL10037α **3**,[11] and MT 35214 **4**[12] also act as antitumor antibiotics (Fig. 1). The latter observation indicates that it should be worthwhile to prepare simplified *meta*-substituted aniline (*m*-C_7N) antibiotic analogues, which may display biological activity. We have recently reported a convenient diastereoselective synthesis of the racemic *cis*-aminoepoxyquinol **5,** in which we employed an effective sequence of photooxygenation, reduction and Weitz-Scheffer epoxidation.[13] Herein, we report the successful implementation of this strategy, resulting in the synthesis of enantiomerically pure analogues **10a** and **10b** of *meta*-substituted aniline antibiotics.

2. Result and discussion

Tetraphenylporphine (TPP)-sensitized photooxygenation of **7**, obtained from the reaction of acetanilide **6** with enantiomerically pure (*S*)-1-chloro-1-oxopropan-2-yl acetate,[14] at 20 °C in the presence of tetrabutylammonium fluoride gave a mixture of diasteromeric hydroperoxides **8a** and **8b** in a ratio of 1:1 (Scheme 1). These products were separated by fractional crystallization and silica column chromatography at room temperature. The structural assignments of hydroperoxides **8a** and **8b** are made on the basis of their spectral data. Elemental analysis confirmed the empirical formula $C_{12}H_{15}NO_6$, while the cyclohexadienyl hydroperoxide structures were established by their 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR and IR spectra. The IR spectra exhibited the characteristic hydroperoxide band and a strong, highly conjugated carbonyl absorption. In the ^{1}H NMR spectrum, the olefinic protons displayed an AB pattern, as required by the α,β-unsaturated enone functionality, of which the olefinic proton proximate to the methyl group is further split into a

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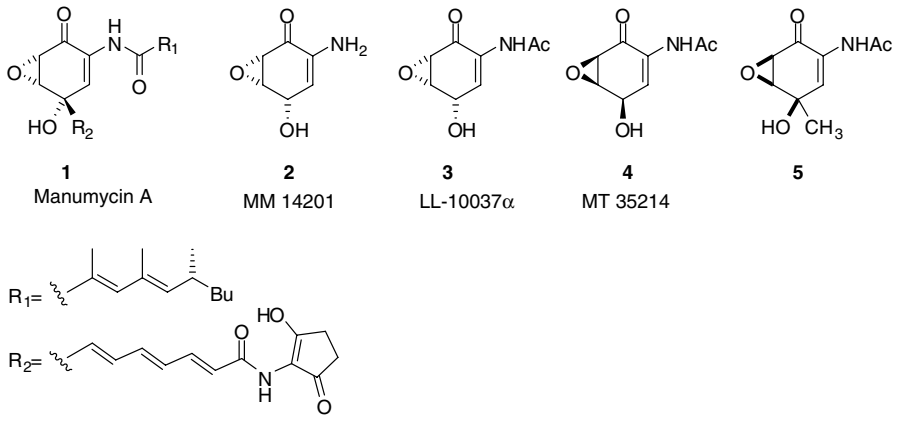
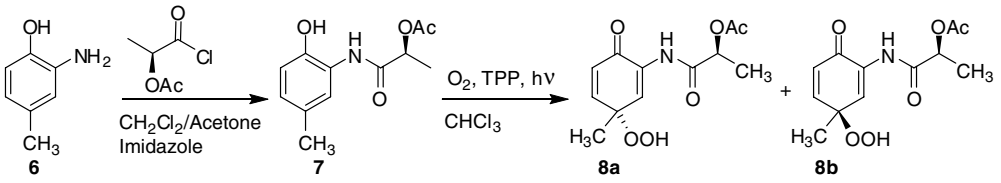


Figure 1. Some members of the manumycin family of antibiotics.



Scheme 1. Synthesis and photooxygenation of acetanilide **7**.

doublet by the vinylic proton next to the acetamide group through *W* coupling. The ^{13}C NMR spectra possess the three expected carbonyl resonances, which confirm the presence of the conjugated enone, amide, and acetate functionalities in **8a** and **8b**. Having confirmed the structures of the hydroperoxides, the exact structure of **8a** was determined by X-ray analysis. Unfortunately, an acceptable crystal of **8b** for the X-ray analysis could not be obtained. The absolute configuration of **8a** was determined by X-ray analysis as (3*R*,8*S*). The absolute configuration of the new stereogenic center linked to the hydroperoxide functionality, C3, was determined relatively by taking account of the C8 center as the reference point (Fig. 2).

The reduction of hydroperoxides **8a** and **8b** was achieved by using titanium tetraisopropoxide in the presence of dimethyl sulfide as a reductant,[15] which gave the desired quinols **9a** and **9b** (Scheme 2) in high yield. The proposed structures for quinols **9a** and **9b** are based on spectral and analytic data. Thus, in an efficient two-step sequence, the hydroxyl and enone functionalities were conveniently introduced in acetanilide **7**. The Weitz-Scheffer epoxidation of quinols **9a** and **9b** with *t*-butyl hydroperoxide (TBHP) and catalytic amounts of DBU as base afforded the enantiomerically pure *cis*-epoxides **10a** and **10b** as a single diastereomer (relative to the hydroxy group) in 80% yield (Scheme 2). We knew from our previous work with *rac*-**5** that epoxidation occurs regioselectively and diastereoselectively at the more electrophilic, unfunctionalized enone C=C double bond and not at the N-substituted double bond. The hydroxy-directing effect operates efficiently in the Weitz-Scheffer epoxidation to afford the *cis*-configured epoxide exclusively. A hydrogen bond between the quinol hydroxy group and the *tert*-butyl hydroperoxide anion directs the delivery of the oxygen atom to the dienone face towards which the hydroxy group points. The structural assignment of *cis*-epoxides **10a** and **10b** was based on their ^{1}H, ^{13}C NMR spectra and X-ray analysis. The olefinic proton occurs as a doublet, the epoxide protons display an AB pattern, in which the low-field portion is further coupled to the olefinic proton proximate to the acetamide group. The ^{13}C NMR spectrum consists of five sp^2 and six sp^3 carbon signals, in support of the assigned structures for the epoxides **10a** and **10b**. Having confirmed the structures of the hydroperoxides, the exact structure of **10b** was determined by X-ray analysis. Unfortunately, we could not obtain an

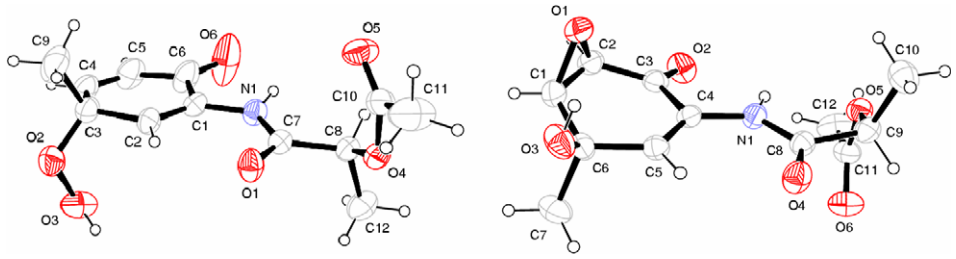
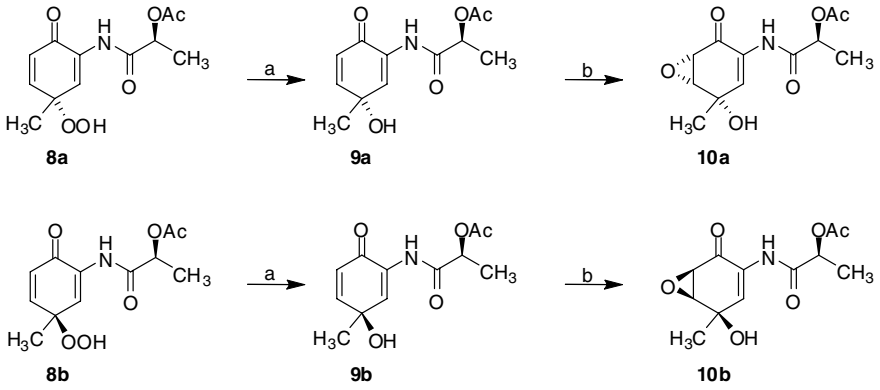


Figure 2. X-ray crystal structures of hydroperoxide **8a** (left) and epoxide **10b** (right).



Scheme 2. Reagents and conditions: (a) Me_2S, (3.0 equiv), Ti(O-*i*-Pr)$_4$ (60 mol %), CH_2Cl_2, 1 h, 4 Å molecular sieves; (b) TBHP (3.0 equiv), DBU, CH_2Cl_2, 4 h.

acceptable crystal of **10a** for X-ray analysis. The stereochemistry of **10b** was fully determined by X-ray crystallographic analysis, and the absolute configuration of the new stereogenic centers were established unequivocally to be (1*S*,2*R*,6*R*) (Fig. 2 displacement ellipsoids are plotted at the 50% probability level and chloroform has been omitted from structure **10b** for clarity). Hydroperoxide **10b** crystallizes in the trigonal space group R_3 with $Z = 3$. There are three chloroform molecules in the unit cell. Each one is trapped with the three neighbouring epoxide O-molecule, causing intermolecular H-bonding [$C_{chlf} \cdots O1^{i,ii,iii} = 3.193(7)$ Å; symmetry codes: (i) $2/3 + x$, $1/3 + y$, $-2/3 + z$, (ii) $2/3 - y$, $1/3 + x - y$, $-2/3 + z$, (iii) $2/3 - x + y$, $1/3 - x$, $-2/3 + z$)]. The epoxide ring is approximately an equilateral triangle. Its bond angles are about 60°, but O1–C1 bond length [1.425(4) Å] is slightly shorter than O1–C2 [1.440 (4) Å]. The angle between hydroxyl O3 and methyl C7 atom is 106.7°. This result led us to the conclusion that diastereomer **10a** should have a (1*R*,2*S*,6*S*)-configuration, and the hydroperoxide **8b** should have a (3*S*,8*S*)-configuration. Hydroperoxide **8a** crystallizes in the non-centrocymmetric monoclinic space group *C*2 with $Z = 4$ (Fig. 2). It possess (3*R*,8*S*) stereogenic centers, so hydroperoxide **8b** should have the (3*S*,8*S*)-configuration. The cyclohexa-1,4-diene ring is almost planar, maximum deviations from mean plane (C1/C2/C4/C5) are 0.042 Å and 0.039 Å for C6 and C3 atoms, respectively. The angle between hydroperoxide (O2) and methyl (C9) atoms is 102.3°. Moreover, the crystal structure is effectively stabilized by hydrogen bonding networks [$O3–H \cdots O1^{i} = 2.763(2)$ Å (angle 156°); $C11–H \cdots O6^{ii} = 3.130(7)$ Å (angle 160°); symmetry codes: (i) $1 - x$, y, $-z$, (ii) $1/2 - x$, $1/2 + y$, z].

3. Conclusion

The present methodology employing photooxygenation, reduction and diastereoselective Weitz-Scheffer epoxidation would be applicable to the synthesis of enantiomerically pure analogues of the *meta*-substituted aniline antibiotics. We are currently applying the methodology described herein to prepare other enantiomers of **10a** and **10b** starting from D-lactic acid and carrying out a programme to assess the biological activity of the synthesised enantiomerically pure analogues of the *meta*-substituted aniline antibiotics.

4. Experimental

4.1. General

(*S*)-1-Chloro-1-oxopropan-2-yl acetate was synthesized from L-lactic acid according to the literature.[14] Reagents and solvents were purchased from standard chemical suppliers and purified to match the reported physical and spectral data. Melting points were determined with a Buchi apparatus. Solvents were concentrated at reduced pressure (ca. 20 °C, 20 Torr). IR spectra were obtained on KBr pellets with a Perkin–Elmer apparatus. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 spectrometer in $CDCl_3$. Enantiomeric excesses were determined by HPLC analysis using a chiral column (Chiralcel OD) with eluent *n*-hexane–*i*-PrOH, 90:10, flow rate of 0.6 mL/min, detection performed at 254 nm. Optical rotations were measured with a Bellingham + Stanley, ADP220, 589 nm spectropolarimeter in a 1dm tube; Concentrations are given in g/mL. A polarimetric Chiralyser detector was used to assess the sign of configuration of the enantiomer formed. All column chromatography was performed on silica gel.

4.1.1. (*S*)-1-(2-Hydroxy-5-methylphenylamino)-1-oxopropan-2-yl acetate 7. To a stirred solution of **6** (2.0 g, 16 mmol) in 100 mL of CH_2Cl_2/acetone (80:20) was added imidazole (1.2 g, 17 mmol) and cooled to 10 °C in an ice-water bath. Then 10 mL of (*S*)-acetic acid 1-chlorocarbonyl-ethyl ester (2.6 g, 17 mmol) in CH_2Cl_2 was added within 1 h. The resulting mixture was stirred for 2 h at room temperature. After evaporation of the solvent at ~20 °C and 15 Torr, the mixture was chromatographed on silica gel (120 g) with hexane–EtOAc (3:2) as eluent to afford 3.6 g (97%) of acetanilide **7** as colourless solids: mp 138–139 °C from CH_2Cl_2–hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.99 (br s, 1H), 7.07 (s, 1H,), 6.86–6.92 (AB system, 2H), 5.38 (q, $J = 6.4$ Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 1.57 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.6, 145.9, 130.4, 127.9, 124.5, 122.7, 119.0, 70.7, 21.3, 20.6, 18.2; IR

(KBr, cm^{-1}) 3397, 3160, 3012, 2935, 2871, 1741, 1664, 1600, 1554, 1510, 1457, 1380, 1355, 1234, 1151, 925. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.72; H, 6.24; N, 6.03; $[\alpha]_D^{19} = -50$ (*c* 0.05, $CHCl_3$); retention time: 7.1 min, Chiralcel OD, *n*-hexane–*i*-PrOH, 60:40, flow rate of 0.6 mL/min, 254 nm.

4.1.2. Photooxygenation of acetanilide 7: preparation of 8a and 8b. A sample of acetanilide **7** (0.5 g, 2.0 mmol), *meso*-tetraphenylporphine (TPP, 10 mg) and tetrabutylammonium fluoride (0.2 g,) in chloroform (70 mL) was irradiated for 2 d at room temperature with a 250 W tungsten lamp, while a gentle stream of dry oxygen gas was allowed to pass through the solution. After removal of the solvent (~10 °C, 15 Torr), the mixture was chromatographed on silica gel (120 g) with hexane–EtOAc (1:1) as eluent to remove TPP as the first fraction. Further elution gave a mixture of hydroperoxides **8a** and **8b** (0.4 g, 70%) as white solids. Hydroperoxide **8a** was obtained after fractional crystallization from hexane–diethyl ether as colourless plates. The rest of the mixture was chromatographed on silica gel (100 g) with hexane–EtOAc (3:1) as eluent to give **8b**.

4.1.2.1. (*S*)-1-((*R*)-3-Hydroperoxy-3-methyl-6-oxocyclohexa-1,4-dienylamino)-1-oxopropan-2-yl acetate 8a. Mp 150–151 °C (dec) from $CHCl_3$–hexane; ^{1}H NMR (400 MHZ, $CDCl_3$) δ 9.52 (br s, 1H), 8.74 (br s, 1H), 7.73 (d, $J = 3.0$ Hz, 1H), 7.05 (dd, A part AB system, $J = 10.0$, 3.0 Hz, 1H), 6.36 (d, B part of AB system, $J = 10.0$ Hz, 1H), 5.20 (q, $J = 7.0$ Hz, 1H), 2.19 (s, 3H), 1.48 (s, 3H), 1.47 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 170.3, 169.7, 153.1, 131.9, 129.6, 127.6, 79.5, 70.6, 23.4, 21.1, 17.9; IR (KBr, cm^{-1}) 3275, 3084, 2984, 2818, 1729, 1693, 1670, 1618, 1546, 1427, 1398, 1303, 1251, 1143, 1070, 983. Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.26; H, 5.61; N, 5.27; $[\alpha]_D^{19} = -12$ (*c* 0.05, $CHCl_3$); retention time: 12.7 min, Chiralcel OD, *n*-hexane–*i*-PrOH, 80:20, flow rate of 0.6 mL/min, 254 nm.

4.1.2.2. (*S*)-1-((*S*)-3-Hydroperoxy-3-methyl-6-oxocyclohexa-1,4-dienylamino)-1-oxopropan-2-yl acetate 8b. Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 8.73 (br s, 1H), 7.69 (d, $J = 3.0$ Hz, 1H), 7.04 (dd, A part AB system, $J = 10.0$, 3.0 Hz, 1H), 6.37 (d, B part of AB system, $J = 10.0$ Hz, 1H), 5.25 (q, $J = 7.0$ Hz, 1H), 2.21 (s, 3H), 1.50 (d, $J = 7.0$ Hz, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 170.1, 169.7, 152.9, 132.1, 129.4, 127.7, 79.5, 70.7, 23.4, 21.1, 17.9; IR (KBr, cm^{-1}) 3327, 2991, 2852, 1742, 1663, 1616, 1539, 1451, 1395, 1375, 1354, 1140, 1101, 1038. Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.28; H, 5.54; N, 5.21; $[\alpha]_D^{19} = -38$ (*c* 0.05, $CHCl_3$); retention time: 12.1 min, Chiralcel OD, *n*-hexane–*i*-PrOH, 80:20, flow rate of 0.6 mL/min, 254 nm.

4.1.3. General procedure for the preparation of 9a and 9b. Dimethyl sulfide (0.19 g, 3.0 mmol) and titanium tetraisopropoxide (18.0 mg, 0.6 mmol) were added to a magnetically stirred solution of the hydroperoxide (0.27 g, 1 mmol) and 4 Å molecular sieves (1 g) in methylene chloride (30 mL) at room temperature. After 1 h of stirring, the reaction was stopped by the addition of water (25 μL), and the solids were removed by filtration. The solvent was evaporated (~25 °C, 15 Torr), the residue was loaded onto a short silica gel column (30 g), and eluted with a 4:1 mixture of hexane–EtOAc to afford the title compounds (0.21 g, 83%) as white solids.

4.1.3.1. (*S*)-1-((*R*)-3-Hydroxy-3-methyl-6-oxocyclohexa-1,4-dienylamino)-1-oxopropan-2-yl acetate 9a. Crystallization from a mixture of EtOAc–hexane gave colourless needles, mp 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 7.68 (d, $J = 3.0$ Hz, 1H), 6.98 (dd, A part AB system, $J = 10.0$, 3.0 Hz, 1H), 6.14 (d, B part of AB system, $J = 10.0$ Hz, 1H), 5.18 (q, $J = 7.0$ Hz, 1H), 3.52 (br s, 1H), 2.17 (s, 3H), 1.49 (s, 3H), 1.45 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 169.9, 169.7, 155.5, 132.7, 129.3, 124.4, 70.7, 67.9, 27.7, 21.1, 17.9; IR (KBr, cm^{-1}) 3373, 2984, 2937, 1748, 1709, 1668, 1530, 1451, 1371, 1228, 1124, 1093, 1054. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.44; H, C.6.30; N, 5.08; $[\alpha]_D^{19} = -29$ (*c* 0.05, $CHCl_3$); retention time: 11.9 min, Chiralcel OD, *n*-hexane–*i*-PrOH, 80:20, flow rate of 0.6 mL/min, 254 nm.

4.1.3.2. (*S*)-1-((*S*)-3-Hydroxy-3-methyl-6-oxocyclohexa-1,4-dienylamino)-1-oxopropan-2-yl acetate 9b. Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 7.71 (d, $J = 3.0$ Hz, 1H), 6.98 (dd, A part AB system, $J = 10.0$, 3.0 Hz, 1H), 6.16 (d, B part of AB system, $J = 10.0$ Hz, 1H), 5.21 (q, $J = 7.0$ Hz, 1H), 3.21 (br s, 1H), 2.17 (s, 3H), 1.50 (s, 3H), 1.46 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 169.8, 169.8 155.2, 132.5, 129.4, 124.5, 70.7, 68.1, 27.8, 21.1, 17.9; IR (KBr, cm^{-1}) 3373, 2981, 2931, 2873, 2856, 1745, 1704, 1666, 1619, 1529, 1452, 1400, 1375, 1226, 1128, 1099. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.62; H, C.6.45; N, 5.02; $[\alpha]_D^{19} = -40$ (*c* 0.05, $CHCl_3$); retention time: 10.9 min, Chiralcel OD, *n*-hexane–*i*-PrOH, 80:20, flow rate of 0.6 mL/min, 254 nm.

4.1.4. General procedure for the preparation of 10a and 10b. Anhydrous *tert*-butylhydroperoxide (TBHP) (0.27 g, 3.0 mmol) and one drop of DBU were added to a magnetically stirred solution of the quinol (0.25 g, 1.0 mmol) in CH_2Cl_2 (25 mL) at room temperature (~20 °C). The resulting mixture was stirred (~20 °C) for 4 h, the solvent was removed (10 °C, 10 Torr), and the mixture was chromatographed on silica gel (30 g), by eluting with a 4:1 mixture of EtOAc–hexane. The first fraction consisted of unreacted TBHP; further elution gave the epoxide (0.21 g, 80%) as a white solid.

4.1.4.1. (*S*)-1-((1*S*,5*S*,6*R*)-5-Hydroxy-5-methyl-2-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-ylamino)-1-oxopropan-2-yl acetate 10a. Crystallization from a mixture of $CHCl_3$–hexane gave colourless needles, mp 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.44 (d, $J = 2.5$ Hz, 1H), 5.18 (q, $J = 7.0$ Hz, 1H), 3.66 (dd, dd, A part AB system, $J = 3.6$, 2.5 Hz, 1H), 3.61 (d, B part of AB system,

$J = 3.6$ Hz, 1H), 2.85 (br s, 1H), 2.18 (s, 3H), 1.53 (s, 3H), 1.48 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 169.7, 169.6, 130.6, 126.9, 70.7, 68.5, 58.8, 53.3, 26.7, 21.1, 17.8. IR (KBr, cm^{-1}) 3454, 3427, 3367, 2981, 2948, 1754, 1683, 1631, 1523, 1375, 1234, 1112, 1074, 1054, 1027. Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.26; H, 5.64; N, 5.27; $[\alpha]_D^{19} = -122$ (c 0.05, $CHCl_3$); retention time: 18.1 min, Chiralcel OD, *n*-hexane–*i*-PrOH, 80:20, flow rate of 0.6 mL/min, 254 nm.

4.1.4.2. (*S*)-1-((1*R*,5*R*,6*S*)-5-Hydroxy-5-methyl-2-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-ylamino)-1-oxopropan-2-yl acetate 10b. Crystallization from a mixture of $CHCl_3$–hexane gave colourless needles, mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.42 (d, $J = 2.5$ Hz, 1H), 5.22 (q, $J = 7.0$ Hz, 1H), 3.66 (dd, A part AB system, $J = 3.8$, 2.5 Hz, 1H), 3.61 (d, B part of AB system, $J = 3.8$ Hz, 1H), 2.85 (br s, 1H), 2.18 (s, 3H), 1.52 (s, 3H), 1.47 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 169.7, 169.6, 130.5, 126.9, 70.8, 68.6, 58.8, 53.3, 26.7, 21.1, 17.9. IR (KBr, cm^{-1}) 3462, 3429, 3371, 2994, 2941, 1749, 1675, 1643, 1517, 1380, 1222, 1126, 1089, 1076, 1024. Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.28; H, 5.54 N, 5.21; $[\alpha]_D^{19} = +115$ (c, 0.05, $CHCl_3$); retention time: 15.1 min, Chiralcel OD, *n*-hexane–*i*-PrOH, 80:20, flow rate of 0.6 mL/min, 254 nm.

4.2. X-ray structure analysis

For the crystal structure determination, a single crystal of the compounds $C_{12}H_{15}NO_6$ hydroperoxide **8a** and $C_{12}H_{15}NO_6$ epoxide **10b** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer equipped with a two-dimensional area IP detector. The graphite-monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. Images for hydroperoxide **8a** and epoxide **10b** were successfully taken by varying ω with three sets of different χ and ϕ values. For each compound, the 108 images for six different runs covering about 99.7% of the Ewald spheres were performed. The lattice parameters were determined by least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear software.[16] The structures were solved by direct methods (SHELXS-97) and non-H atoms were refined by a full-matrix least-squares method with anisotropic temperature factors (SHELXL-97).[17]

4.2.1. Crystal data for compound 8a. $C_{12}H_{15}NO_6$, crystal system, space group: monoclinic, $C2$; (No. 5); unit cell dimensions: $a = 20.7316(9)$ Å, $b = 6.2512(3)$ Å, $c = 14.4451(9)$ Å, $\beta = 132.853(12)°$; volume: 1372.40(35) Å^3; $Z = 4$; calculated density: 1.30 mg/m^3; absorption coefficient: 0.105 mm^{-1}; $F(000)$: 568; crystal size: 0.027 mm × 0.023 mm × 0.012 mm; θ range for data collection 2.7–30.6°; completeness to θ: 30.6°, 99.7%; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 3396/0/177; goodness-of-fit on F^2: 1.141; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.065$, $wR_2 = 0.146$; R indices (all data): $R_1 = 0.080$, $wR_2 = 0.153$; extinction coefficient: 0.00; largest diff. peak and hole: 0.148 and −0.183e Å^{-3}.

4.2.2. Crystal data for compound 10b. $C_{12}H_{15}NO_6{\cdot}CHCl_3$, crystal system, space group: trigonal, R_3; (No. 146); unit cell dimensions: $a = 15.939(5)$ Å, $b = 15.939(5)$ Å, $c = 14.570(5)$ Å, $\gamma = 120°$; volume: 3205.62(12) Å^3; $Z = 3$; calculated density: 1.44 mg/m^3; absorption coefficient: 0.293 mm^{-1}; $F(000)$: 1452; crystal size: 0.023 mm × 0.017 mm × 0.012 mm; θ range for data collection 2.6–30.5°; completeness to θ: 30.5°, 99.7%; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 3217/0/192; goodness-of-fit on F^2: 1.105; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.082$, $wR_2 = 0.229$; R indices (all data): $R_1 = 0.099$, $wR_2 = 0.244$; extinction coefficient: 0.0046; largest diff. peak and hole: 0.512 and −0.578e Å^{-3}.

Crystallographic data (excluding structure factors) for the structures of hydroperoxide **8a** and epoxide **10b** in this paper have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication Numbers CCDC 636629 and 636628, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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