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Synthesis, Isomerisation and Diels–Alder Reactions of (5*S*)–5–Phenyl–3,4–dehydromorpholin–2–one[1]

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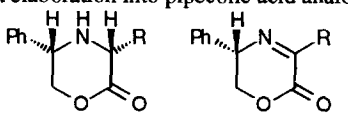
Abstract: (5*S*)–5–Phenyl–3,4–dehydromorpholin–2–one [(5*S*)–5–phenyl–5,6–dihydro–2*H*–1,4–oxazin–2–one] **2a** is prepared by a one–pot bromination / dehydrobromination of (5*S*)–5–phenyl morpholin–2–one and undergoes regio– and diastereocontrolled catalysed Diels–Alder reactions.

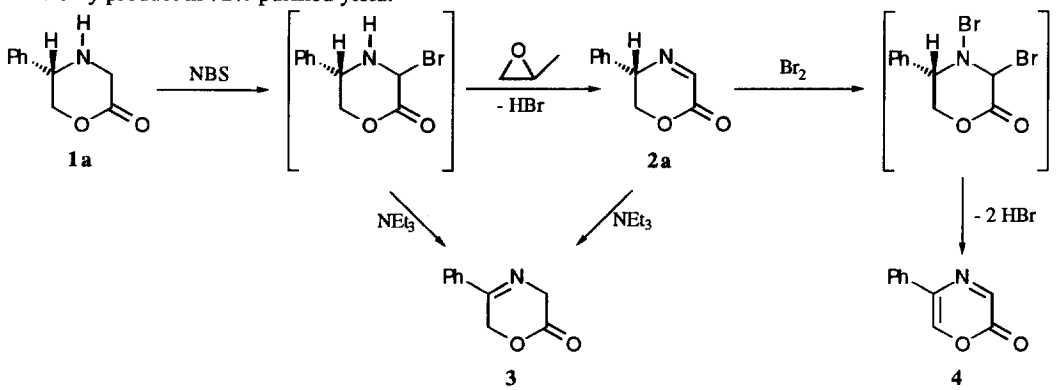
We have previously shown that 5–phenylmorpholin–2–one systems **1** are excellent templates for diastereocontrolled reactions leading to enantiomerically pure cyclic and acyclic amino acids[2] and have also demonstrated good diastereocontrol in the reduction of 3–substituted (5*S*)–5–phenyl–3,4–dehydromorpholin–2–one substrates **2**, resulting in enantiocontrolled reductive amination of α–ketoacids.[3] Following the studies of Stella and Bailey on acyclic chirally modified imino esters,[4] we decided to investigate the potential for stereocontrol in Diels–Alder reactions of (5*S*)–5–phenyl–3,4–dehydromorpholin–2–ones **2** leading to adducts with potential for subsequent elaboration into pipecolic acid analogues.[4,5]



1a **2a** R= H
1b **2b** R= alkyl, phenyl

Preliminary work established that presence of a C–3 substituent inhibited Diels–Alder reactions under all conditions investigated, so we turned our attention to the parent system **2a**, (R = H) in the hope that reduced steric hindrance at the reacting site would permit reaction. At the outset of our studies, the parent system **2a** was unknown (although subsequent to our initial disclosure,[1] a report of an alternative approach to this system *via* oxidative rearrangement of oxazolines has appeared in the literature[6]) and our initial efforts to obtain the imine were thwarted, when our standard method for preparing 3–substituted 3,4–dehydromorpholinones[3] proved ineffective as the glyoxylate ester precursor would not undergo condensative cyclisation. However, aware of the work of Williams in which *N*–Cbz protected (5*R*,6*S*)–5,6–diphenylmorpholinone underwent C–2 bromination using *N*–bromosuccinimide,[7] we were pleased to find that modification of these conditions by the addition of an acid trap permitted a one–pot C–2 bromination–dehydrobromination of unprotected **1a**[8] to give the desired imine **2a** directly (**Scheme**). Depending upon conditions employed, (5*S*)–5–phenyl–3,4–dehydromorpholin–2–one **2a** was contaminated by varying amounts of the isomeric 5–phenyl–4,5–dehydromorpholinone **3**,[9] and 5–phenyl–3,4,5,6–didehydromorpholin–2–one **4**.[10] Utilising propylene oxide as a non–basic proton sponge in dichloromethane at room temperature for periods of less than 2 hours yielded a product mixture consisting of (5*S*)–5–phenyl–3,4–dehydromorpholin–2–one **2a** and 5–phenyl–3,4,5,6–didehydromorpholin–2–one **4**. However, leaving the reaction for longer periods resulted in formation of **2a** as the sole product; 5 equivalents of propylene oxide proving optimal. Chromatography on triethylamine–washed silica induced isomerisation of

2a to **3**. Likewise, use of triethylamine in the reaction with *N*–bromosuccinimide with **1a** led to **3** being isolated as the only product in 72% purified yield.



1a **2a** **3** **4**

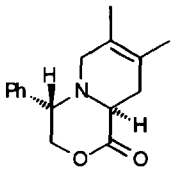
Scheme

Chromatography on silica or alumina furnished pure **2a** but also led to extensive decomposition and a maximum isolated yield of 55% {$[\alpha]_D^{25}$ +250 (c 1, $CHCl_3$); Lit.[6] (5*R*)–**2a**, $[\alpha]_D$ –252 (c 5.23, $CHCl_3$)}. Consequently, material isolated directly from the reaction, consisting of a single component by NMR analysis, was used for subsequent Diels–Alder investigations.

As any equilibration between **2a** and **3** would result in degradation of the enantiomeric integrity of **2a**, a sample of purified **2a** was hydrogenated **1a** using platinum oxide catalyst in dichloromethane. The recovered material showed effectively the same specific rotation as the sample of (*S*)–5–phenylmorpholin–2–one **1a** used to prepare **2a** in the first instance {$[\alpha]_D^{24}$ –112.3 *versus* –112.7 (c 1, $CHCl_3$)} and it may be concluded that any equilibration between **2a** and **3** under the reaction and isolation conditions is negligible.

The effect of the nature of the base and length of reaction may be rationalised by invoking initial formation of **2a** which subsequently undergoes base–promoted isomerisation to **3**. Although formation of **4** may result from further reaction of NBS with imines **2a** or **3** followed by dehydrobromination, this does not appear to be consistent with the fact that longer reaction times avoid formation of this by–product. The observation that bromine is produced during work–up in those cases when **4** is isolated, leads us to propose that quenching the reaction before all the HBr has been trapped by the propylene oxide leads to bromine formation, giving rise to **4** as an artefact of the work–up procedure.

With **2a** readily available, we adapted procedures of Stella[4a] and Bailey,[4b] using mixed Brønsted acid–Lewis acid catalyst systems to study its potential as a heterodienophile. Under optimised conditions, 2,3–dimethyl–1,3–butadiene (1.7 equiv, AcOH, $BF_3.Et_2O$, –78°C → r.t.) furnished pure (2*S*,6*S*)–8,9–dimethyl–2–phenyl–1–aza–4–oxabicyclo[4.4.0]dec–8–en–5–one **5** in 37 % overall yield from **1a**. With isoprene (1.5 equiv, TFA, $BF_3.Et_2O$, –78°C) a single adduct, shown to be (2*S*,6*S*)–8–methyl–2–phenyl–1–aza–4–oxabicyclo[4.4.0]dec–8–en–5–one **6**, was produced in 37 % overall yield. The reaction performed with cyclopentadiene (1.2 equiv, TFA, $BF_3.Et_2O$, –78°C) furnished the *endo*–cycloadduct (1*S*,3*S*,7*S*,8*S*)–3–phenyl–2–aza–5–oxo[6.2.1.$0^{2,7}$]tricycloundec–9–en–6–one **7**, in 28 % overall yield. The stereochemistries were assigned by n.O.e. difference experiments [**5** $H^2 \rightarrow H^{10}_{endo}$ 4.4%, $H^6 \rightarrow H^7_{exo}$ 9.5%; **6** $H^2 \rightarrow H^{10}_{endo}$ 5.3%, H^{10}_{exo} 5.3%; **7** $H^9 \rightarrow H^2$ 4.7%]. It is noteworthy that only a single cycloadduct could be identified in each reaction, demonstrating not only excellent diastereocontrol at C–3 but also excellent regiocontrol in the case of formation of **6** and *endo*–selectivity in the case of **7**.



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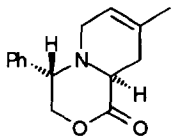

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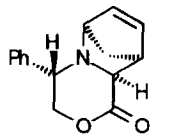

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In conclusion we have described a one–pot synthesis of (*S*)–5–phenyl–3,4–dehydromorpholin–2–one **2a** from (5*S*)–5–phenylmorpholin–2–one **1a** by reaction with *N*–bromosuccinimide, using propylene oxide as a proton sponge. Representative Diels–Alder reactions of the crude material furnish cycloadducts in moderate overall yield from **1a** with excellent regio– and diastereocontrol.

Experimental

(5*S*)–5–Phenyl–3,4–dehydromorpholin–2–one 2a. (5*S*)–5–Phenylmorpholin–2–one **1** (250 mg, 1.41 mmol) was dissolved in dichloromethane (10 mL), in a dry flask under nitrogen. Propylene oxide (0.5 mL) was added, followed by *N*–bromosuccinimide (252 mg, 1.41 mmol). The reaction mixture was stirred at room temperature for 3 h, then cooled to 0 °C and filtered. The filtrate was washed with water (4 x 50 mL), dried over K_2CO_3 and the solvent removed *in vacuo* to yield crude (5*S*)–5–phenyl–3,4–dehydromorpholin–2–one **2a** as a yellow–orange oil (quant). Purification by chromatography, eluting with ethyl acetate–light petroleum (20:80) to give the title compound in 55% yield. $[\alpha]_D^{25}$ +250 (c 1.0, $CHCl_3$). ν_{max} (KBr) 2927, 1747), 1632, 1455, 1030, 760, 734 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 4.29 (t, *J* 11.3 Hz, 1H), 4.62 (dd, *J* 4.6 Hz, 11.8 Hz, 1H), 4.92 (dt, *J* 4.1 Hz, 10.2 Hz, 1H), 7.38–7.48 (m, 5H), 8.06 (d, *J* 3.0 Hz, 1H). ^{13}C (125.7 MHz, $CDCl_3$) δ 59.9, 71.1, 127.3, 128.7, 129.2, 136.4, 153.5, 154.5; $^m/_z$ (CI, NH_3) 176 (85%, MH^+).

Diels–Alder reactions: (5*S*)–5–phenyl–3,4–dehydromorpholin–2–one **2a** (100 mg, 0.57 mmol, 1 equiv.), trifluoroacetic acid or acetic acid (1 equiv), boron trifluoride etherate (1 equiv.) and the appropriate diene (1.2 to 1.7 equiv.) were stirred at –78°C under argon for 3 to 6 hours (until t.l.c. analysis indicated disappearance of **2a**). After warming to room temperature the mixture was quenched with sat. sodium bicarbonate (10 mL) and extracted with dichloromethane. Drying over potassium carbonate, solvent removal *in vacuo* and chromatography, eluting with ethyl acetate–light petroleum (1:4), gave the title compounds.

(2*S*,6*S*)–8,9–dimethyl–2–phenyl–1–aza–4–oxabicyclo[4.4.0]dec–8–en–5–one 5: $[\alpha]_D^{25}$ –113.9 (c 1.0, $CHCl_3$). ^1H (500 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.68 (s, 3H), 2.34–2.38 (m, 1H), 2.45–2.51 (m, 1H), 2.90 (d, *J* 16.3 Hz, 1H), 3.04 (d, *J* 16.3 Hz, 1H), 3.70 (dd, *J* 5.3 Hz, 10.1 Hz, 1H), 4.05 (dd, *J* 4.5 Hz, 6.0 Hz, 1H), 4.48 (dd, *J* 6.1 Hz, 11.1 Hz, 1H), 4.67 (dd, *J* 4.5 Hz, 11.1 Hz, 1H), 7.32–7.41 (m, 5H). ^{13}C (125.7 MHz, $CDCl_3$) δ 16.0, 18.2, 31.8, 53.7, 55.8, 57.9, 73.0, 123.0, 123.2, 128.5, 128.6, 128.8, 135.55, 170.5; $^m/_z$ (CI, NH_3) 258 (100%, MH^+); $C_{16}H_{20}NO_2$ requires 258.1494, found 258.1483.

(2*S*,6*S*)–8–methyl–2–phenyl–1–aza–4–oxabicyclo[4.4.0]dec–8–en–5–one 6: $[\alpha]_D^{22}$ –68.5 (c 1.0, $CHCl_3$). ^1H (500 MHz, $CDCl_3$) δ 1.71 (s, 3H), 2.34–2.37 (m, 1H), 2.44–2.50 (m, 1H), 3.04–3.15 (m, 2H), 3.74 (dd, *J* 5.3 Hz, 9.9 Hz, 1H), 4.05 (dd, *J* 4.5 Hz, 6.6 Hz, 1H), 4.45 (dd, *J* 6.6 Hz, 11.1 Hz, 1H), 4.64 (dd, *J* 4.5 Hz, 11.1 Hz, 1H), 5.27–5.29 (m, 1H), 7.31–7.39 (m, 5H). ^{13}C (125.7 MHz, CDCl) δ 22.8, 29.6, 30.5, 48.6, 55.5, 57.8, 72.9, 118.2, 128.4, 128.5, 128.8, 131.1, 135.7, 170.4. $^m/_z$ (CI, NH_3) 244 (100%, MH^+), 199(10%); $C_{15}H_{18}NO_2$ requires 244.1343, found 244.1338.

(1*S*,3*S*,7*S*,8*S*)-3-phenyl-2-aza-5-oxo[6.2.1.$0^{2,7}$]tricycloundec-9-en-6-one 7. $[\alpha]_D^{23}$ +35.0 (c 0.44, $CHCl_3$). ^1H (500 MHz, $CDCl_3$) δ 1.54–1.56 (m, 1H), 1.80–1.82 (m, 1H), 3.60 (d, *J* 0.8 Hz, 1H), 3.63 (dd, *J* 3.1 Hz, 10.5 Hz, 1H), 3.80 (d, *J* 1.5 Hz, 1H), 4.08 (dd, *J* 3.2 Hz, 11.2 Hz, 1H), 4.16 (d, *J* 11.0 Hz, 1H), 4.24 (d, *J* 3.1 Hz, 1H), 6.37 (dd, *J* 2.0 Hz, 5.7 Hz, 1H), 6.53–6.55 (m, 1H), 7.34–7.47 (m, 5H). ^{13}C (125.7 MHz, $CDCl_3$) δ 47.4, 47.9, 59.7, 61.0, 62.9, 72.1, 127.6, 128.3, 128.7, 136.6, 137.6, 138.1, 138.4, 172.2. $^m/_z$ (CI, NH_3) 242 (50%, MH^+), 176(100%); $C_{15}H_{15}NO_2$ requires 241.1103, found 241.1102.

Acknowledgements

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9 5–phenyl–4,5–dehydromorpholin–2–one **3**: pale yellow crystals m.p. 62–65 °C. υ_{max} (KBr) 2927, 1762, 1646, 1448, 1237, 1042 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 4.57 (t, *J* 2.0 Hz, 2H), 5.41 (t, *J* 2.0 Hz, 2H), 7.45–7.54 (m, 3H), 7.75–7.77 (m, 2H). ^{13}C(125.7 MHz, $CDCl_3$) δ 50.6, 67.3, 126.0, 128.9, 131.5, 134.2, 163.1, 166.7. $^m/_z$ (CI, NH_3) 176 (100%, MH^+), 132 (35), 118 (65).

10 5–phenyl–3,4,5,6–didehydromorpholin–2–one **4**: pale yellow solid m.p. 90–92°C. υ_{max} (KBr) 1756, 1492, 1194, 1150, 1008 cm^{-1}; ^1H (200 MHz, $CDCl_3$) δ 7.35–7.50 (m, 3H), 7.60–7.75 (m, 3H) 8.15 (d, J 2.0 Hz, 1H). ^{13}C(50 MHz, $CDCl_3$) δ 50.6, 125.2, 129.0, 132.7, 133.1, 137.5, 146.1, 152.4. $^m/_z$ (CI, NH_3) 191 (10%, MNH_4^+), 174 (55%, MH^+), 173 (65%), 145 (100%), 117 (40%), 90 (40%).

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