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Formation of a Tetracyclic Isoquinoline Derivative by Rearrangement of a [(Bromophenyl)butyryl]oxazolidinone

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Treatment of 3-[4-(2-bromophenyl)-2-phenylbutyryl]-4,4-dimethyloxazolidin-2-one with LDA in THF launched a domino rearrangement sequence ending in the assembly of a tetracyclic cyclopentaoxazolo[3,2-*b*]isoquinolin-6-one derivative. Two mechanisms involving an $S_{RN}1$-type process were proposed. EPR spectroscopic and ^{13}C-labelling experiments suggested that both were operative.

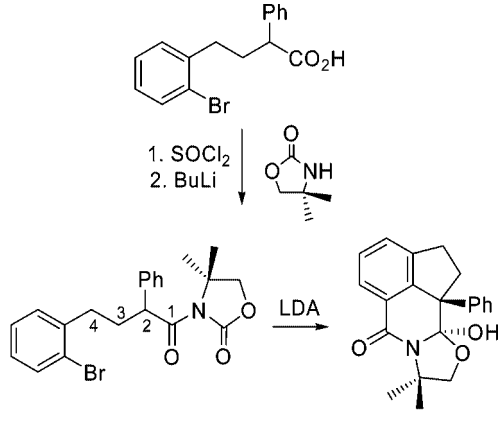
Introduction

Classic radical-mediated ring closures proceed by intramolecular additions onto alkene acceptors and usually yield five-membered rings.[1] Recently, we have been studying a novel cyclisation strategy that involves fast intramolecular coupling of a radical and an anion ($S_{RN}1$ process). This strategy has previously been used by Wolfe and co-workers to prepare, for example, isoquinolines and oxindoles from haloaryl amides.[2] The process works for a different range of functionality and has potential for the formation of *quaternary* centres and larger ring sizes.[3] Rossi et al. have ably reviewed the limited number of such cyclo-couplings in the context of $S_{RN}1$ processes in general.[4] We previously reported that precursors containing bromoaryl groups attached to oxazolines by propyl and butyl linkers yielded indane and tetralin derivatives, respectively, when treated with LDA.[5] We decided to investigate analogous precursors containing oxazolidinones in the hope that more efficient and selective methodology could be developed. Accordingly, we carried out exploratory experiments with [(bromophenyl)butyryl]oxazolidinone derivatives **1**, but found that, in practice, LDA-promoted reactions of **1** led to the assembly of a new fused tetracyclic cyclopentaoxazoloisoquinoline system in a remarkable multistage rearrangement.

Results and Discussion

The precursor oxazolidinone was prepared by treatment of 2-(2-bromophenyl)ethyl iodide with the dianion derived from phenylacetic acid. The resulting acid was converted to its acyl chloride and treated with 4,4-dimethyloxazolidin-2-one to afford [(bromophenyl)butyryl]oxazolidinone (**1a**).

Good conditions for the promotion of ring closure via $S_{RN}1$ processes involve the use of 3 equiv. of LDA in THF.[2d,5] When the oxazolidinone **1a** was treated with LDA in this way at –78 °C, and the solution was subsequently warmed to room temperature and stirred for 48 h, a waxy-white solid was isolated after column chromatography (75%). It was deduced that the structure was cyclopenta-oxazolo-isoquinolin-6-one derivative **2a** (Scheme 1) from a careful study of the COSY, HSQC and HMBC spectra, and of model systems.[6] Two new stereocentres were created during the rearrangement so that four stereoisomers were possible. However, two of these with *cis* HO and Ph groups were shown by DFT computations to be 46 kJ mol^{-1} higher in energy. Furthermore, their formation would be strongly sterically disfavoured during the ring-closure steps. Thus **2a** was a 50:50 mixture of only



1a: 64 %
b: C(1) = ^{13}C, 81 %

2a, 75 %
b, 38 %

Scheme 1.

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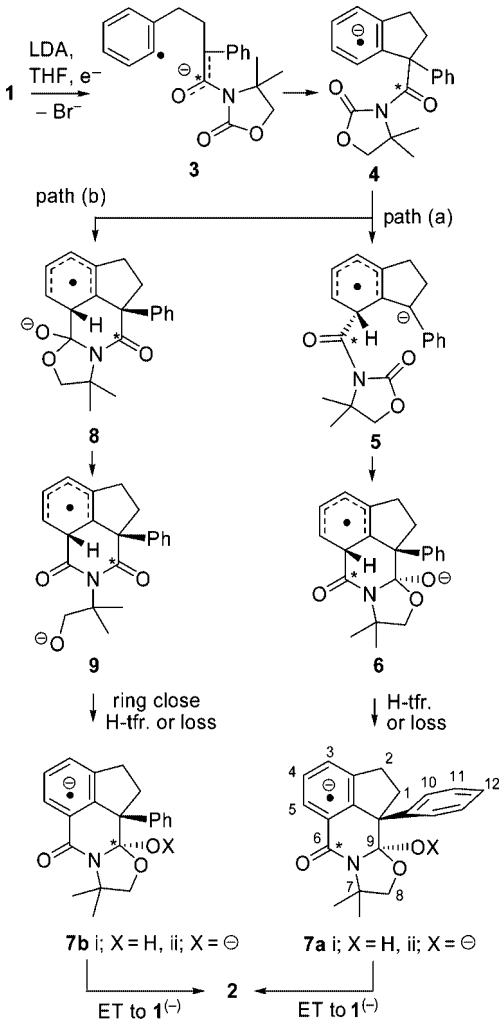
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

the (10*R*,10a*R*) and (10*S*,10a*S*) enantiomers. The fused tetracyclic structure must have been assembled by a rather novel rearrangement.

There are several possibilities for the mechanism of the rearrangement and two of these are outlined in Scheme 2.[7] By analogy with previous $S_{RN}1$ reactions involving oxazolines, we expected enolate formation from **1**, accompanied by electron transfer and fast loss of bromide, to give the radical anion intermediate **3**. Intramolecular cyclo-coupling of this enolate with the internal aryl radical would yield a dihydroindene radical anion **4**. Path (a) depicts a 1,3-arene-otropic migration of the oxazolidinone group, yielding resonance-stabilized radical anion **5**, followed by a 6-*exo-trig* nucleophilic cyclisation onto the oxazolin-ring carbonyl to afford the radical anion **6**. 1,5-Hydrogen transfer from the bis(allylic) H atom to the oxyanion in **6** will yield the tetracyclic radical anion **7a**i. Alternatively, **6** would be readily deprotonated by the LDA to yield the radical dianion **7a**ii. Electron transfer from **7a**i or **7a**ii to more of the anion derived from precursor **1** and LDA, i.e. $\mathbf{1}^-$, will yield the tetracycle **2**, simultaneously propagating the $S_{RN}1$-type chain. In the case of **7a**ii a final protonation during work-up yields **2**. We are not aware of any previous reports of 1,3-acyl-type group migrations of this type for radical anions. However, Yoshida et al. have described related migrations following attack on arynes by acyl anions.[8a,8b] Clearly, the first steps in our rearrangement could be formation of an aryne and ring closure by intramolecular nucleophilic addition to give an aryl carbanion analogous to **4**. Path (a) could then proceed more or less as shown, except that the H atom and electron-transfer steps would not be necessary. The penultimate intermediate would be an oxy anion analogous to **6** (without the cyclohexadienyl H atom) which would pick up a proton during work-up to yield **2a**.

Alternatively, product **2a** could have been formed through path (b) which shows a 6-*exo-trig* cyclisation within **4** onto the oxazolidinone ring carbonyl yielding intermediate **8**. Ring opening of the oxazolidinone, subsequent re-cyclisation and proton transfer lead to **7b**i and thence to the observed product **2** after electron transfer to more of the anion derived from **1**, i.e. $\mathbf{1}^-$. Again, reaction might proceed by deprotonation of **9** to yield the analogous radical dianion **7b**ii. An analogous path starting from an aryne intermediate is also possible.

Both mechanisms of Scheme 2 involve radical anion intermediates and, in the hope of spectroscopically characterising them, a smaller-scale reaction of **1a** with LDA in THF was carried out under identical conditions and samples were removed under nitrogen and examined by 9-GHz EPR spectroscopy. Broad, weak spectra were observed before irradiation, but they became stronger and better resolved in the temperature range 240–195 K, after a few minutes UV photolysis (Figure 1). The spectrum persisted over many hours. The computer simulation (Figure 1 and Table 1) of the main component indicated two fairly large H atom hyperfine splittings (hfs) together with five small hfs and suggested that a broad central signal was also present.[9] The *g* factor (2.0032) and the magnitudes of the hfs



Scheme 2.

were appropriate for a radical anion, but it was not obvious which intermediate was responsible for the main spectrum. DFT computations, with the UB3LYP functional,[10] were implemented for the three species **4**, **5** and **7**i. Only the computed parameters for radical anion **7**i showed satisfactory

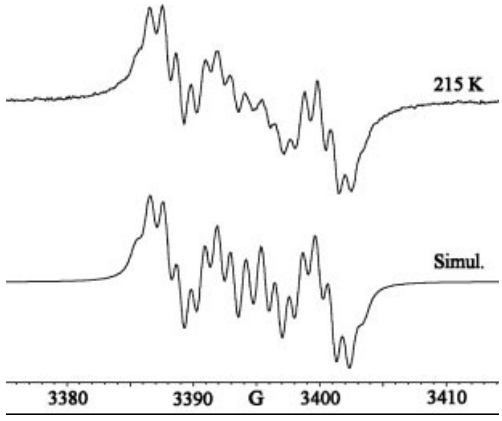


Figure 1. 9-GHz EPR spectrum obtained on treatment of **1a** with LDA in THF at 215 K with UV photolysis. Lower panel: computer simulation.

agreement with experiment. In **7**i the unpaired electron resides mainly in the indane aromatic ring and hence H(3) and H(5) of this ring have fairly large hfs.[11]

Table 1. Experimental and computed hfs (G)[a] for radical anion **7**i.

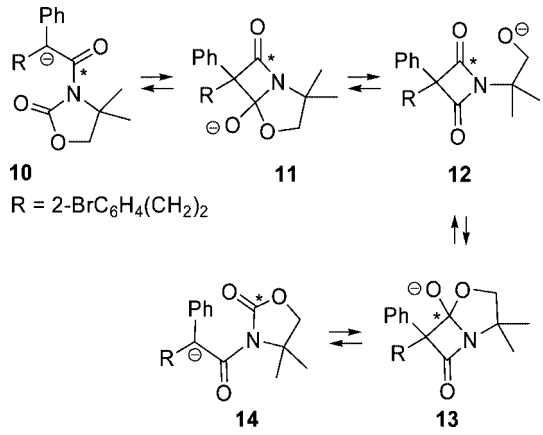
	H(3)	H(5)	H(2)	H(1)	H(4)	H(1′)	H(11)
7i exptl.[b]	7.7	4.5	1.4	1.0	1.0	1.0	1.0
7i DFT[c]	–7.3	–3.5	–0.8	0.7	0.7	0.5	–0.4

[a] 1 G = 0.1 mT. [b] Data at 215 K in THF; g = 2.0032, tentative assignments of hfs to specific H atoms. [c] UB3LYP/6-311++G(d,p)//UB3LYP/6-31G*.

The EPR data, together with the sensitivity of the reaction to light and oxygen, support the $S_{RN}1$-like mechanisms of path (a) or (b), rather than aryne-mediated routes, although the latter cannot be definitely ruled out. The concentration of the radical anion, measured by double integration of the EPR signal, was 0.54 mM at 215 K and changed little with temperature. The ratio of the radical anion concentration to initial precursor [**7**]/[**1a**] was 0.96%.[12] This is consistent with the chain process of Scheme 2 with a moderate chain length. Note that radical anion **7** is formed in the penultimate H atom transfer step of path (a) *and* of path (b), and hence the EPR experiment cannot distinguish between these two pathways.

According to path (a), the butyryl carbonyl C atom ends up attached to the benzo ring as C(6) in **7a**, whereas, according to path (b), the butyryl carbonyl C atom remains where it is and becomes C(9) of **7b** (Scheme 2). Potentially the two mechanistic pathways could be distinguished by labelling this C atom. Accordingly, precursor **1b** labelled with ^{13}C at the butanoyl carbonyl was prepared from $PhCH_2{}^{13}CO_2H$. When **1b** was treated with LDA in THF under the same conditions, tetracycle **2b** was isolated. We were able to obtain crystals of **2b**, and X-ray diffraction confirmed the tetracyclic structure (see the supporting information; for supporting information see also the footnote on the first page of this paper).

The ^{13}C label was shown to be distributed to *both* C(6) and C(9) in **2b** (ratio 52% to 48%). This seemed to indicate that both pathways were operative. However, the fact that the ^{13}C distribution was close to 50:50 opened the possibility that a pre-equilibration of the label between the butanoyl and oxazolidinyl carbonyl groups might have taken place via a symmetrical intermediate. Such a mechanism, involving symmetrical four-membered-ring intermediate **12**, is shown in Scheme 3. If this pre-equilibrium were operational, the ^{13}C label should be scrambled to both the butanoyl and oxazolidinyl carbon atoms in *unreacted* precursor **1b** remaining at the end of the reaction. A separate reaction of **1b** with LDA under identical conditions was therefore carried out but stopped after 3 h, leaving about 1/3 of the precursor unreacted. However, it was found that *all* the ^{13}C label in the unreacted **1b** *remained* at the butanoyl carbon and *none* was found in the oxazolidine ring, although product **2b** again showed ca. 50:50 scrambling. This result indicated that pre-equilibration of label did not occur. The azabicyclo[3.2.0]heptyl-type species **11** and **13**, which might of course be transition states, would contain large amounts of strain so the absence of this process is easily explained.



Scheme 3.

The fact that some ^{13}C was found attached to the benzo ring of **2b** [C(6)] proves that some arenotropic migration [route (a)] must have taken place, but obviously this was accompanied by the cyclisation/ring opening route (b).

Conclusions

We conclude that ring closure of bromophenyl oxazolidinone **1** takes place efficiently, even though this involves formation of a *quaternary* centre. The presence and siting of the two carbonyl groups facilitate further rearrangement, which results in the one-pot assembly of an unusual isoquinolinone derivative with an alkyl bridge between the benzo and heterocyclic rings. The initial steps were most likely similar to those reported for the analogous oxazoline[5] and led to the radical anion **3**, which closed by $S_{RN}1$-type cyclo-coupling to produce **4**. An analogous process via initial aryne formation could not be ruled out. By analogy with the oxazoline system, isoquinolinones with other bridge sizes should be accessible.

Experimental Section

3-[4-(2-Bromophenyl)-2-phenylbutyryl]-4,4-dimethyloxazolidin-2-one (1a): To a solution of 4,4-dimethyloxazolidin-2-one[13] (0.65 g, 5.6 mmol) in dry distilled THF (17 mL) under nitrogen at –78 °C was added 2.5 M *n*BuLi solution in hexanes (2.24 mL, 5.6 mmol). After stirring for 10 min, 4-(2-bromophenyl)-2-phenylbutyryl chloride (1.9 mL, 5.6 mmol) in THF (5 mL) was added with a syringe. The resulting nearly colourless solution was stirred for 30 min at –78 °C and then warmed to room temperature within 30 min. Excess acyl chloride was quenched by addition of saturated ammonium chloride solution (10 mL). The THF and hexane were evaporated and the resultant slurry extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with NaOH solution (10 mL) and brine (10 mL). After drying (Na_2SO_4) and removal of the solvent, the crude product was purified by column chromatography (SiO_2, hexanes/EtOAc, 9:1) to give pure **1a** as a

clear oil (1.5 g, 64%); R_f = 0.1 (SiO_2, hexanes/EtOAc, 9:1). IR (nujol): $\tilde{\nu}_{max}$ = 1698 (C=O), 1778 (C=O). ^{1}H NMR: δ = 1.39 (s, 3 H), 1.58 (s, 3 H), 1.98–2.14 (m, 1 H), 2.33–2.45 (m, 1 H), 2.51–2.76 (m, 2 H), 3.76 (d, J = 8.4 Hz, 1 H), 3.91 (d, J = 8.4 Hz, 1 H), 5.03 (t, J = 7.4 Hz, 1 H), 6.98–7.03 (m, 1 H), 7.14–7.37 (m, 1 H), 7.46–7.49 (m, 1 H) ppm. ^{13}C NMR: δ = 24.2 (CH_3), 25.2 (CH_3), 34.0 (CH_2), 34.2 (CH_2), 49.9 (CH), 60.6 (*C*), 74.9 (CH_2), 124.4 (C), 127.3 (CH), 127.5 (CH), 127.7 (CH), 128.6 (CH), 128.7 (CH), 130.4 (CH), 132.8 (CH), 138.8 (C), 141.0 (C), 153.6 (C), 174.5 (C) ppm. MS (CI): *m*/*z* (%) = 416 (100) [M + H$^+$]. Calcd. for $C_{21}H_{23}{}^{79}BrNO_3$ (MH)$^+$: 416.0861; found 416.0855.

[1-^{13}C]4-(2-Bromophenyl)-2-phenylbutyric Acid and Corresponding Acyl Chloride: To a solution of [1-^{13}C]phenylacetic acid (1 g, 7.3 mmol) in THF (30 mL), under N_2 at –78 °C was added carefully dropwise 2 equiv. of *n*BuLi (5.9 mL, 14.7 mmol). After stirring for 20 min 2-bromophenethyl iodide (2.3 g, 7.3 mmol) in THF (5 mL) was added dropwise over 5 min. The mixture was warmed to room temp. over 2 h and stirred overnight. The mixture was quenched by addition of solid ammonium chloride and the solvent removed. The residue was dissolved in 2 M HCl (100 mL), and the cloudy mixture extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude acid which was purified by column chromatography (SiO_2, hexanes/EtOAc, 9:1) to give a clear oil, (502 mg, 22%); R_f = 0.2 (SiO_2, hexanes/EtOAc, 9:1). ^{1}H NMR: δ = 2.05–2.19 (m, 1 H), 2.33–2.47 (m, 1 H), 2.62–2.78 (m, 2 H), 3.62 (apparent q, J = 7.6 Hz, 1 H), 7.04 (ddd, J = 7.8, 6.8, 2.0 Hz, 1 H), 7.12–7.37 (m, 7 H), 7.50 (dd, J = 7.8, 1.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 32.8 (CH_2), 34.0 (CH_2), 51.0 (d, J = 49.0 Hz, CH), 124.4 (C), 127.5 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.8 (CH), 130.5 (CH), 132.9 (CH), 137.9 (C), 140.5 (C) and 179.5 (^{13}C, enhanced) ppm. The acyl chloride was prepared by addition of oxalyl chloride (0.3 mL, 3.12 mmol) dropwise over 20 min to the acid (0.5 g, 1.56 mmol) and DMF (3 drops) in DCM (5 mL) at 0 °C. The resulting mixture was stirred at room temp. for 2 h, followed by concentration to give the crude product which was dissolved in dry distilled THF and used immediately.

[2-^{13}C]3-[4-(2-Bromophenyl)-2-phenylbutyryl]-4,4-dimethyloxazolidin-2-one (1b): To a solution of 4,4-dimethyloxazolidinone (0.18 g, 1.56 mmol) in dry, distilled THF (5 mL) under nitrogen at –78 °C was added 2.5 M *n*BuLi solution in hexanes (0.63 mL, 1.56 mmol). After stirring for 10 min, [1-^{13}C]4-(2-bromophenyl)-2-phenylbutyryl chloride (0.53 g, 1.56 mmol) in THF (2 mL) was added with a syringe. The resulting nearly colourless solution was stirred for 30 min at –78 °C and then allowed to warm to room temperature over 30 min. Excess acyl chloride was quenched by addition of saturated ammonium chloride solution (5 mL). The THF and hexane were removed in vacuo and the resultant slurry extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with NaOH solution (5 mL) and brine (5 mL). After drying (Na_2SO_4) and removal of the solvent, the crude product was purified by column chromatography (SiO_2, hexanes/EtOAc, 9:1) to give pure **1b** as a clear oil (81%); R_f = 0.1 (SiO_2, hexanes/EtOAc, 9:1). IR (film): $\tilde{\nu}_{max}$ = 1660 (C=O), 1774 (C=O) cm^{-1}. ^{1}H NMR: δ = 1.39 (s, 3 H), 1.58 (s, 3 H), 1.98–2.14 (m, 1 H), 2.33–2.45 (m, 1 H), 2.51–2.76 (m, 2 H), 3.76 (d, J = 8.4 Hz, 1 H), 3.91 (d, J = 8.4 Hz, 1 H), 5.03 (apparent q, J = 7.1 Hz, 1 H), 6.98–7.03 (m, 1 H), 7.14–7.37 (m, 1 H) and 7.46–7.49 (m, 1 H) ppm. ^{13}C NMR: δ = 24.2 (CH_3), 25.2 (CH_3), 34.0 (CH_2), 34.2 (CH_2), 49.9 (d, J = 49.9 Hz, CH), 60.6 (*C*), 74.9 (CH_2), 124.4 (C), 127.3 (CH), 127.5 (CH), 127.7 (CH), 128.6 (CH), 128.7 (CH), 130.4 (CH), 132.8 (CH), 138.8 (C), 141.0 (C), 153.6 (C) and 174.5 (enhanced, ^{13}C) ppm. MS (CI): *m*/*z* (%) = 417 (100) [M + H$^+$]. Calcd. for $^{12}C_{20}{}^{13}CH_{23}{}^{79}BrNO_3$ (MH)$^+$: 417.0895; found 417.0893.

10a-Hydroxy-8,8-dimethyl-10b-phenyl-8,9,10a,10b-tetrahydro-1*H*-cyclopenta[*de*]oxazolo[3,2-*b*]isoquinolin-6(2*H*)-one (2a): A solution of the oxazolidinone **1a** (0.5 g, 1.2 mmol) in THF (3.5 mL) was added to a solution of LDA in THF (7.5 mL, 0.48 M) at –78 °C under nitrogen. After stirring for 10 min the solution was warmed to room temperature within 30 min, at which time more THF (21 mL) was added. The mixture was then stirred 48 h at room temp. After this time a saturated solution of ammonium chloride (4 mL) was added and the aqueous layer was extracted with diethyl ether (3 × 6 mL). The combined organic layers were washed with water (10 mL) and dried ($MgSO_4$) to give the crude product. Column chromatography (SiO_2, hexanes/THF, 9:1) yielded pure **2a** as a white wax (301 mg, 75%); R_f = 0.2 (SiO_2, hexanes/EtOAc, 9:1). ^{1}H NMR: δ = 0.70 (s, 3 H), 1.60 (s, 3 H), 2.64–2.69 (m, 1 H), 2.76–2.85 (m, 1 H), 2.91–2.99 (m, 2 H), 3.13 (br. s, 1 H), 3.42 (d, J = 8.2 Hz, 1 H), 3.94 (d, J = 8.2 Hz, 1 H), 7.07–7.10 (m, 2 H), 7.17–7.21 (m, 3 H), 7.40–7.45 (m, 2 H), and 7.80–7.82, (m, 1 H) ppm. ^{13}C NMR: δ = 22.4 (C13), 25.0 (C13), 31.3 (C1), 36.3 (C2), 58.9 (C7), 59.5 (C9b), 78.1 (C8), 112.4 (C9a), 123.8 (C5), 127.1 (C12), 127.4 (C11), 128.0 (C5a), 128.5 (C3), 128.8 (C4), 129.6 (C10), 139.1 (C9d), 142.5 (C2a), 145.8 (C9c) and 162.6 (C6) ppm. MS (CI): *m*/*z* (%) = 336 (100) [M + H$^+$]. Calcd. for $C_{21}H_{22}NO_3$ (MH)$^+$: 336.1600; found 336.1604.

The reaction of **1a** (250 mg, 0.6 mmol) with LDA in THF was repeated on half the above scale in a quartz flask. After warming the solution to room temp. it was photolysed for 3 h with light from a 400-W medium-pressure Hg lamp placed ca. 20 cm from the flask. After similar work-up, the ^{1}H NMR spectrum the whole product (186 mg) showed it to consist of a 50:50 mixture of **2a** and unreacted **1a** together with moderate amounts of unidentified by-products. The results were consistent with faster formation of **2a** but also diversion of the reaction into other channels.

^{13}C-Labelled 10a-Hydroxy-8,8-dimethyl-10b-phenyl-8,9,10a,10b-tetrahydro-1*H*-cyclopenta-[*de*]oxazolo[3,2-*b*]isoquinolin-6(2*H*)-one (2b): A solution of oxazolidinone **1b** (320 mg, 0.76 mmol) in THF (2 mL) was added to a solution of LDA in THF (0.48 M, 6 mL) at –78 °C under nitrogen. After stirring for 10 min the solution was allowed to warm to room temp. over 30 min, at which time more THF (15 mL) was added. The mixture was then stirred 48 h at room temp. After this time a saturated solution of ammonium chloride (3 mL) was added and the aqueous layer was extracted with diethyl ether (3 × 4 mL). The combined organic layers were washed with water (8 mL) and dried ($MgSO_4$) to give the crude product. Column chromatography (SiO_2, hexanes/THF, 9:1) yielded pure **2b** as clear needles (38% after recrystallisation from DCM/hexane) m.p. 210–211 °C; R_f = 0.2 (SiO_2, hexanes/EtOAc, 9:1). ^{1}H NMR: δ = 0.70 (s, 3 H), 1.60 (s, 3 H), 2.64–2.69 (m, 1 H), 2.76–2.85 (m, 1 H), 2.91–2.99 (m, 2 H), 3.13 (br. s, 1 H), 3.42 (d, J = 8.2 Hz, 1 H, 50% of signal shows J_{HC} = 5.8), 3.94 (d, J = 8.2 Hz, 1 H), 7.07–7.10 (m, 2 H), 7.17–7.21 (m, 3 H), 7.40–7.45 (m, 2 H), and 7.80–7.82, (m, 1 H) ppm. ^{13}C NMR: δ = 22.4 (C13), 25.0 (C13), 31.3 (C1), 36.3 (C2), 58.9 (C7), 59.5 (C9b), 78.1 (C8), 112.4 (≈ 50% enhanced, ^{13}C9a), 123.8 (C5), 127.1 (C12), 127.4 (C11), 128.0 (C5a), 128.5 (C3), 128.8 (C4), 129.6 (C10), 139.1 (C9d), 142.5 (C2a), 145.8 (C9c) and 162.6 (≈ 50% enhanced ^{13}C6) ppm. The proportions of the ^{13}C label at the two sites were determined from the ^{13}C NMR spectrum observed with inverse gated decoupling so as to provide valid integral values [52% ^{13}C(6) and 48% ^{13}C(9a)] *and* from integration of the two sets of multiplets at δ = 3.42 ppm in the ^{1}H NMR spectrum [51% ^{13}C(6) and 49% ^{13}C(9a)]. One set

showed coupling to the ^{13}C nucleus and the other did not (see supporting information). The tetracyclic structure was confirmed by X-ray diffraction which showed the Ph and OH groups to be *trans*.

CCDC-606950 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): General experimental methods, preparative details of **1a**,**b** and for their rearrangements, X-ray structure for **2a**, NMR spectra for **1a**,**b**, 1D and 2D NMR spectra for **2a**,**b**.

Acknowledgments

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[9] The broad feature could be due to radical anion **4** or **5**.
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[11] The EPR spectrum of radical dianion **7a**ii (or its lithium salt) is expected to be virtually identical to that of **7a**i and hence the EPR spectrum does not exclude this mechanistic possibility.
[12] Assuming the spectrum corresponds to **7**i, i.e. ignoring the contribution from the broad component.
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