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Asymmetric induction using chiral 1,2,4-triazole and benzimidazole derivatives †

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Abstract: Lithiated *N*-substituted 1,2,4-triazoles **3** and **8** and benzimidazole **11** reacted with (1*R*)-fenchone to give derivatives **5c**, **9** and **12** in good yields as single diastereoisomers. (*S*)-Lactic acid **16** reacted with *o*-phenylenediamine **15** to give optically pure (*S*)-2-(1-hydroxyethyl)benzimidazole **17** (85%). Ring closures converted the fenchone derivative **12** into novel tricyclic fused benzimidazoles **13** and **14**, and converted oxazolidine derivative **17** into compound **18** in yields of 50–70% as single diastereoisomers. Lithiated derivative **18** was alkylated to give compound **19** as a single diastereoisomer in high yield.

1,2,4-Triazole[1] and benzimidazole[2] derivatives possess biological activity which has increased interest in their synthesis and chemical behavior. Recent examples of biological activity include 1*H*,3*H*-thiazolo[3,4-a]benzimidazoles, which have been found to possess some activity as HIV-1 reverse transcriptase inhibitors[3–5] and fluconazole, a bis-triazole containing compound effective against fungal infections.[6]

We previously synthesized a (*S*,*S*)-3,5-bis(1-hydroxyethyl)-1,2,4-triazole which gave excellent diastereoselectivities, but contained a chiral auxiliary which was difficult to cleave.[7] In our continuing efforts to use heterocycles, particularly triazoles, as sources of molecular chirality,[7,8] we have now investigated the use of a chiral triazole, to synthesize optically pure alcohols or α-hydroxy ketones. We planned to construct a fused 1*H*,3*H*-oxazolidino[3,4-a]-1,2,4-triazole with chirality built into the 5-position of the oxazolidine ring, and to use this optically pure chiral center to induce chirality into the 2-position of the oxazolidine ring. Cleavage of the triazole unit with either retention or inversion of configuration could lead to optically pure target molecules. Use of a ketone or aldehyde as an electrophile allows the introduction of further functionality, hopefully with control of both the newly formed chiral centers.

Results and discussion

1,2,4-Triazole approach

N-Substituted 1,2,4-triazoles undergo lithiation and electrophilic attack at the 5-position of the heterocyclic ring[9–12] although exceptions are known when the electrophile is a benzyl halide.[13] Suitable *N*-substituents include benzyl, SEM and aminals such as pyrrolidinomethyl.[11,12,14] Of these, the pyrrolidinomethyl protecting group was chosen due to its ease of introduction *via* a Mannich-type reaction, and its subsequent ease of removal using sodium borohydride.[11]

1,2,4-Triazole **1** was refluxed with formaldehyde and pyrrolidine **2** in ethanol to give the 1-(1-pyrrolidinomethyl)-1,2,4-triazole **3** as a colorless oil in 86% yield (Scheme 1).[11] The protected triazole was lithiated, using *n*-butyllithium, and quenched with an electrophile. Reactions with cyclohexanone

† Keywords: triazole; benzimidazole; (1*R*)-fenchone; (*S*)-lactic acid.
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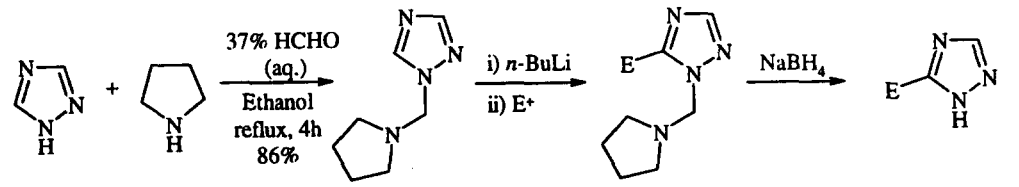
and benzophenone (Scheme 1) proceeded well, therefore the reaction was attempted using a chiral ketone and initially camphor was chosen. However, camphor has acidic protons α to the carbonyl group, and the 5-lithiated triazole acted as a base rather than a nucleophile. Such problems are well known and are usually overcome by the use of cerium chloride.[15–17] However, this failed for our system and so fenchone, which does not have any α protons, was chosen as the chiral ketone. This led to **5c** as a single diastereoisomer in 69% overall yield (Scheme 1).



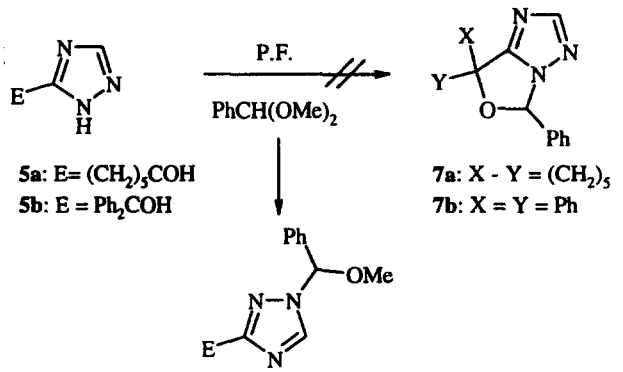
1 **2** **3** **4** (in equilibrium with 3-isomer) **5**

E^+ = cyclohexanone, Ph_2CO, (1*R*)-fenchone

a: E= $(CH_2)_5COH$
b: E = Ph_2COH
c: E = 2-hydroxy-(1*R*)-2-fenchyl

Scheme 1.

Condensation reactions were attempted with products **5** to form bicyclic ring structures. Using benzaldehyde dimethyl acetal, with or without an acid catalyst or molecular sieves, in refluxing performance fluid, gave hemiaminals **6a** and **6b** from **5a** or **5b** respectively (Scheme 2). However, none of the desired bicycles **7a,b** were formed. This is believed to be due to the equilibrium that was shown to exist between certain 3- and 5-substituted triazoles.[12,14] The 3-substituted triazole shown to be the more stable of these tautomers cannot cyclize to form the bicycle.



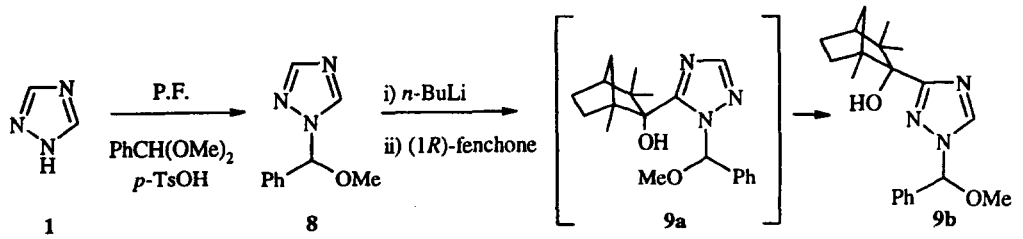
5a: E= $(CH_2)_5COH$
5b: E = Ph_2COH

7a: X - Y = $(CH_2)_5$
7b: X = Y = Ph

6a: E= $(CH_2)_5COH$
6b: E = Ph_2COH

Scheme 2.

We attempted to overcome this problem by initially introducing the hemiacetal onto the 1-position of the triazole and then carrying out the lithiation in the 5-position as previously described with fenchone as the chiral auxiliary. It was hoped that the resulting oxygen anion would then undergo nucleophilic attack at the α-carbon thus, displacing methanol and forming the bicycle in one-step. The first two reaction steps succeeded, but no nucleophilic displacement of methanol occurred. Probably, the initial product **9a** rearranged rapidly into the alcohol **9b** (Scheme 3).



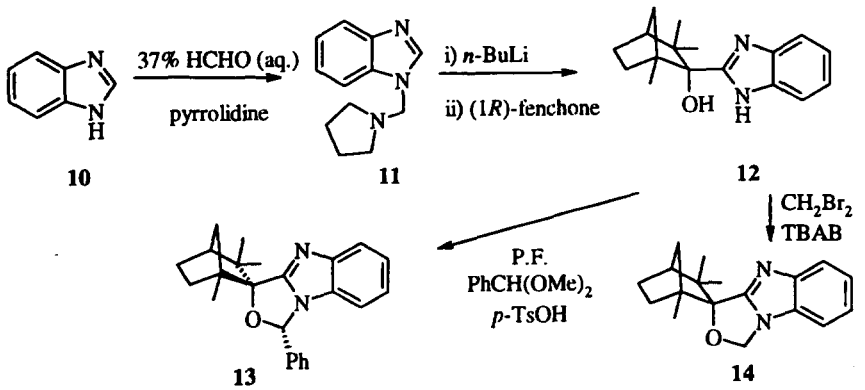
Scheme 3.

Attempts at (i) nucleophilic displacement of the *N*-substituent of the triazole **9b** with a Grignard reagent and (ii) lithiation of the CH group both failed and we therefore, transferred our efforts from the 1,2,4-triazole to the benzimidazole system.

Benzimidazole approach

Since it was believed that isomerization was taking place between the 1,5-substituted and 1,3-substituted triazoles, with the 1,3-substituted being more stable, we decided to use benzimidazole as the heterocycle, where such isomerization is not possible. Like triazoles, benzimidazoles are known to readily undergo ring lithiation in the 2-position provided a suitable group protects the nitrogen atom.[2,18,19]

The pyrrolidinomethyl protecting group was introduced onto benzimidazole **10** to give **11** in 80% yield.[11] Lithiation, followed by electrophilic substitution using (1*R*)-fenchone as the electrophile and an acidic work-up, gave directly the deprotected benzimidazole **12** as a single diastereoisomer in 70% yield (Scheme 4).



Scheme 4.

Ring closure using benzaldehyde dimethyl acetal in refluxing performance fluid using catalytic *p*-toluenesulfonic acid proceeded well to yield the novel tricycle **13** as a single diastereoisomer in 51% yield (Scheme 4).

To establish unambiguously the relative stereochemistry in **13**, a single crystal X-ray structure was carried out. Compound **13** crystallizes with two independent molecules in the asymmetric unit, one of which is shown in Figure 1. The two independent molecules differ only in the torsional orientation of the phenyl ring which is inclined to the plane of the oxazolidine ring at angles of 65.2° and 88.6° in the two molecules. This structure determination confirms the structures of both **12** and **13** and establishes the configuration of the spiro center as *R* and the newly formed stereocenter as *S*. There are no unusual bond lengths or angles in this structure, which represents the first X-ray determination

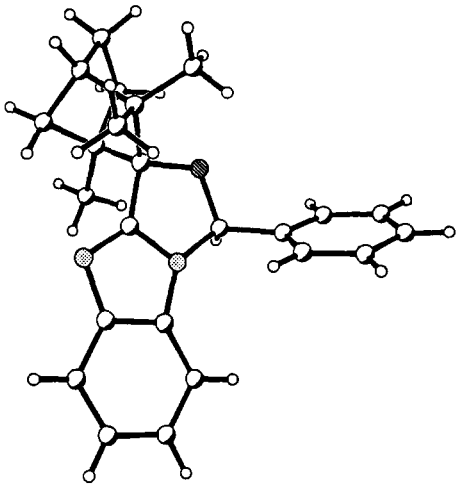


Figure 1. X-Ray crystal structure of one of the independent molecules of **13**.

of an oxazolidino[3,4-a]benzimidazole. Attack at the *exo* face of the carbonyl group in fenchone is consistent with known reactions of aryl lithium reagents with fenchone.[20]

However, attempts to displace the benzimidazole residue in **13** using a Grignard reagent failed. Lithiation occured at the α-CH group, as shown by the epimerization at the newly formed chiral center, but attempts to introduce a methyl group by reaction of the anion with methyl iodide also failed.

It was believed that steric hindrance was the reason for electrophilic attack not taking place on the anion of **13** other than by a proton, and so it was decided to synthesize the tricycle **14** with a methylene group at position 2 which would hopefully, facilitate the introduction of other electrophiles into this position. Chiral benzimidazole **12** reacted with dibromomethane in the presence of tetrabutylammonium bisulfate, as a phase transfer catalyst, to yield the desired tricycle **14** in 70% yield (Scheme 4). However, attempts to lithiate compound **14** failed, probably due to the low acidity of the methylene group.

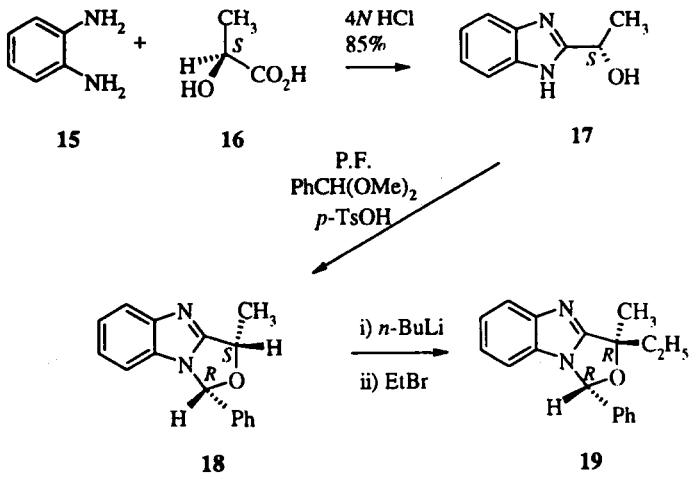
Another way to relieve possible steric hindrance to lithiation at the 2-position is to reduce the size of the chiral auxiliary. We therefore, replaced the fenchone group by reacting *o*-phenylenediamine **15** with (*S*)-lactic acid **16** to form **17**[21,22] (Scheme 5). Condensation of **17** with benzaldehyde dimethyl acetal gave **18** as a single diastereoisomer in 50% yield. NOE measurements and X-ray crystal structure determination (Figure 2) confirmed that the methyl and phenyl groups are on the same side of the molecule. Thus, the newly formed chiral center has the *R* configuration in this case. Once again the orientation of the phenyl ring is orthogonal to the oxazolidine ring (angle between meanplanes=84.4°).

Lithiation of compound **18** with *n*-butyllithium followed by quenching with ethyl bromide gave **19** as a single diastereoisomer in 72% yield. This corresponds to substitution at the 5-position of the oxazole ring (Scheme 5): in **18** the proton at the 5-position of the oxazole ring is evidently more acidic than that in the 2-position.[13] NOE measurements confirmed that lithiation took place with retention of configuration to give the diastereoisomer shown.

We conclude that the rapid isomerization of certain *N*-substituents in C-monofunctionalized 1,2,4-triazoles renders problematic ring closure to form sterically constrained bicycles. However, the corresponding 2-substituted benzimidazoles appear now promising and we are continuing to search for diastereoisomers that would form suitable chiral auxiliaries.

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Gemini 300 MHz spectrometer; *J* values are given in



Scheme 5.

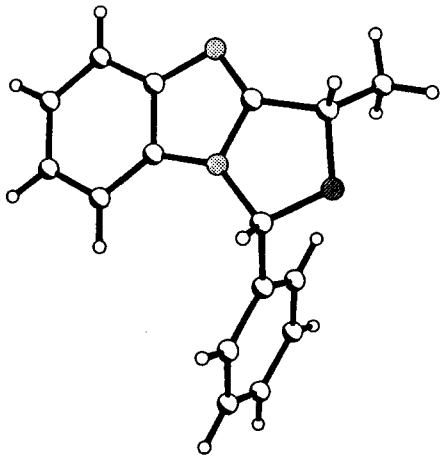


Figure 2. X-Ray crystal structure of **18**.

Hz. Elemental analyses were performed on a Carlo Erba-1106 instrument. $[\alpha]_D$ were recorded on a Perkin Elmer 341 polarimeter. Tetrahydrofuran was predried and freshly distilled from sodium and benzophenone. Column chromatography was carried out on MCB silica gel (230–400 mesh).

1-(1-Pyrrolidinomethyl)-1,2,4-triazole 3

1,2,4-Triazole (7.81 g, 0.11 mol), pyrrolidine (8.5 g, 0.12 mol) and a 37% solution of formaldehyde in water (10 mL, 0.12 mol) were dissolved in ethanol (50 mL). The mixture was refluxed for 4 h. and the solvent removed under vacuum. The resulting residue was diluted with water and extracted with chloroform (3×25 mL) before drying over anhydrous Na_2SO_4. This was filtered, concentrated and the resulting oil distilled under vacuum (100°C/1.2 torr) to give compound **3** as a colorless oil in 86% yield.[11] $\delta_H(CDCl_3)$: 8.15 (1H, s), 7.95 (1H, s), 5.14 (2H, s), 2.74–2.69 (4H, m), 1.79–1.74 (4H, m); $\delta_C(CDCl_3)$: 151.3, 143.2, 66.3, 49.5, 23.6.

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1-(1-pyrrolidinomethyl)-1,2,4-triazole 4b

1-(1-Pyrrolidinomethyl)-1,2,4-triazole **3** (760 mg, 5 mmol) was dissolved in dry THF (50 mL) under argon and cooled to −78°C before adding *n*-butyllithium (2.2 *M*, 2.5 mL, 1.1 equiv.) dropwise.

The mixture was stirred at −78°C for 1 h. before adding benzophenone (5 mmol, 1 equiv.) in THF (10 mL). After addition was complete the mixture was maintained at −78°C for a further 1 h. before allowing it to warm to room temperature overnight. The mixture was extracted with diethyl ether and washed with saturated ammonium chloride solution (50 mL), dried and evaporated to dryness to give the mixture of 3- and 5-isomers in a ratio of 1: 1as a white solid. Yield=80%, m.p. 121–122°C. $\delta_H(CDCl_3)$: 8.71 (1H, br. s, (5)), 8.06 (1H, s, (3)), 7.77 (1H, s, (5)), 7.45–7.24 (20H, m), 5.07 (2H, s, (3)), 4.57 (1H, br. s, (3)), 4.44 (2H, s, (5)), 2.71–2.66 (4H, m, (3)), 2.50–2.48 (4H, m, (5)), 1.85–1.79 (4H, m, (5)), 1.79–1.71 (4H, m, (3)); $\delta_C(CDCl_3)$: 167.8, 160.5, 148.8, 145.3, 143.8, 143.7, 128.0, 127.7, 127.5, 127.4, 127.2, 126.9, 77.8, 76.3, 69.0, 66.7, 50.9, 49.7, 23.9, 23.3. For $C_{20}H_{22}N_4O$: Anal. Calcd: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.36; H, 6.69; N, 16.76.

3(5)-(1-Hydroxycyclohexyl)-1,2,4-triazole ***5a***

1-(1-Pyrrolidinomethyl)-1,2,4-triazole **3** (1 g, 6.6 mmol) was dissolved in THF (50 mL) and cooled to −78°C. This was then treated with *n*-butyllithium (2.0 *M*, 3.5 mL, 7 mmol, 1.05 equiv.) and stirred for 2 h. before adding cyclohexanone (0.7 g, 7.1 mmol, 1.1 equiv.). The mixture was maintained at −78°C for a further 4 h. before allowing it to warm to room temperature overnight. This was then quenched with saturated ammonium chloride solution (100 mL) and extracted with diethyl ether (2×50 mL). The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give the pure product as a white solid in 63% yield. m.p. 184°C, (lit.[11] 183–185°C); $\delta_H(CDCl_3)$: 13.75 (1H, br. s), 7.97 (1H, br. s), 5.26 (1H, br. s), 2.10–1.12 (10H, m); $\delta_C(d_6\text{-DMSO})$: 164.0, 149.1, 68.9, 36.9, 25.1, 21.4.

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1,2,4-triazole ***5b***

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1-(1-pyrrolidinomethyl)-1,2,4-triazole **4b** (5 g, 0.015 mol) was dissolved in ethanol and treated with sodium borohydride (0.57 g, 0.015 mol, 1 equiv.) and refluxed for 2 h. Removal of the ethanol, under reduced pressure, was followed by refluxing the residue in ethyl acetate overnight. The solution was then dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give the product in 70% yield. m.p. 116°C; $\delta_H(d_6\text{-DMSO})$: 13.93 (1H, s), 7.93 (1H, br. s), 7.53–7.20 (10H, m), 7.00 (1H, br. s); $\delta_C(d_6\text{-DMSO})$: 160.5 151.0, 145.5, 127.6, 127.1, 76.9 (the signal of one carbon of the triazole ring is not observed). For $C_8H_{13}N_3O$: Anal. Calcd: C, 57.45; H, 7.84; N, 25.13. Found: C, 57.79; H, 8.02; N, 25.37.

*3(5)-[2-(2(S)-Hydroxy-1(*R*),3,3-trimethyl[2.2.1]heptyl)]-1,2,4-triazole* ***5c***

1-(1-Pyrrolidinomethyl)-1,2,4-triazole **3** (2.3 g, 0.015 mol) was dissolved in THF (50 mL) and cooled to −78°C. This was then treated with *n*-butyllithium (2.0 *M*, 7.5 mL, 0.016 mol) and stirred for 2 h. before adding (1*R*)-fenchone (2.4 mL, 0.016 mol). The mixture was maintained at −78°C for a further 4 h. before allowing it to warm to room temperature overnight. This was then quenched with saturated ammonium chloride solution and extracted with diethyl ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give the crude product which, when washed with cold diethyl ether, afforded the pure product as a white solid in 69% yield. m.p. 117°C, $[\alpha]_D$=14.7 at 30°C (c=0.01 g/mL, methanol); $\delta_H(d_6\text{-DMSO})$: 7.90 (1H, br. s), 4.94 (1H, br. s), 2.69 (1H, d, *J*=9 Hz), 2.09–2.01 (1H, m), 1.71–1.65 (2H, m), 1.46–1.34 (1H, m), 1.13 (1H, d, *J*=9 Hz), 1.02 (1H, dt, *J*=12, 3 Hz), 0.94 (6H, d, *J*=6 Hz), 0.50 (3H, s); $\delta_C(d_6\text{-DMSO})$: 160.3, 150.2, 81.7, 52.9, 48.0, 45.2, 40.5, 29.4, 28.0, 25.2, 22.0, 17.1. For $C_{12}H_{19}N_3O$: Anal. Calcd: C, 65.13; H, 8.65; N, 18.99. Found: C, 65.13; H, 8.78; N, 19.15.

General procedure for formation of hemiacetals ***6a*** *and* ***6b***

Benzaldehyde dimethyl acetal (3 g, 0.02 mol) and a catalytic amount of *p*-toluenesulfonic acid were added to a solution of **5a** or **5b** (0.01 mol) in dry toluene and then refluxed for 24 h. using a reverse Dean–Stark. The reaction mixture was then cooled and the solvent was removed under vacuum to give the desired product as a white solid.

3(5)-(1-Hydroxycyclohexyl)-1-(1-methoxy-1-phenylmethyl)-1,2,4-triazole ***6a***

Yield=43%, m.p. 110°C; δ_H(d_6-DMSO): 8.59 (1H, s), 7.42–7.38 (5H, m), 6.54 (1H, s), 4.84 (1H, s), 3.34 (3H, s), 2.00–1.94 (2H, m), 1.72–1.62 (4H, m), 1.41–1.29 (4H, m); δ_C(d_6-DMSO): 169.5, 144.0, 137.2, 128.8, 128.3, 126.3, 89.3, 68.9, 56.1, 36.8, 25.2, 21.9. For $C_{16}H_{21}N_3O_2$: Anal. Calcd: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.65; H, 7.48; N, 14.59.

3(5)-(1-Hydroxy-1,1-diphenylmethyl)-1-(1-methoxy-1-phenylmethyl)-1,2,4-triazole ***6b***

Yield=36%, m.p. 120°C; δ_H(d_6-DMSO): 8.70 (1H, s), 7.43–7.18 (15H, m), 6.58 (1H, s), 6.42 (1H, s), 3.37(1H. s); δ_C(d_6-DMSO): 168.3, 146.4, 146.3, 144.2, 137.0, 128.9, 128.4, 127.3, 127.1, 126.6, 126.3, 89.5, 77.0, 56.2. For $C_{23}H_{21}N_3O_2$: Anal. Calcd: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.43; H, 5.73; N, 11.33.

1-(1-Methoxy-1-phenylmethyl)-1,2,4-triazole ***8***

1,2,4-Triazole (6.9 g, 0.1 mol) and benzaldehyde dimethyl acetal (22.8 g, 0.15 mol, 1.5 equiv.) were refluxed in performance fluid using a reverse Dean–Stark with a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was cooled and the solvent removed under reduced pressure to give the crude product, which was purified by Kugelrohr distillation to give **8** in 89% yield. m.p. 50°C (lit.[23] b.p. 150°C). δ_H($CDCl_3$): 8.16 (1H, s), 8.01 (1H, s), 7.40–7.38 (5H, m), 6.40 (1H, s), 3.50 (3H, s); δ_C($CDCl_3$): 151.4, 142.1, 136.2, 129.4, 128.6, 125.9, 90.9, 57.1.

1-(1-Methoxy-1-phenylmethyl)-5-[2-(2(S)-hydroxy-1(R),3,3-trimethyl[2.2.1]heptyl)]-1,2,4-triazole ***9***

A solution of compound **8** (0.02 mol, 3.78 g) was dissolved in THF and cooled to −78°C. This was then treated with 2.2 *M* *n*-butyllithium (0.022 mol, 10 mL), dropwise. The resulting mixture was stirred at −78°C for 2 h. before quenching with (1*R*)-fenchone (0.02 mol, 3.1 g). The reaction mixture was maintained at this temperature for a further 2 h. before being allowed to warm to room temperature overnight. This was then quenched with saturated ammonium chloride solution, extracted with diethyl ether and dried over anhydrous magnesium sulfate. The mixture was filtered and evaporated to dryness to give the pure product as a single diastereoisomer in 70% yield as a white solid. m.p. 72–74°C, $[\alpha]_D$=−16.4 at 30°C (c=0.01 g/mL, chloroform); δ_H($CDCl_3$): 7.88 (1H, s), 7.36–7.27 (5H, m), 7.07 (1H, s), 3.50 (3H, s), 2.95–2.91 (1H, m), 2.84–2.82 (1H, m), 1.93–1.86 (1H, m), 1.76–1.66 (1H, m), 1.58 (1H, s), 1.52–1.41 (1H, m), 1.29–1.11 (2H, m), 1.05 (6H, s), 0.94 (3H, s); δ_C($CDCl_3$): 158.5, 149.2, 137.5, 128.6, 128.2, 126.5, 91.3, 84.2, 56.7, 54.8, 48.8, 46.2, 46.2, 40.6, 30.4, 28.3, 24.8, 22.0, 17.1. HRMS (POS FAB NBA) m/e 342.2190 (M+1). Calcd. For $C_{20}H_{28}O_2N_3$ 342.2181.

1-(1-Pyrrolidinomethyl)benzimidazole ***11***

Benzimidazole (3.5 g, 0.03 mol), pyrrolidine (2.1 g, 0.03 mol) and a 37% solution of formaldehyde in water (2.7 g, 0.03 mol) were dissolved in ethanol (50 mL). The mixture was refluxed for 4 h. and then the solvent was removed under vacuum. The resulting residue was diluted with water and extracted with chloroform (3×25 mL) before drying over anhydrous Na_2SO_4. This was then filtered and concentrated and the resulting oil was distilled under vacuum (110°C/5 mmHg) to give compound **11** as a colorless solid in 80% yield. m.p. 25°C[18]; δ_H($CDCl_3$): 7.90 (1H, s), 7.81–7.77 (1H, m), 7.49–7.46 (1H, m), 7.28–7.25 (2H, m), 4.98 (2H, s), 2.63–2.59 (4H, m), 1.75–1.70 (4H, m); δ_C($CDCl_3$): 143.4, 143.3 134.4, 122.9, 122.0, 120.0, 110.1, 62.8, 50.6, 23.5.

2-[2-(2(S)-Hydroxy-1(R),3,3-trimethyl[2.2.1]heptyl)]benzimidazole ***12***

1-(1-Pyrrolidinomethyl)benzimidazole **11** (3 g, 0.015 mol) was dissolved in THF (50 mL) under argon and cooled to −78°C before treating with 2.0 *M* *n*-butyllithium (7.5 mL, 0.016 mol), dropwise. The resulting mixture was kept at this temperature for 2 h. before quenching with (1*R*)-fenchone (2.4 mL, 0.016 mol). This was then maintained at −78°C for a further 4 h. before allowing to warm to room temperature overnight. The mixture was acidified with 2*N* hydrochloric acid and this was washed with diethyl ether. The aqueous phase was then neutralized with sodium bicarbonate and

then extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. Column chromatography of the crude material on silica gel using hexane:diethyl ether (1:1) as eluant gave the pure material as a white solid in 70% yield. m.p. 187°C, $[\alpha]_D$=−27.7 at 27°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 9.55 (1H, br. s), 7.77–7.74 (1H, m), 7.42–7.39 (1H, m), 7.25–7.18 (2H, m), 2.81(1H, s), 2.85 (1H, s), 1.96–1.75 (3H, m), 1.59–1.48 (1H, m), 1.39 (1H, d, *J*=10.8 Hz), 1.27 (1H, dt, *J*=12.9, 3.6 Hz), 1.05 (6H, d, *J*=3.3 Hz), 0.74 (3H, s); $\delta_C(CDCl_3)$: 157.3, 143.1, 132.3, 122.3, 121.7, 119.4, 110.5, 83.8, 53.3, 48.4, 45.9, 41.2, 30.2, 28.2, 25.1, 22.0, 17.1. For $C_{17}H_{22}N_2O$: Anal. Calcd: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.60; H, 8.35; N, 10.16.

*Spiro[1(*R*),3,3-trimethyl[2.2.1]heptyl-2(*S*),5′-2′(*S*)-phenyl-1*H*,3*H*-oxazolo[3,4-a]benzimidazole]* ***13***

Benzaldehyde dimethyl acetal (3 g, 0.02 mol) and a catalytic amount of *p*-toluenesulfonic acid were added to a solution of **12** (2.7 g, 0.01 mol) in dry toluene and then refluxed for 24 h. using a reverse Dean–Stark. The reaction mixture was then cooled and the solvent was removed under vacuum to give a crude product which was columned on silica gel using a 1:1 mixture of hexane:diethyl ether as eluant to give pure **13** as a white solid in a 51% yield. m.p. 121°C, $[\alpha]_D$=−4.6 at 28°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 7.83 (1H, d, *J*=8.1 Hz), 7.45–7.36 (5H, m), 7.23 (1H, t, *J*=7.2 Hz), 7.08 (1H, t, *J*=7.3 Hz), 6.85 (1H, d, *J*=8.1 Hz), 6.62 (1H, s), 2.63 (1H, d, *J*=10.2 Hz), 2.16–2.09 (1H, m), 1.89–1.79 (2H, m), 1.54–1.48 (1H, m), 1.32–1.26 (2H, m), 1.22 (3H, s), 0.90 (3H, s), 0.81 (3H, s); $\delta_C(CDCl_3)$: 160.0, 149.4, 137.0, 130.2, 129.6, 128.9, 127.1, 122.2, 122.1, 120.2, 109.8, 93.2, 88.2, 54.0, 48.3, 43.9, 40.4, 28.9, 28.6, 26.1, 23.4, 17.5. For $C_{24}H_{26}N_2O$: Anal. Calcd: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.50; H, 7.47; N, 7.66.

*Spiro[1(*R*),3,3-trimethyl[2.2.1]heptyl-2(*S*),5′-1*H*,3*H*-oxazolo[3,4-a]benzimidazole]* ***14***

A solution of compound **12** (1 g, 3.7 mmol) in methylene bromide was refluxed overnight with a 40% aqueous solution of sodium hydroxide (40 mL) in the presence of a catalytic amount of tetrabutylammonium bisulfate. The crude product was isolated by separating the organic layer and evaporating it to dryness. Column chromatography on silica gel using a 1:2 mixture of hexane/diethyl ether gave the pure product as a white solid in 50% yield. m.p. 179–180°C, $[\alpha]_D$=−218.5 at 29°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 7.74 (1H, d, *J*=7.8 Hz), 7.32 (s, 1H), 7.25 (s, 1H), 7.13 (1H, t, *J*=8.1 Hz), 6.94 (1H, t, *J*=7.2 Hz), 6.57 (1H, d, *J*=8.1 Hz), 3.12 (1H, br. d, *J*=9.5 Hz), 2.29 (1H, s), 1.90–1.72 (4H, m), 1.57–1.09 (7H, m), 0.66 (3H, s); $\delta_C(CDCl_3)$: 155.6, 142.0, 134.7, 123.0, 122.1, 120.1, 110.7, 85.1, 57.8, 55.2, 49.7, 45.9, 41.0, 31.3, 27.9, 25.0, 22.6, 17.7. HRMS (POS FAB NBA) m/e 283.1809 (M+1). Calcd. For $C_{18}H_{23}ON_2$ 283.1810.

*(*S*)-2-(1-Hydroxyethyl)benzimidazole* ***17***

o-Phenylene diamine (2.16 g, 0.02 mol), (*S*)-lactic acid (2.7 g, 0.03 mol) and 4*N* hydrochloric acid (20 mL) were heated under reflux for 40 min. The solution was then filtered and neutralized with ammonia to afford the product as a brownish solid which when recrystallised from ethanol gave pure **17** as a white solid in 85% yield. m.p. 180–182°C (lit.[21] 178–179°C), $[\alpha]_D$=−34.1 at 30°C (c=0.01 g/mL, methanol); $\delta_H(d_6\text{-DMSO})$: 12.3 (1H, br. s), 7.53–7.50 (2H, m), 7.15–7.13 (2H, m), 5.89 (1H, br. s), 5.03–4.97 (1H, m), 1.55 (3H, d, *J*=6 Hz); $\delta_C(d_6\text{-DMSO})$: 158.7, 142.6, 121.3, 117.2, 63.8, 23.0. For $C_9H_{10}N_2O$: Anal. Calcd: C, 66.63; H, 6.22; N, 17.28. Found: C, 66.73; H, 6.31; N, 17.36.

*5(*S*)-Methyl-2(*R*)-phenyl-1*H*,3*H*-oxazolo[3,4-a]benzimidazole* ***18***

(*S*)-2-(1-Hydroxyethyl)benzimidazole **17** (1.5 g, 9.3 mmol), benzaldehyde dimethyl acetal (1.4 g, 9.2 mmol) and a catalytic amount of *p*-toluenesulfonic acid were refluxed in performance fluid (5080) for 24 h., using a reverse Dean–Stark. The reaction mixture was then allowed to cool before removing the solvent and purifying the product by Kugelrohr distillation. Yield=50%, m.p. 141–142°C, $[\alpha]_D$=145.8 at 26°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 7.75 (1H, d, *J*=9 Hz), 7.45 (5H, s), 7.22 (1H, t, *J*=9 Hz), 7.07 (1H, t, *J*=9 Hz), 6.79 (1H, d, *J*=9 Hz), 6.59 (1H, s), 5.39 (1H, q, *J*=6 Hz), 1.82 (3H, d, *J*=6 Hz); $\delta_C(CDCl_3)$: 159.7, 149.3, 135.3, 130.5, 130.3, 129.0, 127.3, 122.5, 122.4, 120.1, 109.9, 88.8,

72.3, 19.4. For $C_{16}H_{14}N_2O$: Anal. Calcd: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.56; H, 5.88; N, 11.30.

5(R)-Ethyl-5-methyl-2(R)-phenyl-1H,3H-oxazolo[3,4-a]benzimidazole ***19***

A solution of 5-methyl-2-phenyl-1*H*,3*H*-oxazolo[3,4-a]benzimidazole **18** (0.2 g, 0.8 mmol) in THF, under argon, was cooled to −78°C before being treated with *n*-butyllithium (1.6 *M*, 0.55 mL, 0.88 mmol, 1.1 equiv.), dropwise. The temperature of the mixture was maintained at −78°C for 2 h. before adding ethyl bromide (870 mg, 0.8 mol, 1 equiv.). This was stirred for a further 2 h. at −78°C before being allowed to warm to room temperature overnight. The reaction was then quenched with saturated ammonium chloride solution and extracted with diethyl ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to give the crude product as a white solid. Column chromatography on silica gel using a 1:2 mixture of hexane:diethyl ether as eluant gave the pure product in 72% yield. m.p. 122–124°C, $[\alpha]_D$=103.0 at 30°C (c=0.01 g/mL, chloroform); $\delta_H(CDCl_3)$: 7.75 (1H, d, *J*=6 Hz), 7.43 (5H, s), 7.23 (1H, t, *J*=6 Hz), 7.08 (1H, t, *J*=6 Hz), 6.85 (1H, d, *J*=6 Hz), 6.70 (1H, s), 2.07 (2H, q, *J*=6 Hz), 1.82 (3H, s), 1.01 (3H, t, *J*=6 Hz); $\delta_C(CDCl_3)$: 161.4, 149.4, 136.2, 130.3, 130.3, 129.0, 127.1, 122.4, 122.4, 120.1, 110.0, 88.5, 82.6, 32.9, 25.4, 8.4.

X-Ray crystallography

Intensity data were collected with a Nicolet P4s four-circle diffractometer, operating at −110°C, using monochromatized Mo Kα (λ=0.71073 Å) radiation. Cell constants were determined by least-squares refinements of at least 34 accurately centered reflections. Throughout the data collections the intensities were monitored at regular intervals and the intensities were corrected for minor fluctuations (<6%). The intensities were also corrected for Lorentz and polarization effects, but not for absorption.

The structures were solved by direct methods using SHELXS90, [24] and refined on F^2, using all data, by full-matrix least-squares procedures using SHELXL93.[25] All non-hydrogen atoms were refined with anisotropic displacement coefficients equal to 1.3 times the isotropic equivalent of their carrier carbons. The functions minimized were $\Sigma w(F_o^2-F_c^2)$, with $W=[\sigma^2(F_o^2)+aP^2]^{-1}$, where $P=[\max(F_o^2)+2F_c^2]/3$. Final difference maps showed no features greater or less than $0.29e^-/Å^3$. Full tables of atom coordinates, anisotropic displacement parameteres, bonding geometry, structure factors and equations of meanplanes are available as supplementary material from the author PJS.

Crystal data for ***13*** *— at 110°C*: $C_{24}H_{26}N_2O$, Mr=358.5, colorless block, 0.69×0.54×0.21 mm, triclinic, space group P1, *a*=9.675(1), *b*=9.796(2), *c*=11.984(1) Å, α=76.92(1), β=73.72(1)°, γ=65.20(1), U=982.0(2) $Å^3$, F(000)=384, Z=2, D_c=1.212 g cm^{-3}, μ(Mo−Kα)=0.74 cm^{-1}, ω scans, $2\theta_{max}$=50°, 487 parameters, S=0.94, wR2=0.1441 for all 3667 data, (a=0.098), R1=0.0544 for 2690 data with $F_o>4\sigma(F_o)$.

Crystal data for ***18*** *— at 110°C*: $C_{16}H_{14}N_2O$, Mr=250.3, colorless rod, 0.96×0.29×0.14 mm, orthorombic, space group $P2_12_12_1$, *a*=4.848(3), *b*=9.579(3), *c*=27.643(8) Å, U=1284(1) $Å^3$, F(000)=528, Z=4, D_c=1.295 g cm^{-3}, μ(Mo−Kα)=0.82 cm^{-1}, ω scans, $2\theta_{max}$=50°, 172 parameters, S=0.87, wR2=0.1552 for all 1356 data, (a=0.081), R1=0.0592 for 763 data with $F_o>4\sigma(F_o)$.

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