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Stereoselective synthesis of tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-3-ones and related compounds as precursors of serotonin 5-HT$_{2C}$ receptor agonists

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ABSTRACT

Tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-3-ones and the related 3a-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]isoindole analogues were synthesised by an intramolecular Diels–Alder reaction. The observed stereoselectivity was dependent upon the nature of the tethered dienophile as well as the judicious placement of the amide.

The Diels–Alder reaction is a very efficient and powerful tool for the synthesis of both carbocyclic and heterocyclic systems.[1] One method of harnessing the Diels–Alder reaction involves utilising the benzocyclobutene motif as a latent diene equivalent. Benzocyclobutenes, following photo or thermal activation, undergo cycloreversion to reactive *o*-quinodimethane species, which if tethered to a dienophile, can rapidly react to construct elaborate polycyclic systems with defined stereochemistry. The utility of this approach was elegantly demonstrated by Oppolzer during his total synthesis of the polycyclic natural product chelidonine.[2] This has been followed with several groups exploiting this strategy to assemble a range of 6,6,5 tricycles.[3] However, these reports concede several deficits including long reaction times, high temperatures and the need to utilise electron-rich precursors, which have generally given poor yields. Furthermore, stereoselective hetero Diels–Alder reactions to afford *trans*-tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-3-ones have not been reported so far.

Interestingly, recent literature has shown that microwave heating has broadened the utility of this reaction allowing electron poor systems to undergo transformations in good yields.[4] This observation ties in well with our own recent experience, utilising microwave heating to affect high yielding intramolecular hetero Diels–Alder reactions from benzocyclobutene intermediates.[5] We had previously reported a series of tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-1-ones which had displayed interesting activity at the 5-HT$_{2C}$ receptor.[6] Using benzocylobutene **1** in an intramolecular hetero Diels–Alder reaction, via an *o*-quinodimethane, a mixture of *cis*/*trans* lactams **14a**:**14b** was obtained, which, following further derivatisation, gave a mixture of *cis*-**5a** and *trans*-bridgehead **5b** compounds (Fig. 1). These could be readily separated by silica gel chromatography or, using more vigorous conditions, could be driven to give *cis*-bridgehead compound **5a**, exclusively.

Herein we further elaborate on several modifications of our previously reported synthesis: firstly transposing the amide from benzocyclobutene **1** to that of benzocyclobutene **7** allowed exquisite control in delivering solely *trans*-bridgehead **5b** relative stereochemistry. Secondly substituting the tethered dienophile by replacing the ketone with various alkenes allowed access to the carbocyclic 3a-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]isoindoles **6a** and **6b** and related derivatives.

Intermediate **9**, a previously disclosed synthetically useful benzocyclobutene carboxylic acid intermediate, was coupled with benzylamine to give amide **10** (Scheme 1).[5] Following reduction with borane, the amine **11** could be coupled with a range of α-keto acids. The coupling of amine **11** with pyruvic acid using 1-propylphosphonic acid anhydride as the coupling reagent yielded amide **7** efficiently. Due to the high temperatures often required during the Diels–Alder reaction, many literature methods employ *o*-dichlorobenzene as a high boiling solvent, commonly refluxing for many hours or even days.[7] We found that toluene coupled with microwave heating could still achieve the high temperatures required and so was an expedient surrogate, which greatly facilitated product isolation due to the relative ease of solvent removal. Microwave irradiation promoted an intramolecular Diels–Alder reaction to yield the *trans*-lactam **12**, exclusively. However, it was necessary to use higher temperatures and longer reaction times (220 °C for 2 h) than our previously reported conditions for complete conversion of **1**.[5] A flexible synthesis for efficiently synthesising both pairs of diastereomers, merely by placement of the amide, was now in hand. Lactam **12** was reduced using borane-THF to give **13** which was subsequently converted into amine **5b** via treatment with 1-chloroethyl chloroformate (ACE-Cl), followed by methanol.[8] It is noteworthy that the transformations involved going from benzocyclobutene **7** through to **5b**, universally

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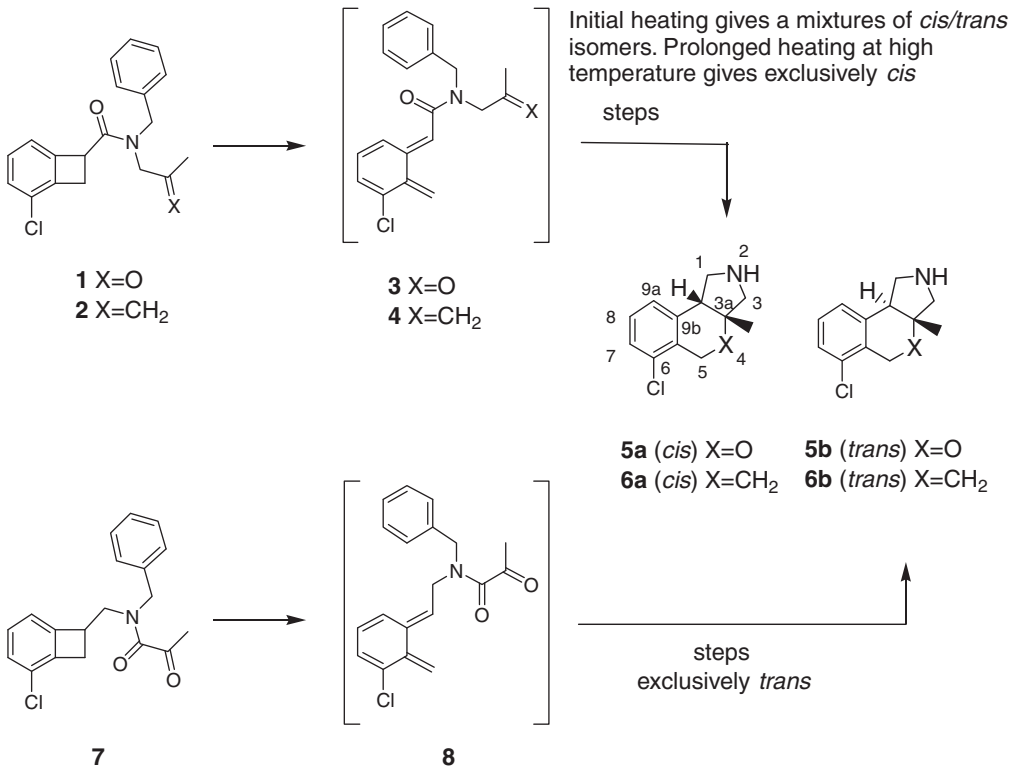
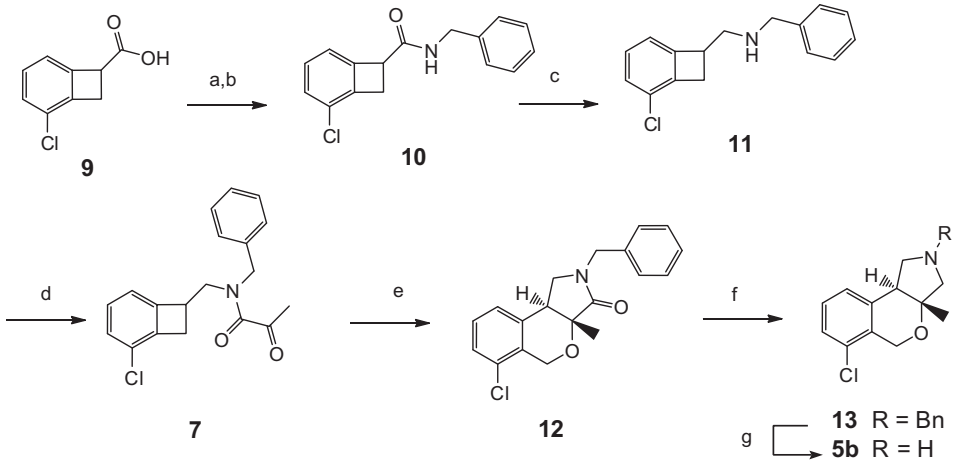


Figure 1. Benzocyclobutene intermediates undergo intramolecular (hetero) Diels–Alder reaction proceeding via an *o*-quinodimethane intermediate giving varying ratios of *cis*/*trans* products depending on the amide position and the tethered dienophile.

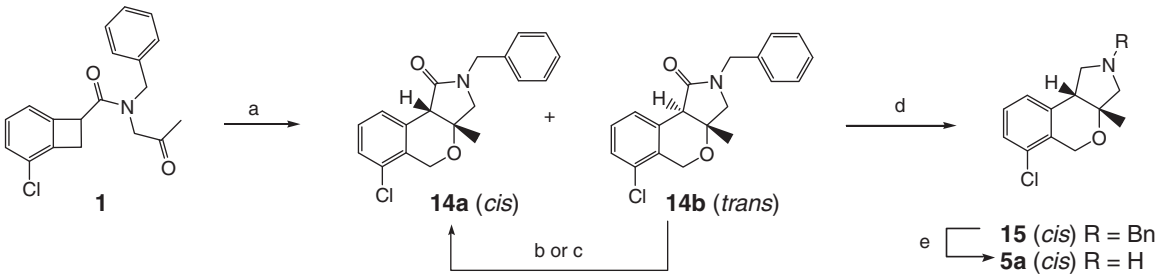


Scheme 1. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2 0 °C, 16 h, 100%; (b) benzylamine, Et_3N, CH_2Cl_2, 0 °C, 99%; (c) BH_3·DMS, CH_2Cl_2, reflux, 4 h, then 2 N HCl, 55%; (d) pyruvic acid, 1-propylphosphonic acid anhydride, DIPEA, CH_2Cl_2, 16 h, 69%; (e) toluene, microwave irradiation, 220 °C, 100%; (f) BH_3·THF, THF, reflux, 4 h, then 2 N HCl, 69%; (g) 1-chloroethyl chloroformate, toluene, reflux, 16 h, then MeOH, 78%.

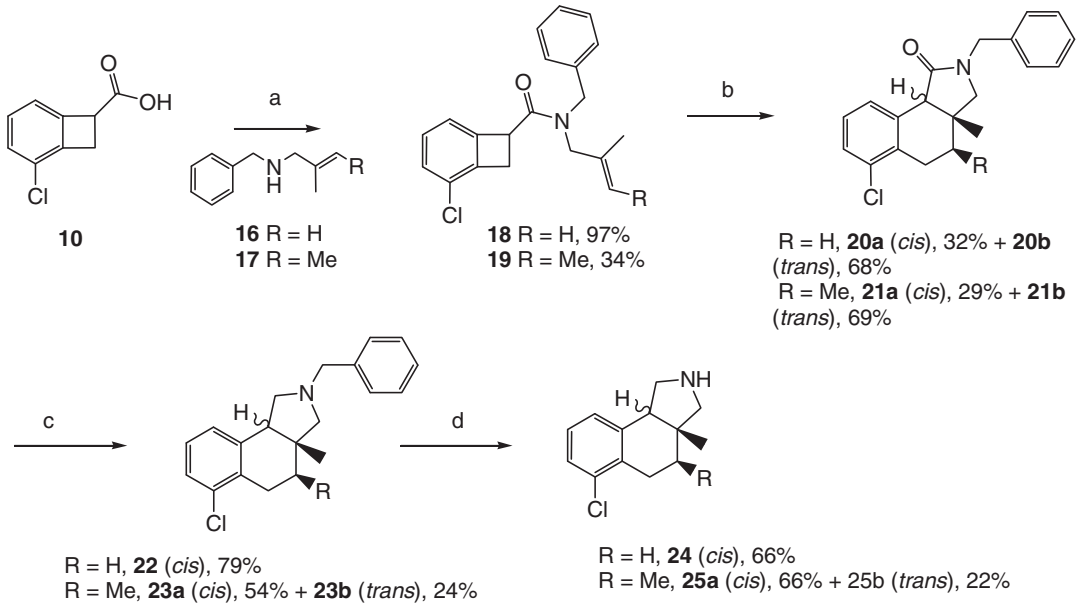
required either more forcing conditions or gave lower yields. It is suspected that the inherent ring strain of the *trans*-system is responsible for this, where the five-membered ring could be especially susceptible to alternative reaction pathways such as ring-opening.

During the course of this work it became increasingly clear that there was an intrinsic instability within the *trans*-6,6,5 fused system. This observation was supported with several pieces of evidence, which we believe illustrates the inherent strain within these systems: prolonged heating at temperatures of 210 °C and above gradually converted any initial *trans*-lactam **14b** completely into *cis*-**14a** (Scheme 2). This epimerisation could also be performed at lower temperature with the addition of a catalytic base such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).[9] It has also been possible to epimerise non-lactam systems similar to *trans*-compound **13** into their corresponding *cis*-equivalent **15**. However, without the carbonyl conferring high acidity to the benzylic position a stronger base such as sodium hydride is required along with a higher temperature.[10]

To access the analogous 3a-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]isoindoles **6a** and **6b** and their derivatives, we chose to utilise the previously described chemistry with the slight



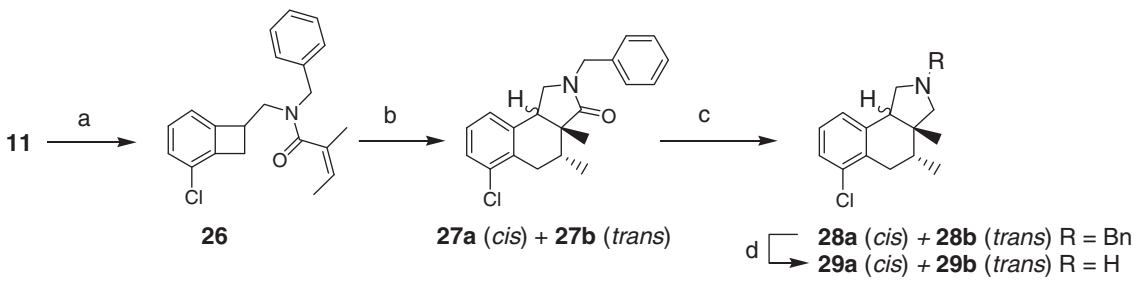
Scheme 2. Reagents and conditions: (a) toluene, microwave irradiation, 210 °C, 100%; (b) toluene, microwave irradiation, 220 °C, 100%; (c) DBN, toluene 110 °C, 80%; (d) BH_3·THF, THF, reflux, 4 h, then 2 N HCl, 69%; (e) 1-chloroethyl chloroformate, toluene, reflux, 16 h, then MeOH, 78%.



Scheme 3. Reagents and conditions: (a) 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide, Et_3N, rt, 16 h; (b) bromobenzene, 190 °C, microwave irradiation, 1 h; (c) (i) BH_3·THF, THF, reflux, 4 h, (ii) 2 N HCl; (d) 1-chloroethyl chloroformate, toluene, 160 °C, microwave irradiation, 15 min, then MeOH.

modification of attaching the appropriately decorated alkene (Scheme 3). The aforementioned acid **9** was again the key precursor which was coupled readily with benzylamine **16** to yield amide **18** in almost quantitative yield. Likewise amine **17**, synthesised in 30% yield by reductive amination of benzylamine with *trans*-2-methyl-2-butenal, could be coupled with **9** to give amide **19**. Following heating at 190 °C for 30 min in a microwave, both systems underwent the Diels–Alder reaction in high overall yields. Interestingly the *trans/cis* ratio was almost identical in both cases and perhaps even more intriguing was the very similar ratio obtained with the comparable ketone system 1, albeit with significantly improved overall conversion.[5] Furthermore, amide **18** showed the same predilection for complete conversion into the *cis*-diastereomer **20a** as ketone analogue **1**, when heated under more vigorous conditions (220 °C for 1 h in the microwave).

To access C-4 epimers **29a** and **29b**, amine **11** was coupled with angelic acid in moderate yield, and subsequently the Diels–Alder reaction transferred the *trans*-relationship of the methyl groups of angelic acid into the desired *anti*-relationship with respect to the **3a** and 4-positions of the newly formed ring (Scheme 4). In this instance however, despite the complete conversion, the products were obtained as an inseparable mixture of *cis/trans*-lactams **27a**



Scheme 4. Reagents and conditions: (a) angelic acid, 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide, Et_3N, rt, 16 h, 48%; (b) bromobenzene, 190 °C, microwave irradiation, 1 h, 100%; (c) (i) BH_3·THF, THF, reflux, 4 h, (ii) 2 N HCl, **28a** (21%), **28b** (58%); (d) 1-chloroethyl chloroformate, toluene, 160 °C, microwave irradiation, 15 min, then MeOH, **29a** (12%), **29b** (50%).

and **27b**.[11] This problem was easily circumvented by carrying out the borane reduction on the crude amide, which delivered a separable mixture (by silica gel chromatography) with a 3:1 ratio in favour of *trans*-product **28b**. This result proved to be consistent with several closely related publications. These show that similar benzocyclobutene systems undergoing a Diels–Alder reaction with a tethered alkene have great difficulty in delivering high levels of diastereocontrol.[3] However, in direct contrast, we have clearly

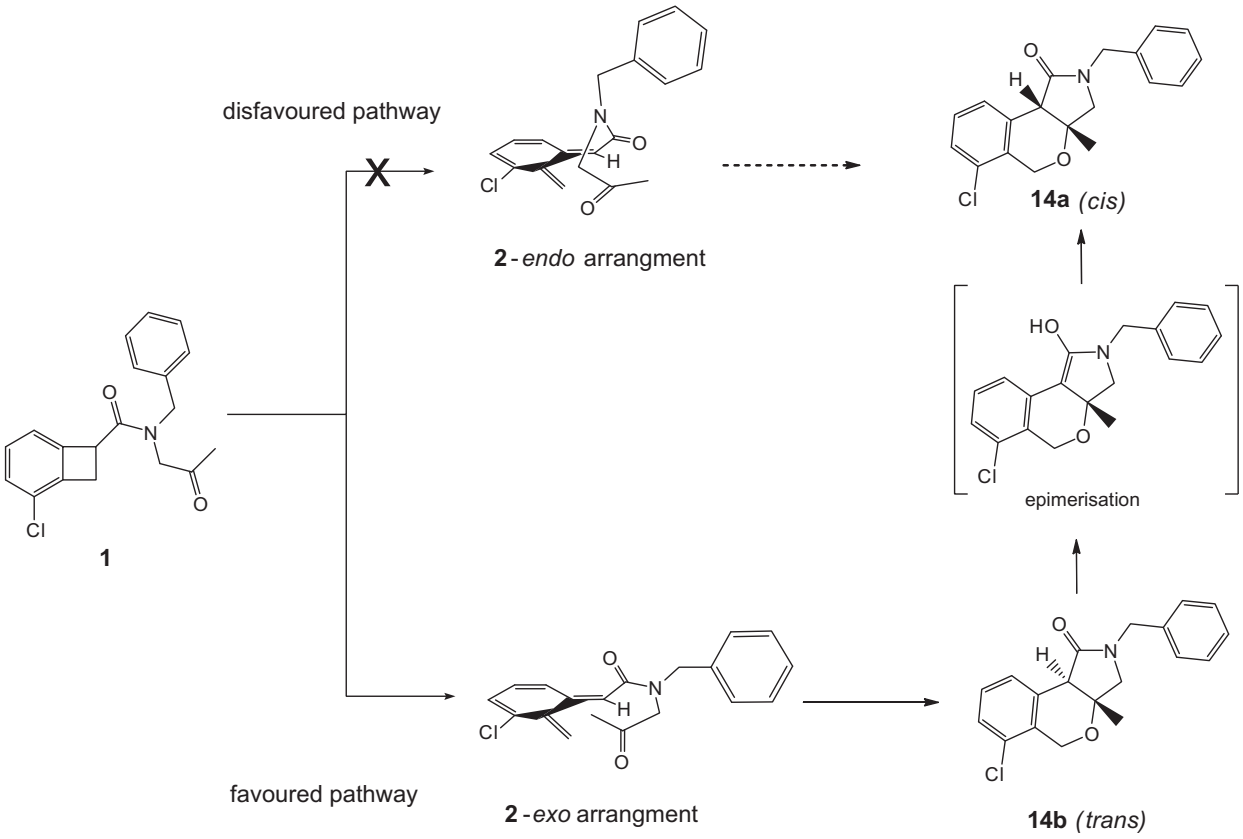


Figure 2. Proposed arrangement of the *o*-quinodimethane prior to the Diels–Alder reaction giving *cis*/*trans* mixtures.

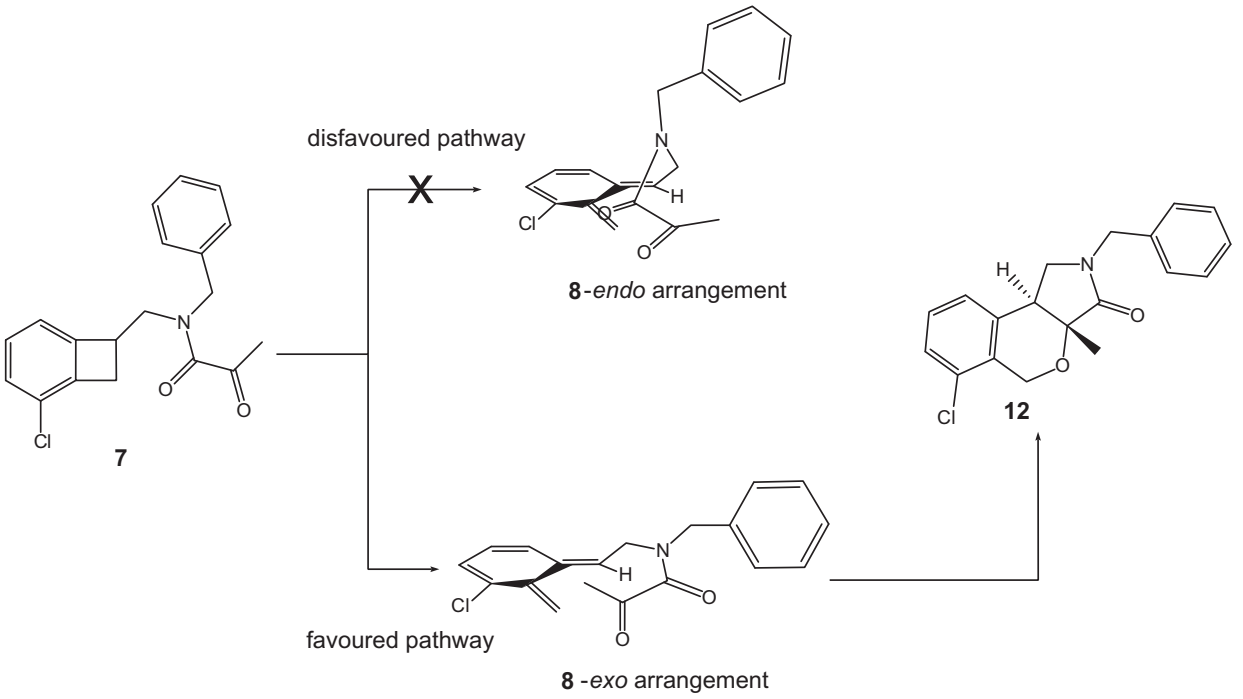


Figure 3. Proposed arrangement of the *o*-quinodimethane prior to the Diels–Alder reaction leading to the *trans*-product.

demonstrated that with the ketone-derived tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-3-ones, complete diasteroselectivity can be obtained. This evidence led us to believe that the intramolecular Diels–Alder reaction on the *o*-quinodimethane **2** derived from ring opening of **1** proceeds via an *exo* transition state giving the *trans*-lactam **14b** as the kinetic product (Fig. 2). However, excessive heating or addition of base readily leads to epimerisation of the benzylic α-amide proton giving the thermodynamically more stable *cis*-bridgehead compound **14a**.

When the amide is transposed as in compound **7**, *trans*-lactam **12** was obtained exclusively (Fig. 3). We believe that the reaction must again proceed via a lower energy *exo* transition state. However, in this instance, despite the highly strained nature of *trans*-lactam **12**, transposition of the amide carbonyl now renders the benzylic proton significantly less acidic and so epimerisation does not occur under the reaction conditions. Thus epimerisation to the *cis*-derivative can only be achieved with the addition of a strong base and hence we ultimately achieve high yields of solely *trans*-product **12**.

In summary, we have disclosed a versatile synthesis which harnesses the intramolecular Diels–Alder reaction. Judicious placement of the amide carbonyl, coupled with microwave heating, eliminated the need for either electron-rich aromatic substituents or excessively long reactions at high temperatures as previously required within similar systems. This has allowed us to synthesise both tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-3-ones with exquisite *cis* or *trans* selectivity and 3a-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]isoindole analogues exhibiting complex stereochemistry as precursors of biologically interesting 5-HT_{2C} agonists.

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10. Typical conditions used to achieve epimerisation of a range of *trans*-amine **10** derivatives were NaH, DMF at 240 °C, in the microwave reactor for 10 min.
11. Typical procedure for the intramolecular Diels–Alder reaction: a solution of *N*-benzyl-3-chloro-*N*-(2-methylbut-2-enyl)-1,2-dihydrocyclobutabenzene-1-carboxamide (**26**) (0.97 mmol, 330 mg) in bromobenzene (6 ml) was subjected to microwave irradiation using a microwave synthesiser (Initiator™ Eight, Biotage) at 190 °C for 1 h. The reaction mixture was purified directly using a silica gel column (eluting with heptane then 5–20% EtOAc in heptane) to afford an inseparable mixture of *cis*-**27a** (96 mg, 0.3 mmol, 29%) and *trans*-**27b** (229 mg, 0.67 mmol, 70%). *cis*-**27a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (1H, d, ArH), 7.45–7.13 (7 H, m, 7 × ArH), 4.55 (1H, d, CHHPh), 4.47 (1H, d, CHHPh), 3.40 (1H, s, CH), 3.07–2.94 (3H, m, 3 × CH), 2.40 (1H, dd, CH), 2.21–2.10 (1H, m, CH_2), 0.99 (3H, d, CH_3), 0.68 (3H, s, CH_3); *trans*-**27b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, d, ArH), 7.33–7.22 (7H, m, ArH), 4.57 (1H, d, CHHPh), 4.34 (1H, d, CHHPh), 3.34 (1H, s, CH), 3.24 (1H, d, CH), 3.01 (1H, d, CH), 2.90 (1H, dd, CH), 2.38 (1H, dd, CH), 1.77 (1H, m, CH), 1.04 (3H, s, CH_3), 0.91 (3H, d, CH_3).