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Synthesis of hexahydro[2]benzopyrano[3,4-*c*]pyrroles as serotonin 5-HT$_{2C}$ receptor agonists via intramolecular hetero Diels–Alder reactions

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ABSTRACT

[2]Benzopyrano[3,4-*c*]pyrroles were synthesized via an intramolecular hetero Diels–Alder reaction. The reaction was applicable to a wide range of substrates and the products could be easily converted into serotonin 5-HT$_{2C}$ receptor agonists.

Agonists of the serotonin 5-HT$_{2C}$ receptor have become attractive drug targets because of their potential as therapeutic agents for the treatment of obesity, diabetes, schizophrenia, and urinary incontinence.[1] Hexahydro[2]benzopyrano[3,4-*c*]pyrroles (**1**, Fig. 1) were identified as potent 5-HT$_{2C}$ agonists by high throughput screening of our in-house compound library. For further optimization of this series, it was desirable to introduce a range of electron-withdrawing and -donating groups on the aromatic ring.

To date there are a very limited number of reports of the synthesis of hexahydro[2]benzopyrano[3,4-*c*]pyrroles. Although Oppolzer reported one example of an intramolecular hetero Diels–Alder reaction to give **2** which had no substituents on the aromatic ring (R = R′ = R″ = H, Fig. 1), however, the reaction yield was very low (25%) despite a long reaction time (23 h) and high dilution conditions.[2] A similar reaction was reported by Loozen et al. using mono- or di-benzyloxybenzocyclobutenes (**3**) (e.g., R = H, R′ = R″ = OBn) as starting materials. Higher yields were obtained, probably due to the higher reactivity of the electron-rich diene intermediates **A**, associated with the benzyloxy moieties.[3]

We herein report the synthesis of a variety of tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-1-ones (**2**), including examples possessing electron-withdrawing moieties on the aromatic ring, via an intramolecular hetero Diels–Alder reaction using microwave irradiation. The products were easily converted into the target molecules for evaluation as potential 5-HT$_{2C}$ receptor agonists.

Benzocyclobutenes (**3**), the substrates for the hetero Diels–Alder reaction, were synthesized from the corresponding halogenated benzaldehydes in good yields.[3] As a typical example, the synthesis of **3a** is illustrated in Scheme 1. Thus, 2,6-dichlorobenzaldehyde (**4**) was reacted with cyanoacetic acid to give **5**, followed by a selective reduction of the carbon–carbon double bond, and

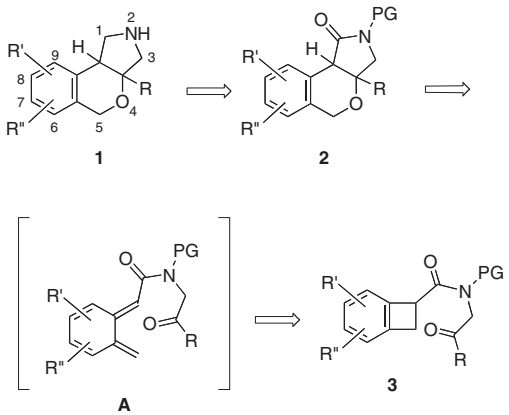

Figure 1. The structure of hexahydro[2]benzopyrano[3,4-*c*]pyrrole 5-HT$_{2C}$ receptor agonists **1** and the proposed retrosynthetic route.

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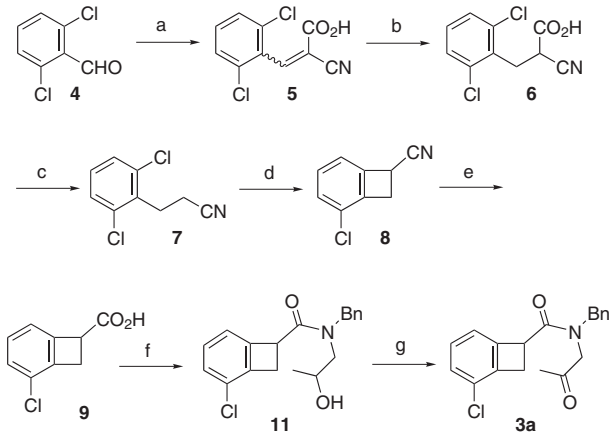
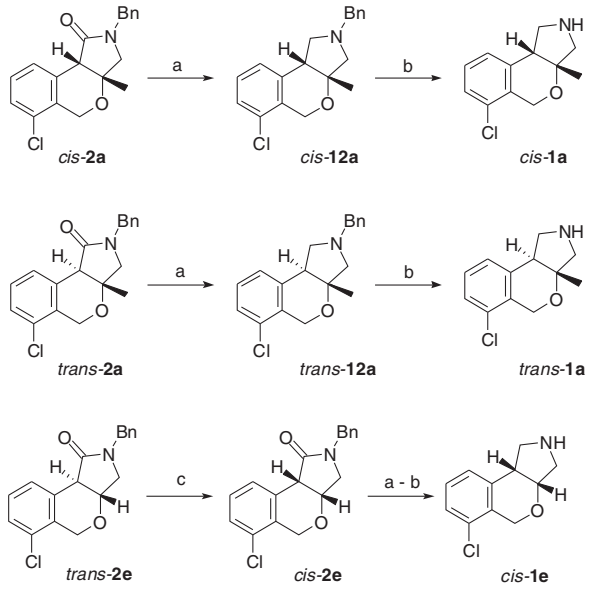
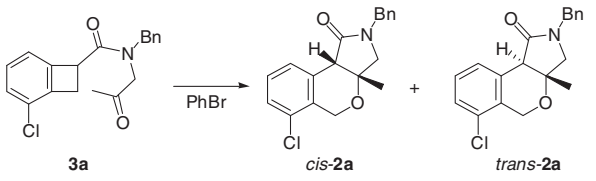


Scheme 1. Reagents and conditions for the synthesis of benzocyclobutene **3a**: (a) HO_2CCH_2CN, pyridine, NH_4OAc, toluene, reflux using a Dean–Stark apparatus, 3 h, 98%; (b) $NaBH_4$, $NaHCO_3$, MeOH/H_2O, rt, 0.5 h, 98%; (c) DMA, 150 °C, 2 h, quant.; (d) $NaNH_2$, liquid NH_3, THF, −55 to −35 °C, 3 h, quant.; (e) KOH, EtOH/H_2O, reflux, 2.5 h, 90%; (f) HN(Bn)$CH_2CHOHCH_3$ (**10**), 1-propanephosphonic acid anhydride, CH_2Cl_2, rt, 2 h, 96%; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h, 76%.



Scheme 2. Reagents and conditions: (a) $BH_3{\cdot}Me_2S$, THF, reflux, 6 h, then 5 N HCl, 68–93%; (b) ACE-Cl, toluene, microwave, 160 °C, 15 min then MeOH, 46–78%; (c) 0.1 equiv DBN, toluene, reflux, 1.2 h, 88%.

Table 1
Intramolecular hetero Diels–Alder reaction of benzocyclobutene **3a**



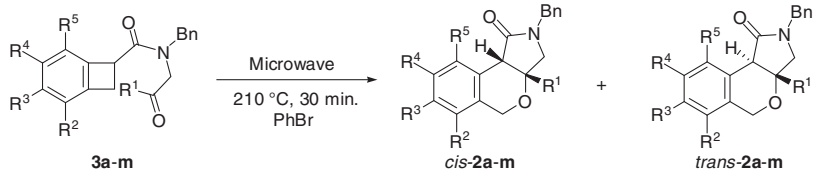
Entry	Reaction conditions	Yield[a] (%)	*cis*:*trans*
1	Reflux, 16 h	51	69:31
2	Microwave, 180 °C, 30 min	50	31:69
3	Microwave, 210 °C, 30 min	93	53:47
4[b]	Microwave, 240 °C, 80 min	73	100:0

[a] Isolated yield.
[b] *o*-Dichlorobenzene was used as solvent.

decarboxylation and sodium amide mediated cyclobutyl ring formation to give **8**. The nitrile group of **8** was hydrolyzed to give the corresponding carboxylic acid and a subsequent condensation reaction with 2-hydroxypropylamine derivative **10** gave amide **11**. The hydroxy group was then oxidized to afford **3a**. Benzocyclobutenes **3b**–**3m** were synthesized in a similar manner.

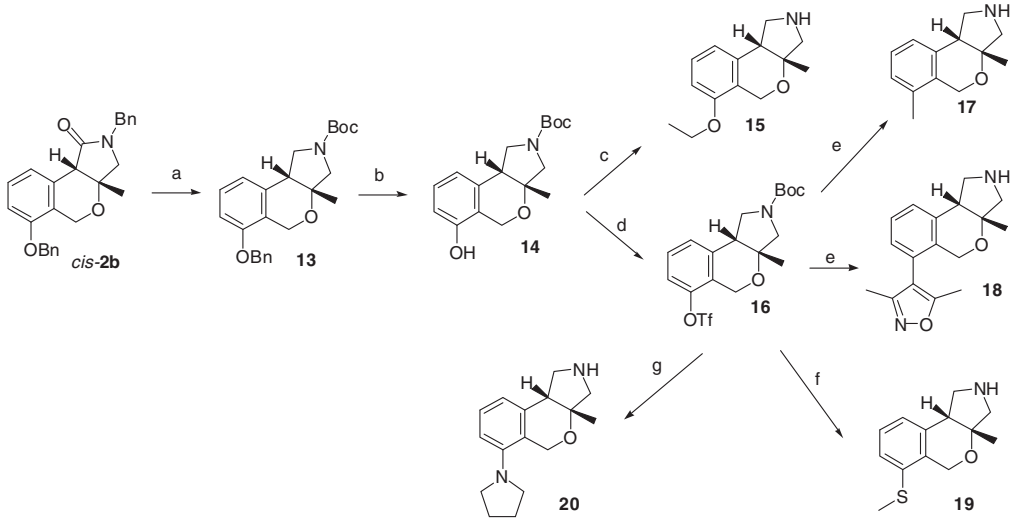
The intramolecular hetero Diels–Alder reaction of **3a** was initially performed using conventional heating under reflux conditions in bromobenzene (bp = 156 °C) as a solvent (Table 1, entry 1). The desired tricyclic product **2a** was obtained in moderate yield as a mixture of *cis*- and *trans*-isomers (*cis*:*trans* = 69:31). When the reaction was performed under microwave irradiation conditions at 180 °C, the product was obtained in a similar yield, although the *trans*-isomer was formed predominantly (Table 1, entry 2). Improved results were obtained with microwave irradiation at

Table 2
Intramolecular hetero Diels–Alder reaction of a variety of benzocyclobutenes



Substrate	R^1	R^2	R^3	R^4	R^5	Yield[a] (%)	*cis*:*trans*
3a	Me	Cl	H	H	H	93	53:47
3b	Me	OBn	H	H	H	86	60:40
3c	Me	Cl	Br	H	H	66	91:9
3d	Me	H	H	H	Cl	0	––
3e	H	Cl	H	H	H	86	55:45
3f	H	CF_3	H	H	H	85	93:7
3g	H	H	OBn	H	H	93	39:61
3h	H	H	H	Cl	H	69	93:7
3i	H	Cl	Br	H	H	65	88:12
3j	H	Me	H	OMe	H	77	65:35
3k	Et	Cl	H	H	H	72	57:43
3l	CH_2F	Cl	H	H	H	81	91:9
3m	CF_3	Cl	H	H	H	50	100:0

[a] Isolated yield.



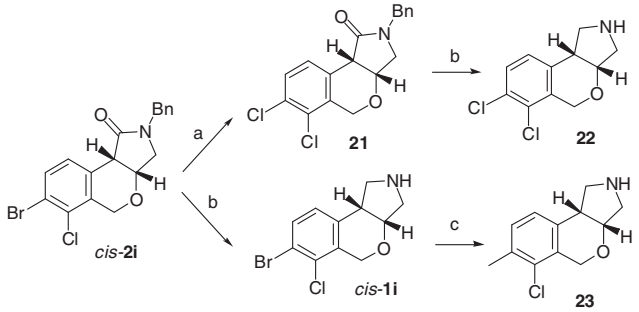
Scheme 3. Reagents and conditions: (a) (i) BH_3·THF, THF, reflux, 9 h, then 5 N HCl, 90%, (ii) ACE-Cl, toluene, microwave 160 °C, 30 min, then MeOH, (iii) Boc_2O, DMAP, Et_3N, CH_2Cl_2, rt, 16 h, 40%; (b) Pd–C, H_2, MeOH, rt, 16 h, quant.; (c) (i) EtI, NaH, DMF, rt, 76%, (ii) 5 N HCl, 1,4-dioxane, MeOH, 70 °C, 1 h, 97%; (d) $PhNTf_2$, NaH, THF, rt, 2 h, 60%; (e) (i) trimethylboroxine or 3,5-dimethylisoxazol-4-yl boronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, microwave, 130 °C, 20 min, 53–95%, (ii) 5 N HCl, 1,4-dioxane, MeOH, 100 °C, 30 min, 20–77%; (f) (i) $Pd(OAc)_2$, BINAP, NaSMe, toluene, microwave, 120 °C, 30 min, 51%, (ii) 5 N HCl, 1,4-dioxane, MeOH, 70 °C, 1 h, 52%; (g) (i) $Pd_2(dba)_3$, BINAP, pyrrolidine, *t*-BuONa, toluene, microwave, 135 °C, 15 min, 25%, (ii) 5 N HCl, 1,4-dioxane, MeOH, 70 °C, 1 h, 45%.

210 °C to give **2a** in 93% yield in a *cis*:*trans* ratio of 53:47 (Table 1, entry 3). It is noteworthy that when the microwave reaction was performed at 240 °C for 80 min using *o*-dichlorobenzenzene as the solvent, the *cis*-isomer was formed stereoselectively, probably due to an in situ isomerisation reaction to form the thermodynamically more stable *cis*-isomer (Table 1, entry 4). The reason for the decreased yield compared to the lower temperature conditions (Table 1, entry 3) may be a result of decomposition of **3a** during the reaction.

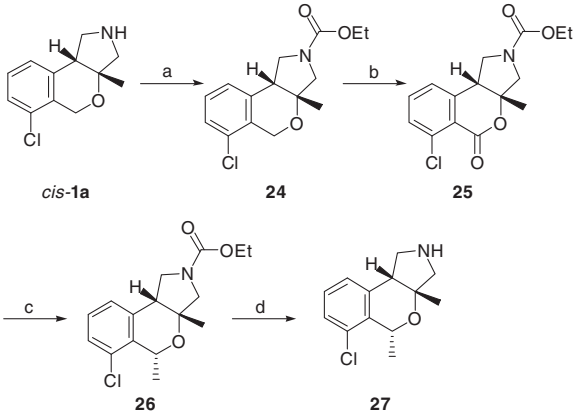
Encouraged by these results, we next applied the optimum conditions (210 °C, 30 min using microwave irradiation) to a variety of benzocyclobutenes to explore the scope of this reaction in making diverse analogs of 5-HT_{2C} agonists.[4] The results are listed in Table 2. As can be seen from Table 2, this intramolecular hetero Diels–Alder reaction tolerates a variety of functional groups. Benzyloxy derivative **3b** afforded the corresponding product in good yield, and di-halogenated analogue **3c** also gave the desired products **2c**. However, the 9-chloro derivative **2d** was not obtained, probably because of the steric repulsion between the chlorine atom and the amide side chain. A variety of aldehydes (R^1 = H, **3e**–**3j**) afforded the corresponding products **2e**–**2j** in good yields as mixtures of *cis*- and *trans*-isomers. When an electron-withdrawing group such as CH_2F or CF_3, was at R^1, the reaction proceeded in a more *cis*-selective manner (**2l** and **2m**).

The hetero Diels–Alder products, *cis*-**2** and *trans*-**2** could be easily separated by silica gel column chromatography and converted into the corresponding pyrrolidines, *cis*-**1** and *trans*-**1**. As shown in Scheme 2, the amide groups of *cis*-**2a** and *trans*-**2a** were reduced to the corresponding amines using BH_3·Me_2S, followed by deprotection of the benzyl group by reaction with α-chloroethyl chloroformate (ACE-Cl) to afford *cis*-**1a** and *trans*-**1a**.[5] The *trans*-isomer of **2e** could also be converted into the *cis*-isomer by treatment with a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) under reflux in toluene.[3] Furthermore, the *cis*-isomer **2e** could be easily converted into *cis*-**1e** as described above.

The benzyloxy group or bromine atom on the aromatic ring (e.g., *cis*-**2b** or *cis*-**2i**) could be readily converted into a variety of functional groups. For example, the benzyl group of **13** was cleaved by hydrogenation and the phenol was further transformed into alkoxy, alkyl, aryl, mercapto, and amino moieties (Scheme 3). The bromine atom of *cis*-**2i** could be converted into chloro[6] or alkyl moieties as shown in Scheme 4. Further functionalization, such as stereoselective alkylation on the 5-position of the tricyclic system, has been achieved by benzylic oxidation of **24** using Jones'



Scheme 4. Reagents and conditions: (a) $NiCl_2$, *N*-methyl-2-pyrrolidone, microwave 180 °C, 10 min, then 210 °C, 60 min, 62%; (b) (i) BH_3·Me_2S, THF, reflux, 3 h, then 5 N HCl, 56–84%, (ii) ACE-Cl, toluene, microwave 160 °C, 15–20 min then MeOH, 77%; (c) trimethylboroxine, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, microwave, 100 °C, 15 min, then 120 °C, 15 min, 33%.



Scheme 5. Reagents and conditions: (a) $ClCO_2Et$, $NaHCO_3$, THF, H_2O, rt, 16 h, quant.; (b) Jones' reagent, rt, 2 h, 62%; (c) (i) MeLi, THF, −78 °C, 2 h, then AcOH, (ii) Et_3SiH, TFA, CH_2Cl_2, −78 °C to rt, 2 h, 70%; (d) KOH, MeOH, H_2O, microwave 150 °C, 30 min, 52%.

reagent to afford lactone **25**. Alkylation and triethylsilane-mediated reduction[7] afforded **26**, which was deprotected to give **27** (Scheme 5).

In summary, a series of [2]benzopyrano[3,4-*c*]pyrroles was synthesized by intramolecular hetero Diels–Alder reaction under microwave irradiation conditions. The reaction was applied to a wide range of substrates bearing a variety of dienes and dienophiles with electron-donating or -withdrawing properties. Although the hetero Diels–Alder reaction afforded a mixture of *cis*- and *trans*-isomers, both of these could be readily separated by silica gel column chromatography and converted into the corresponding pyrrolidine 5-HT_{2C} receptor agonists. The *cis*-isomers (e.g., *cis*-**2a** or *cis*-**2e**) could be obtained stereoselectively using higher temperature conditions or by treatment of the *trans*-isomer with DBN. Benzyloxy or bromo atoms have been shown to be effective functional handles to introduce diversity on to the aryl ring. Moreover, oxidation and stereoselective alkylation of the 5-position were achieved. The stereoselective synthesis of the *trans*-isomers is currently under investigation and will be reported in the near future.

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4. *Typical procedure of the intramolecular Diels–Alder reaction*: a solution of *N*-benzyl-3-chloro-*N*-(2-oxopropyl)-1,2-dihydrocyclobutabenzene-1-carboxamide (**3a**, 936 mg, 2.86 mmol) in bromobenzene (30 ml) was subjected to microwave irradiation in two microwave vials using a microwave synthesizer (Initiator™ Eight, Biotage) at 210 °C for 30 min. The reaction mixture was purified directly using a silica gel column chromatography eluting with heptane followed by ethyl acetate (10–50%) in heptane to afford *trans*-**2a** (409 mg, 1.25 mmol, 44%) followed by *cis*-**2a** (461 mg, 1.41 mmol, 49%). *trans*-**2a**; ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 3H), 3.10 (d, 1H), 3.37 (d, 1H), 3.70 (s, 1H), 4.46 (d, 1H), 4.55 (d, 1H), 4.93 (d, 1H), 4.94 (d, 1H), 7.20–7.35 (m, 7H), 8.11 (d, 1H), EI-MS: *m*/*e* 328.3 $(M+H)^+$. *cis*-**2a**; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 3.30–3.40 (m, 3H), 4.44 (d, 1H), 4.54 (d, 1H), 4.67 (d, 1H), 4.80 (d, 1H), 7.20–7.35 (m, 7H), 7.48 (t, 1H). EI-MS: *m*/*e* 328.2 $(M+H)^+$.
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