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TETRAHEDRON

Parallel Synthesis of Polysubstituted Tetrahydroquinolines

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Abstract : A three-component cycloaddition was used to prepare a library of polysubtituted tetrahydroquinolines. Reaction conditions were optimised and a large range of anilines, aldehydes and alkenes were tested.

Combinatorial chemistry and related technologies have played a significant role in the current revolution of the drug discovery process. To be valuable in the context of drug discovery, the chemical process should be able to accommodate a diverse range of building blocks. The compounds produced should have a solubility/hydrophobicity balance and a limited structural flexibility to avoid hydrophobic collapse. Moreover, the resulting library should be capable of undergoing further reaction to allow rapid entry into analogues of hits. In this context, we have focused part of our efforts on reactions generating heterocycles suitable for high throughput organic synthesis.

Combinatorial strategy :

Tetrahydroquinolines offer most of the required properties for a combinatorial scaffold. Rigid and compact (pharmacophores in the range of 3Å to 6Å), they also contain hydrogen bond donor/acceptor sites and aromatic sites as shown by the 3D model of the simplest compound in this series (Scheme 1).

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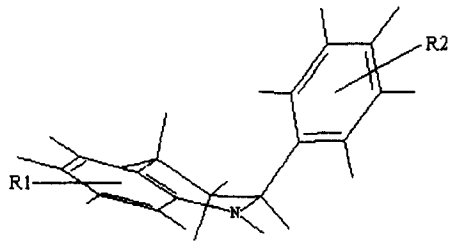
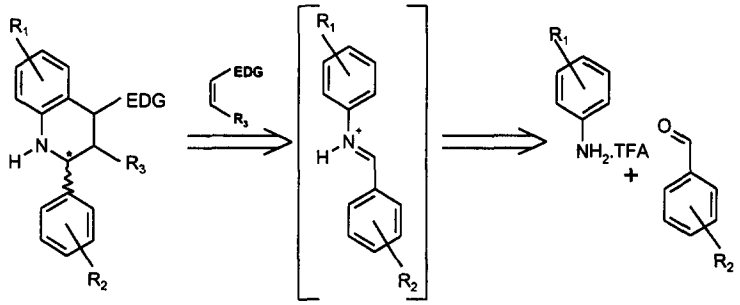


substituted 2-phenyl-1,2,3,4-tetrahydroquinoline

Scheme 1

Numerous interesting drugs display this scaffold : in 1883, three 1,2,3,4-tetrahydroquinolines were marketed as antipyretic agents [1]. A series of 2-aminomethyltetrahydroquinolines showed promising schistosomicidal activity, in particular against *S. mansoni* worms [2], and another series was used as antiischaemic agents, with the most potent NMDA antagonists yet found [3]. Other pharmaceutical and industrial applications of 1,2,3,4-tetrahydroquinolines have been recently reviewed [4].

A retrosynthetic study indicated the possibility of using the three-component cycloaddition [5] shown in Scheme 2 (EDG is an electron donating group) as the primary pathway to the development of the library. This involves employing an iminium ion as the key intermediate which permits maximal use of two major sources of diversity : aldehydes and primary anilines. These families of building blocks have both a large number of members and a wide structural diversity. Alkenes form the third partner in the reaction which, although belonging to a much smaller family, can provide additional diversity in terms of both functionality and steric constraint.



Scheme 2

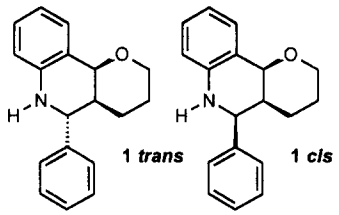
Chemistry :

Based on similar reaction pathways, the solid phase synthesis of several tetrahydroquinolines was reported recently [6]. Starting with one aniline, five alkenes and eight aldehydes, 40 pairs of

diastereoisomers were synthesised. The small size of the library was mainly due to the fact that the aniline component had to be linked to a polymer, with the consequence of drastically limiting the diversity at this level. Moreover, this polymer-bound building block keeps trace of the linker that remains unchanged through to the end products.

These limitations led us to develop a supported synthesis of tetrahydroquinolines, involving a limited number of steps that could be performed in solution using readily available « monofunctional » aldehydes and anilines.

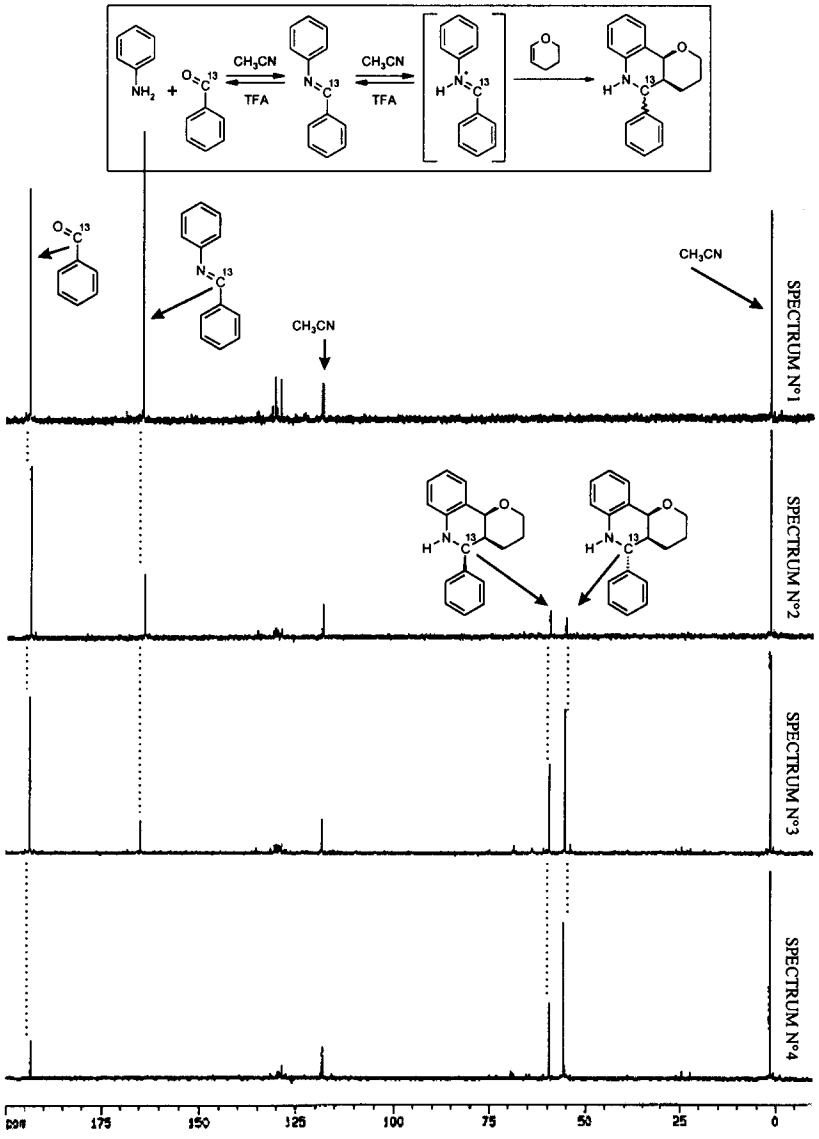
An initial study of the reaction using aniline, benzaldehyde and 3,4-dihydro-2H-pyran was performed. Benzaldehyde was added to the trifluoroacetic salt of aniline in acetonitrile. After stirring for 15 minutes at room temperature, a solution of dihydropyran in acetonitrile was added. After 3 hours at room temperature, HPLC analysis of the reaction medium indicated a conversion of more than 90% based on the disappearance of benzaldehyde. Only two major products, presumably the two expected diastereoisomers (**1**) [7], were formed with virtually no by-products. One of them was isolated and shown by NMR analysis to be the *trans* diastereoisomer (see experimental section). Moreover, identical results were observed when preformed benzylideneaniline was reacted with dihydropyran, indicating that the imine could be formed directly in the reaction medium without affecting the quality of resulting products.



1 *trans* **1 *cis***

In order to investigate the mechanism of the reaction, a NMR study using ^{13}C-labelled benzaldehyde was performed (Scheme 3). When aniline was added to ^{13}C-benzaldehyde (δ=193 ppm), a new signal appeared (δ=164 ppm) after only 20 seconds (Spectrum n°1), corresponding to the imine. Over the next ten minutes, no further signals on the NMR spectra could be detected, indicating the establishment of an equilibrium between the imine and benzaldehyde. The ratio imine/benzaldehyde was 6/5. 3,4-dihydro-2H-pyran was then added. After 1 minute's reaction time (Spectrum n°2), two peaks (δ=55 ppm and δ=59 ppm) corresponding to the two diastereoisomers could be detected. Simultaneously, a sharp decrease in the peak corresponding to the imine was observed (Spectrum n°3 - 7 minutes after addition of dihydropyran) followed by a much slower decrease in the peak corresponding to benzaldehyde (Spectrum n°4 - 30 minutes after addition of dihydropyran). This indicated that the formation of the imine was the rate limiting step in the reaction. After 30 minutes (Spectrum n°4), no further signal could be detected. The overall conversion was 85%. The peak at δ=55 ppm was shown to correspond to the C-5 of the *trans* diastereoisomer. Although this isomer was less represented than the *cis*

diastereoisomer (δ=59 ppm - Spectrum n°2) after 1 minute of reaction, the ratio of the two diastereoisomers was inverted after 7 minutes (Spectrum n°3). The quantity of *trans* isomer gradually increased (Spectrum n°4), with the existence of an equilibrium between the two diastereoisomers confirmed by HPLC.



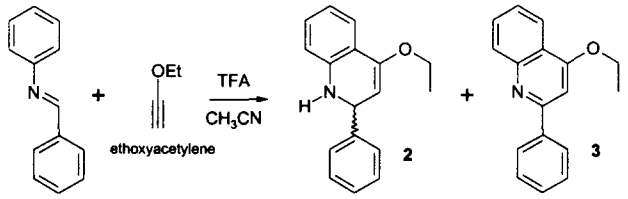
Scheme 3 - NMR study using ^{13}C-benzaldehyde.

Effects of solvents and catalysts :

The effects of solvents and catalysts on the overall yield and on the ratio of the two diastereoisomers were studied to complete already published data [8]. With benzene, CH_2Cl_2, DMF, Et_2O or THF as the solvent, yields of tetrahydroquinolines were lower. The use of Lewis catalysts such as $BF_3.Et_2O$ [9], $FeCl_3$ [10] or $TiCl_4$ [11] at room temperature did not improve yields but promoted side reactions. Therefore, the initial method (using acetonitrile and TFA) was selected.

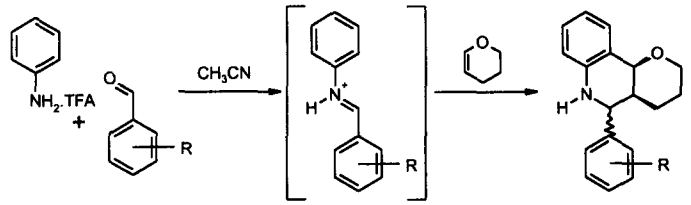
Evaluation of the scope of the reaction and the reactivity-based selection scheme for building blocks:

The reaction under consideration requires the presence of neutral or electron donating groups on the dienophile [11] . In order to evaluate their reactivity, representatives of the various dienophiles meeting this requirement were reacted with benzaldehyde and aniline. 2,3-dihydrofuran led to high conversion and clean reaction medium, as did 3,4-dihydro-2H-pyran. The substituted analogue 3,4-dihydro-2-methoxy-2H-pyran did not react. Among the other known alkenes [11,12], analogues of styrene and enamines were found to react more slowly. Ethyl vinyl ether led to the expected products only at lower temperatures. Expected adducts (**2**) were also obtained with ethoxyacetylene but were slowly oxidised to the fully aromatic quinoline (**3**) (Scheme 4).



Scheme 4

Ten representative aldehydes were tested with aniline and 3,4-dihydro-2H-pyran. The products were purified and fully characterised. Overall conversions were good with neutral aromatic aldehydes (Table 1 - entry 1) and electron deficient aromatic aldehydes (entries 7 and 8) producing tetrahydroquinolines in good yield with almost no by-products. Heterocycles (entries 11 and 12) also gave good results, with the exception of the acid-sensitive 2-furaldehyde (entry 10), where the low yield was probably due to degradation of the heterocycle. Both aliphatic aldehydes (entry 9) and α,β-unsaturated aldehydes (entry 4) led to complex mixtures. When benzaldehyde was substituted with electron donating groups (entries 5 and 6), only the *trans* diastereoisomer was detected and the yield was low.

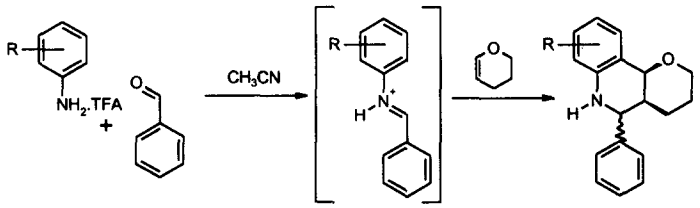


Entry	Aldehyde	Conversion [a]	LC Yield [b]	Analysis [c]
1	benzaldehyde	90%	80%	LC, NMR, MS
4	*trans*-cinnamaldehyde	- [d]	-	LC
5	p-anisaldehyde	80%	35%	LC, NMR
6	2,4-dimethoxybenzaldehyde	70%	45%	LC, NMR, MS
7	4-nitrobenzaldehyde	100%	90%	LC, NMR, MS
8	4-cyanobenzaldehyde	95%	90%	LC, NMR, MS
9	3-phenylpropionaldehyde	- [d]	-	LC
10	2-furaldehyde	100%	45%	LC, NMR, MS
11	2-thiophenecarboxaldehyde	80%	75%	LC, NMR
12	3-pyridinecarboxaldehyde	- [e]	70%	LC, NMR, MS

[a] based on LC determination of the aldehyde. [b] based on LC determination of the product. [c] see experimental section. [d] no reaction or complex mixture. [e] coelution with the solvent.

Table 1.

Nine representative anilines were tested with benzaldehyde and 3,4-dihydro-2H-pyran. The products were purified and fully characterised.

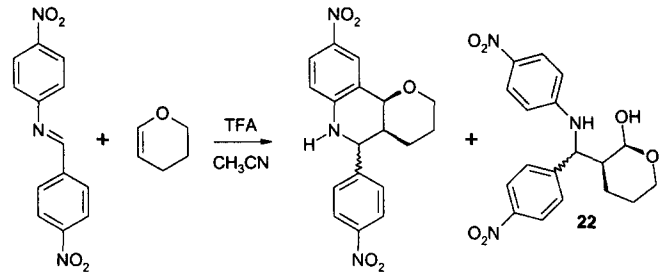


Entry	Aniline	Conversion [a]	LC Yield [b]	Analysis [c]
13	p-anisidine	95%	30%	LC, MS
14	p-chloroaniline	90% [d]	55%	LC, NMR, MS
15	ethyl-4-aminobenzoate	95%	90%	LC, NMR, MS
16	m-anisidine	85% [e]	-	LC
17	m-chloroaniline	85%	- [f]	LC
18	ethyl-3-aminobenzoate	90%	- [f]	LC
19	o-isopropylaniline	90%	90%	LC, NMR
20	o-anisidine	85%	85%	LC, NMR
21	o-chloroaniline	- [g]	60%	LC, NMR, MS

[a] based on LC determination of benzaldehyde. [b] based on LC determination of the product. [c] see experimental section. [d] based on LC determination p-chloroaniline. [e] complex mixture. [f] products not purified. [g]coelution of the starting materials.

Table 2.

In most cases, the conversion into products was high (Table 2). Neutral anilines (entry 19) and electron deficient anilines (entries 15 and 20) gave high conversions and clean reaction media. Anilines that were substituted into the *meta* position led to mixtures of 4 products as expected, since the 2 *ortho* positions became non-equivalent (entries 17 and 18). When the aniline was substituted with electron donating groups (entries 13 and 16), only the *trans* diastereoisomer was detected but the yield was low. In two cases (entries 14 and 21), a side reaction was detected. Further investigation showed that this side reactions was favoured when strong electron withdrawing groups were present in the *ortho* or *para* positions on both aldehydes and anilines. Similar by-products were previously described as resulting from a [2+2] cycloaddition [8a], although this conclusion was later withdrawn [7]. We isolated these by-products during the reaction between 4-nitroaniline and 4-nitrobenzaldehyde, where they were formed in large quantities. NMR-analysis was consistent with the two diastereoisomers of **22** (Scheme 5).

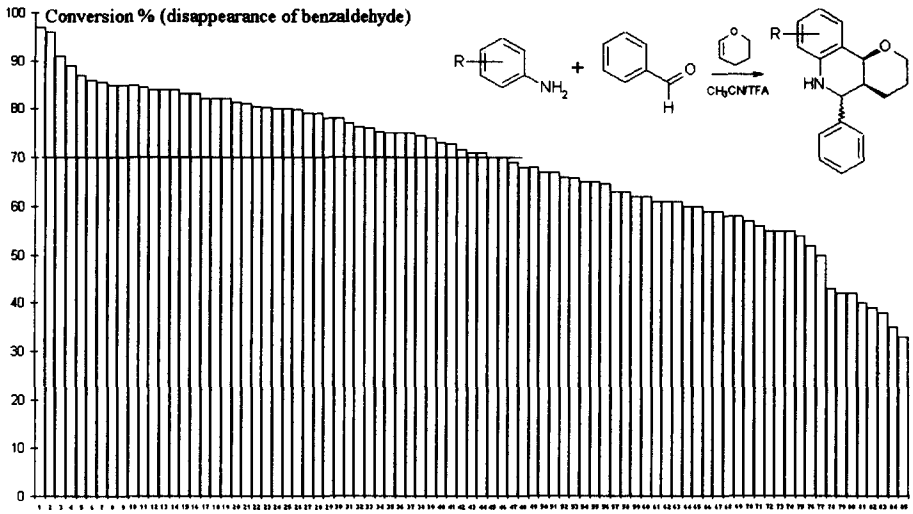


Scheme 5

Building block selection and experimental qualifications :

According to the strategy that we developed, a first series of building blocks was selected in order to prepare a lead-seeking library, moderate in size and of high purity and diversity. Once a hit was detected in this library, structural analogues were then prepared using the complete series of building blocks, including those for which lower conversion rates were observed.

The ACD database was thus searched to select a diverse range of building blocks fitting the previously described reactivity selection scheme. In order to qualify for selection, 100 anilines and 135 aldehydes were selected and subjected to various tests. Among the 100 anilines tested, 15 were not soluble in the reaction conditions, and were eliminated. The remaining 85 anilines were reacted with benzaldehyde and dihydropyran (Scheme 6). Conversion ratios between 97 and 33% were observed, with 46 anilines giving conversions higher than 70%. Among these, 24 were eventually selected for the lead seeking library, producing tetrahydroquinolines in high yield with few or no by products. The other anilines were retained for further hit analoging.

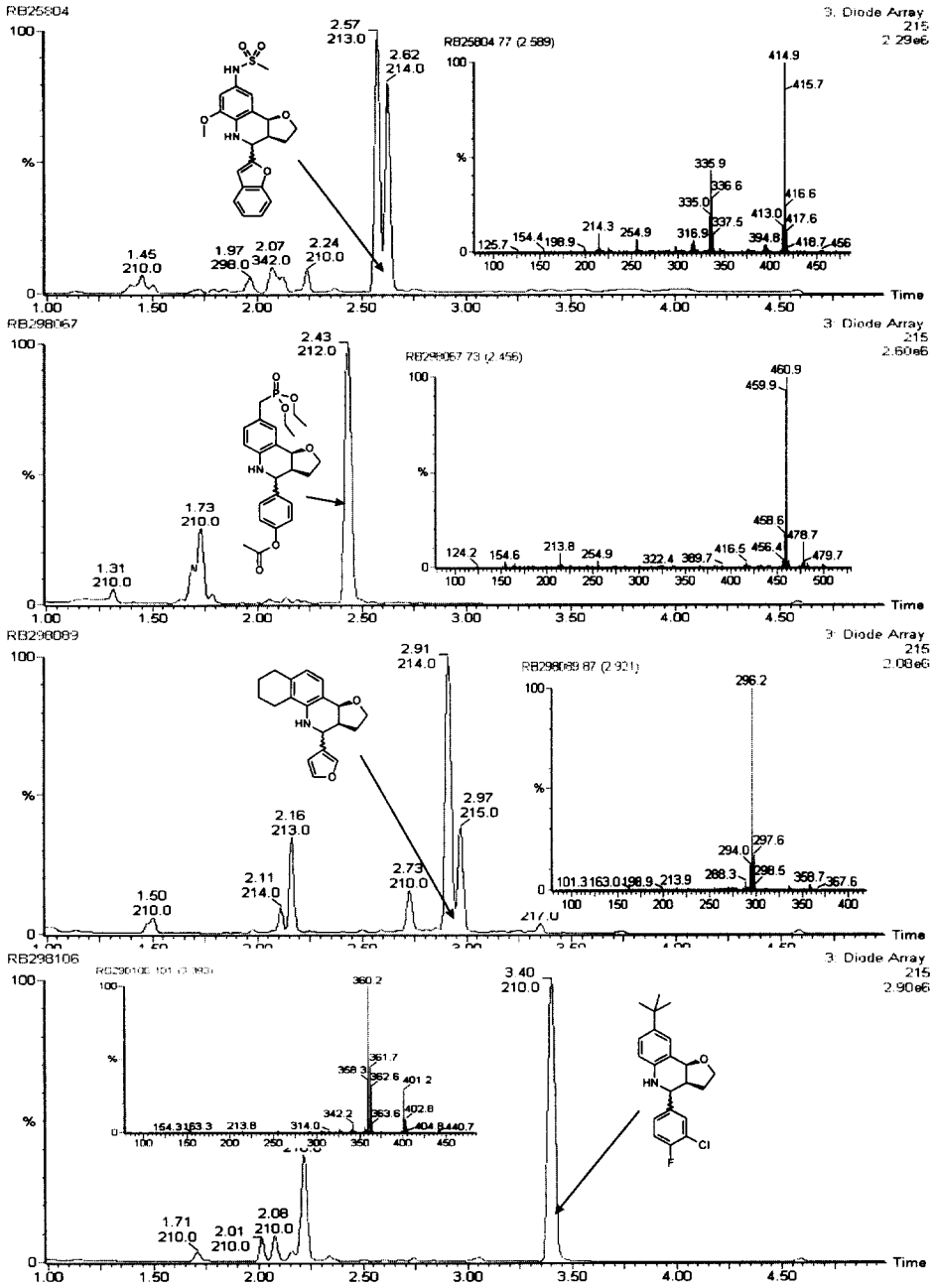


Scheme 6 - Qualification of anilines.

A similar qualification was performed for aldehydes. Among the 135 different aldehydes initially selected, 35 were rejected due to poor solubility, while a further 20 were discarded on the basis of low yields or by-product formation or both. Eventually, 80 aldehydes were selected.

On the basis of the results from the different qualification studies, a lead seeking library, containing 1920 pairs of diastereoisomeric tetrahydroquinolines, was prepared under a 96-well plates format using a high throughput robot starting with 80 aldehydes, 24 anilines and one alkene (2,3-dihydrofuran).

Representative LC/MS analysis of the resulting crude products are shown in Scheme 7. Using slightly modified reaction conditions and, when necessary, simple purification methods, this library is open to the formation of several thousand additional compounds, allowing the easy synthesis of analogues of hits.


RB25804
3: Diode Array
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2.29e6
2.57
213.0
2.62
214.0
1.45
210.0
1.97
298.0
2.07
342.0
2.24
210.0
RB25804 77 (2.589)
414.9
415.7
335.9
336.6
335.0
416.6
337.5
413.0
417.6
214.3
254.9
316.9
394.8
416.7
456
125.7
154.4
198.9
Time
RB298067
3: Diode Array
215
2.60e6
2.43
212.0
1.73
210.0
1.31
210.0
RB298067 73 (2.456)
460.9
459.9
458.6
478.7
124.2
154.6
213.8
254.9
322.4
389.7
416.5
456.4
479.7
Time
RB298089
3: Diode Array
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2.08e6
2.91
214.0
2.97
215.0
2.16
213.0
2.11
214.0
2.73
210.0
1.50
210.0
RB298089 87 (2.921)
296.2
297.6
294.0
298.5
288.3
358.7
367.6
101.3
163.0
198.9
213.9
Time
RB298106
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2.90e6
3.40
210.0
360.2
361.7
358.3
382.6
401.2
342.2
363.6
402.8
404.8
440.7
154.3
163.3
213.8
314.0
1.71
210.0
2.01
210.0
2.08
210.0
Cl
F
Time

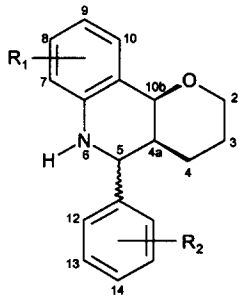
Scheme 7

EXPERIMENTAL SECTION

^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUCKER DRX300 (300Mhz) system using $CDCl_3$ as an internal reference unless otherwise indicated. Chromatography was carried out on Macherey-Nager Silica Gel 60 (230-400 mesh ASTM). HPLC analyses were performed with a Shimadzu LC10A system equipped with an Tosohass TSKgel Super ODS column (4.6mm ID x 5cm). Mass spectra were recorded on a ThermoQuest Automass 150 GC/MS spectrometer or on a Micromass Platform-LC instrument coupled to a Hewlett-Packard HP1100 equipped with an Tosohass TSKgel Super ODS column. Chromatographic method : solvent A (water, 0.5% TFA) solvent B (20% water, 80% acetonitrile, 0.425%TFA) ; run time : 5 minutes ; gradient : 0' [B]=0% - 3' [B]=100% - 4' [B]=100% - 4.01' [B]=0% - 5' [B]=0%. Molecular modelling was performed using MSI Cerius 2 software. The HPLC analysis employed an internal standard method based on the absorbance of a product. A calibration curve was produced from at least three different concentrations of an isolated and pure building block or product. Using linear regression, it was possible to calculate conversions or yields based on the HPLC analysis (named « Estimated yield » in the experimental section).

General procedure for the synthesis of substituted tetrahydroquinolins :

To a solution of 91µL of aniline (1.0 mmol) in 1mL of acetonitrile was added 77µL (1.0 mmol) of TFA . After 5 minutes of stirring, 102µL (1.0 mmol) of benzaldehyde in 1mL of acetonitrile was added. The mixture became rapidly coloured and was stirred for 5 minutes. A solution of 91µL (1.0 mmol) of 3,4-dihydro-2H-pyran in 1mL of acetonitrile was added and the mixture was stirred at room temperature for 30 minutes. The mixture was concentrated *in vacuo* and purified by flash chromatography over silica gel (eluted with ethyl acetate/pentane=5/95) to give a solid that was characterised by LC, MS and NMR.



Synthesis of 1.

Estimated yield = 80% (for the two diastereoisomers). Purification yield = 32% (for one diastereoisomer).

CI+MS : *m/z* 266 $[M+H]^+$ (BP) 206 $[M-OCH_2CH_2CH]^+$ 182 $[M-DHP+H]^+$.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.36 (1H, dm, J_{3gem}=12.9 Hz, 3ax-H) 1.50 (1H, dm, J_{4gem}=13.9 Hz, 4eq-H) 1.70 (1H, tt, J_{4gem}=13.7 Hz, $J_{4ax-3eq}$=4.5 Hz, 4ax-H) 1.90 (1H, tq, J=11.9 Hz, $J_{3eq-4ax}$=4.4 Hz, 3eq-H) 2.13 (1H, dm, J_{4a-5}=10.9 Hz, 4a-H) 3.76 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.5 Hz, $J_{2ax-3eq}$=2.5 Hz, 2ax-H) 4.12 (1H, s, 6-H) 4.14 (1H, dt, J_{2gem}=11.4 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.3 Hz, 2eq-H) 4.43 (1H, d, J_{10b-4a}=2.7 Hz, 10b-H) 4.75 (1H, d, J_{5-}

$_{4a}$=10.8 Hz, 5-H) 6.56 (1H, dd, J_{7-8}=8.0 Hz, J_{7-9}=0.8 Hz, 7-H) 6.74 (1H, dt, J_{9-8}=J_{9-10}=7.4 Hz, J_{9-7}=1.1 Hz, 9-H) 7.13 (1H, dt, J_{8-7}=J_{8-9}=7.6 Hz, J_{8-10}=1.5 Hz, 8-H) 7.26 (1H, dd, J_{10-9}=7.6 Hz, J_{10-8}=1.4 Hz, 10-H) 7.41 (5H, m, Hϕ).

Trans diastereoisomer : ^{13}C NMR (300 MHz, $CDCl_3$) : δ 22.45 (C3) 24.55 (C4) 39.30 (C4a) 55.24 (C5) 69.07 (C2) 74.97 (C10b) 114.55 (C10) 117.88 (C8) 121.07 (Cq) 128.25 (Cϕ) 128.33 (Cϕ) 129.07 (Cϕ) 129.79 (C9) 131.34 (C7) 142.74 (Cq) 145.17 (Cq).

Synthesis of 5.

Estimated yield = 35% (for the only diastereoisomer obtained). Purification yield = 17%.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.36 (1H, m, 3ax-H) 1.52 (1H, dm, J_{4gem}=13.9 Hz, 4eq-H) 1.68 (1H, tt, J_{4gem}=13.1 Hz, $J_{4ax-3eq}$=4.4 Hz, 4ax-H) 1.87 (1H, tq, J_{3gem}=12.9 Hz, $J_{3eq-4ax}$=4.3 Hz, 3eq-H) 2.09 (1H, ddm, J_{4a-5}=11.0 Hz, J_{4a-10b}=2.3 Hz, 4a-H) 3.76 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.6 Hz, $J_{2ax-3eq}$=2.6 Hz, 2ax-H) 3.85 (3H, s, OC$\underline{H}_3$) 4.15 (1H, dt, J_{2gem}=11.3 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.2 Hz, 2eq-H) 4.42 (1H, d, J_{10b-4a}=2.7 Hz, 10b-H) 4.71 (1H, d, J_{5-4a}=10.9 Hz, 5-H) 6.55 (1H, dd, J_{7-8}=8.1 Hz, J_{7-9}=1.1 Hz, 7-H) 6.73 (1H, dt, J_{9-8}=J_{9-10}=7.4 Hz, J_{9-7}=1.1 Hz, 9-H) 6.94 (2H, d, J_{12-13}=6.7 Hz, 12-H) 7.12 (1H, dt, J_{8-7}=J_{8-9}=8.1 Hz, J_{8-10}=1.6 Hz, 8-H) 7.24 (1H, dd, J_{10-9} = 7.6 Hz, J_{10-8}=1.5 Hz, 10-H) 7.37 (2H, d, J_{13-12}=6.6 Hz, 13-H).

Synthesis of 6.

Estimated yield = 45% (for the only diastereoisomer obtained). Purification yield = 28%.

CI+MS : *m/z* 326 $[M+H]^+$ (BP) 266 $[M-OCH_2CH_2CH]^+$.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.38 (1H, m, 3ax-H) 1.55 (1H, ddm, J_{4gem}=13.7 Hz, $J_{4eq-3ax}$=2.4 Hz, 4eq-H) 1.69 (1H, tt, J_{4gem}=13.7 Hz, $J_{4ax-3eq}$=4.6 Hz, 4ax-H) 1.92 (1H, tq, J_{3gem}=11.5 Hz, $J_{3eq-4ax}$=4.6 Hz, 3eq-H) 2.20 (1H, dm, J_{4a-4eq}=5.6 Hz, 4a-H) 3.30 (1H, s, 6-H) 3.72 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=9.6 Hz, $J_{2ax-3eq}$=2.6 Hz, 2ax-H) 3.85 (6H, s, 2 OC$\underline{H}_3$) 4.04 (1H, dm, 2eq-H) 4.45 (1H, d, J_{10b-4a}=3.0 Hz, 10b-H) 5.14 (1H, d, J_{5-4a}=10.4 Hz, 5-H) 6.51 (1H, d, J_{13-15}=2.3 Hz, 13-H) 6.54 (1H, dd, J_{15-13}=2.4 Hz, J_{15-16}=8.3 Hz, 15-H) 6.60 (1H, dd, J_{7-8}=8.1 Hz, J_{7-9}=1.0 Hz, 7-H) 6.77 (1H, dt, J_{9-8}=J_{9-10}=7.4 Hz, J_{9-7}=1.0, 9-H) 7.12 (1H, dt, J_{8-7}=J_{8-9}=7.4 Hz, J_{8-10}=1.5 Hz, 8-H) 7.28 (1H, dd, J_{10-9}=8.0 Hz, J_{10-8}=1.5 Hz, 10-H) 7.37 (1H, d, J_{16-15}=8.3 Hz, 16-H).

Synthesis of 7.

Estimated yield = 90% (for the two diastereoisomers). Purification yield = 58% (for the two diastereoisomers, both isolated pure).

CI+MS : *m/z* 311 $[M+H]^+$ 227 $[M-DHP+H]^+$.

Cis diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.28 (2H, m, 3ax-H + 4eq-H) 1.57 (2H, m, 4eq-H + 3eq-H) 2.24 (1H, m, 4a-H) 3.48 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.0 Hz, $J_{2ax-3eq}$=3.0 Hz, 2ax-H) 3.64 (1H, dm, J_{2gem}=11.5 Hz, 2eq-H) 4.10 (1H, s, 6-H) 4.84 (1H, d, J_{10b-4a}=2.6 Hz, 10b-H) 5.37 (1H, d, J_{5-4a}=5.5 Hz, 5-H) 6.68 (1H, dd, J_{7-8}=8.0 Hz, J_{7-9}=1.1 Hz, 7-H) 6.88 (1H, dt, J_{9-8}=J_{9-10}=7.5 Hz, J_{9-7}=1.2 Hz, 9-H) 7.16 (1H, dt, J_{8-7}=J_{8-9}=8.0 Hz, J_{8-10}=1.5 Hz, 8-H) 7.47 (1H, dd, J_{10-9}=7.6 Hz, J_{10-8}=1.2 Hz, 10-H) 7.64 (2H, d, J_{13-12}=7.3 Hz, 13-H) 8.28 (2H, d, J_{12-13}=8.8 Hz, 12-H).

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.43 (2H, m, 3ax-H + 4eq-H) 1.78 (2H, m, 4eq-H + 3eq-H) 2.14 (1H, dm, $J_{4a\text{-}5}$=10.5 Hz, 4a-H) 2.77 (1H, dt, J_{2gem}=$J_{2ax\text{-}3ax}$=11.3 Hz, $J_{2ax\text{-}3eq}$=2.2 Hz, 2ax-H) 4.12 (1H, s, 6-H) 4.13 (1H, dm, J_{2gem}=11.3 Hz, 2eq-H) 4.43 (1H, d, $J_{10b\text{-}4a}$=2.8 Hz, 10b-H) 4.87 (1H, d, $J_{5\text{-}4a}$=10.5 Hz, 5-H) 6.61 (1H, dd, $J_{7\text{-}8}$=8.1 Hz, $J_{7\text{-}9}$=1.0 Hz, 7-H) 6.79 (1H, dt, $J_{9\text{-}8}$=$J_{9\text{-}10}$=7.4 Hz, $J_{9\text{-}7}$=1.1 Hz, 9-H) 7.16 (1H, dt, $J_{8\text{-}7}$=$J_{8\text{-}9}$= 7.4 Hz, $J_{8\text{-}10}$=1.6 Hz, 8-H) 7.28 (1H, dd, $J_{10\text{-}9}$=8.0 Hz, $J_{10\text{-}8}$=1.5 Hz, 10-H) 7.65 (2H, d, $J_{13\text{-}12}$=8.6 Hz, 13-H) 8.27 (2H, d, $J_{12\text{-}13}$=8.7 Hz, 12-H).

Synthesis of 8.

Estimated yield = 90% (for the two diastereoisomers). Purification yield = 52% (for the two diastereoisomers, both isolated pure).

CI+MS : *m/z* 291 $[M+H]^+$ (BP) 231 $[M\text{-}OCH_2CH_2CH]^+$.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.40 (1H, m, 3ax-H) 1.46 (1H, m, 4eq-H) 1.76 (2H, m, 4ax-H + 3eq-H) 2.14 (1H, dm, $J_{4a\text{-}5}$=10.4 Hz, 4a-H) 3.78 (1H, dt, J_{2gem}=$J_{2ax\text{-}3ax}$=11.2 Hz, $J_{2ax\text{-}3eq}$=2.0 Hz, 2ax-H) 4.12 (1H, s, 6-H) 4.14 (1H, dt, J_{2gem}=11.2 Hz, $J_{2eq\text{-}3eq}$=$J_{2eq\text{-}3ax}$=2.1 Hz, 2eq-H) 4.44 (1H, d, $J_{10b\text{-}4a}$=2.8 Hz, 10b-H) 4.83 (1H, d, $J_{5\text{-}4a}$=10.5 Hz, 5-H) 6.62 (1H, dd, $J_{7\text{-}8}$=8.0 Hz, $J_{7\text{-}9}$=1.0 Hz, 7-H) 6.80 (1H, dt, $J_{9\text{-}8}$=$J_{9\text{-}10}$=7.5 Hz, $J_{9\text{-}7}$= 1.1 Hz, 9-H) 7.17 (1H, dt, $J_{8\text{-}7}$=$J_{8\text{-}9}$=7.4 Hz, $J_{8\text{-}10}$=1.6 Hz, 8-H) 7.29 (1H, dd, $J_{10\text{-}9}$=7.6 Hz, $J_{10\text{-}8}$=1.5 Hz, 10-H) 7.60 (2H, d, $J_{12\text{-}13}$=6.5 Hz, 12-H) 7.71 (2H, d, $J_{13\text{-}12}$=6.5 Hz, 13-H).

Cis diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.53 (1H, m, 3ax-H) 1.63 (2H, m, 4eq-H + 4ax-H) 1.85 (1H, dm, $J_{3eq\text{-}2eq}$=6.3, 3eq-H) 2.23 (1H, dm, $J_{4a\text{-}10b}$=2.6 Hz, 4a-H) 3.48 (1H, dt, J_{2gem}=$J_{2ax\text{-}3ax}$=11.3 Hz, $J_{2ax\text{-}3eq}$=3.1 Hz, 2ax-H) 3.65 (1H, dm, $J_{2eq\text{-}3eq}$=6.2 Hz, 2eq-H) 3.86 (1H, s, 6-H) 4.80 (1H, d, $J_{10b\text{-}4a}$=2.6 Hz, 10b-H) 5.38 (1H, d, $J_{5\text{-}4a}$=5.5 Hz, 5-H) 6.68 (1H, dd, $J_{7\text{-}8}$=8.0 Hz, $J_{7\text{-}9}$=1.1 Hz, 7-H) 6.88 (1H, dt, $J_{9\text{-}8}$=$J_{9\text{-}10}$=7.5 Hz, $J_{9\text{-}7}$=1.1 Hz, 9-H) 7.17 (1H, dt, $J_{8\text{-}7}$=$J_{8\text{-}9}$=7.3 Hz, $J_{8\text{-}10}$=1.3 Hz, 8-H) 7.48 (1H, dd, $J_{10\text{-}9}$=7.6 Hz, $J_{10\text{-}8}$=1.2 Hz, 10-H) 7.60 (2H, d, $J_{12\text{-}13}$ = 6.7 Hz, 12-H) 7.71 (2H, d, $J_{13\text{-}12}$=6.6 Hz, 13-H).

Synthesis of 10.

Estimated yield = 45% (for the two diastereoisomers). Purification yield = 39% (for the two diastereoisomers, one of them isolated pure).

CI+MS : *m/z* 256 $[M+H]^+$ (BP) 195 $[M\text{-}OCH_2CH_2CH]^+$.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.44 (1H, dm, $J_{3ax\text{-}2ax}$=6.1 Hz, 3ax-H) 1.61 (1H, dm, J_{4gem}=6.3 Hz, 4eq-H) 1.78 (1H, m, 4ax-H) 1.81 (1H, m, 3eq-H) 2.44 (1H, ddm, $J_{4a\text{-}5}$=10.9 Hz, $J_{4a\text{-}10b}$=3.1, 4a-H) 3.76 (1H, dt, $J_{2ax\text{-}3ax}$=6.5 Hz, $J_{2ax\text{-}3eq}$=2.6 Hz, 2ax-H) 4.12 (1H, dm, J_{2gem}=11.0 Hz, 2eq-H) 4.53 (1H, d, $J_{10b\text{-}4a}$=2.8 Hz, 10b-H) 4.91 (1H, s, 6-H) 4.93 (1H, d, $J_{5\text{-}4a}$=10.7 Hz, 5-H) 6.42 (2H, m, 12-H + 13-H) 6.75 (1H, d, $J_{7\text{-}8}$=8.1 Hz, 7-H) 6.93 (1H, dd, $J_{9\text{-}8}$=$J_{9\text{-}10}$=7.4 Hz, 9-H) 7.20 (1H, dt, $J_{8\text{-}7}$=8.1 Hz, $J_{8\text{-}9}$=7.2 Hz, $J_{8\text{-}10}$=1.4 Hz, 8-H) 7.31 (1H, d, $J_{10\text{-}9}$=7.6, 10-H).

Synthesis of 11.

Estimated yield = 75% (for the two diastereoisomers). Purification yield = 7% (for one diastereoisomer).

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.40 (1H, dm, J_{3gem}=12.7 Hz, 3ax-H) 1.64 (1H, dm, J_{4gem}=12.2 Hz, 4eq-H) 1.74 (1H, tt, J_{4gem}=12.3 Hz, J_{4ax-4a}=4.4 Hz, 4ax-H) 1.86 (1H, tq, J_{3gem}=12.1 Hz, $J_{3eq-4eq}$=3.8 Hz, 3eq-H) 2.09 (1H, ddm, J_{4a-5}=10.7 Hz, J_{4a-10b}=2.7 Hz, 4a-H) 3.76 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.4 Hz, $J_{2ax-3eq}$=2.7 Hz, 2ax-H) 4.13 (1H, dt, J_{2gem}=11.3 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.2 Hz, 2eq-H) 4.25 (1H, s, 6-H) 4.43 (1H, d, J_{10b-4a}=2.7 Hz, 10b-H) 5.10 (1H, d, J_{5-4a}=10.7 Hz, 5-H) 6.58 (1H, dd, J_{7-8}=8.1 Hz, J_{7-9}=1.0 Hz, 7-H) 6.76 (1H, dt, J_{9-8}=J_{9-10}=7.4 Hz, J_{9-7}=1.2 Hz, 9-H) 7.02 (1H, dd, J_{13-12}=3.5 Hz, J_{13-14}=5.0 Hz, 13-H) 7.10 (1H, J_{12-13}=3.2 Hz, 12-H) 7.12 (1H, dt, J_{8-7}=J_{8-9}=8.0 Hz, J_{8-10}=1.1 Hz, 8-H) 7.26 (1H, dd, J_{10-9}=7.5 Hz, J_{10-8}=1.5 Hz, 10-H) 7.32 (1H, d, J_{14-13}=5.0 Hz, 14-H).

Synthesis of 12.

Estimated yield = 70% (for the two diastereoisomers). Purification yield = 48% (for one diastereoisomer).

EIMS : *m/z* 266 M^+ 206 $[M\text{-}OCH_2CH_2CH]^+$ (BP).

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.41 (1H, m, 3ax-H) 1.48 (1H, m, 4eq-H) 1.75 (1H, tt, J_{4gem}=13.8 Hz, $J_{4ax-3eq}$=4.5 Hz, 4ax-H) 1.87 (1H, tm, J_{3gem}=12.0 Hz, 3eq-H) 2.18 (1H, ddm, J_{4a-5}=11.2 Hz, J_{4a-10b} = 2.2 Hz, 4a-H) 3.78 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.4 Hz, $J_{2ax-3eq}$=2.4 Hz, 2ax-H) 4.13 (1H, s, 6-H) 4.15 (1H, dm, J_{2gem}=10.2 Hz, 2eq-H) 4.46 (1H, d, J_{10b-4a}=2.8 Hz, 10b-H) 4.83 (1H, d, J_{5-4a}=10.9 Hz, 5-H) 6.61 (1H, dd, J_{7-8}=8.1 Hz, J_{7-9}=1.0 Hz, 7-H) 6.79 (1H, dt, J_{9-8}=J_{9-10}=7.4 Hz, J_{9-7}=1.1 Hz, 9-H) 7.16 (1H, dt, J_{8-7}=J_{8-9}=7.4 Hz, J_{8-10}=1.5 Hz, 8-H) 7.28 (1H, dd, J_{10-9}=7.6 Hz, J_{10-8}=1.5 Hz, 10-H) 7.39 (1H, dd, J_{15-16}=7.4 Hz, J_{15-14}=5.0 Hz, 15-H) 7.84 (1H, dt, J_{16-15}=8.0 Hz, J_{16-14}=J_{16-12}=1.9 Hz, 16-H) 8.64 (1H, dm, J_{14-15}=4.9 Hz, 14-H) 8.95 (1H, m, 12-H).

Synthesis of 13.

Estimated yield = 30% (for the only diastereoisomer obtained). Purification yield = 20%.

CI+MS : *m/z* 296 $[M+H]^+$ (BP) 236 $[M\text{-}OCH_2CH_2CH]^+$.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.41 (1H, dm, $J_{3ax-4ax}$=13.5 Hz, 3ax-H) 1.54 (1H, dm, J_{4gem}=14.0 Hz, 4eq-H) 1.71 (1H, tt, $J_{4ax-3ax}$=13.7 Hz, $J_{4ax-3eq}$=4.6 Hz, 4ax-H) 1.88 (1H, tt, J_{3gem}=12.8 Hz, $J_{3eq-4ax}$=4.3 Hz, 3eq-H) 2.17 (1H, ddm, J_{4a-5}=10.7 Hz, J_{4a-10b}=2.5 Hz, 4a-H) 3.77 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.4 Hz, $J_{2ax-3eq}$=2.5 Hz, 2ax-H) 3.84 (3H, s, 15-H) 4.15 (1H, dt, J_{2gem}=11.2 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.4 Hz, 2eq-H) 4.40 (1H, s, 6-H) 4.48 (1H, d, J_{10b-4a}=2.8 Hz, 10b-H) 4.74 (1H, d, J_{5-4a}=10.8 Hz, 5-H) 6.72 (1H, dd, J_{9-8}=7.9 Hz, J_{9-10}=7.2 Hz, 9-H) 6.77 (1H, dd, J_{8-9}=8.2 Hz, J_{8-10}=1.9 Hz, 8-H) 6.94 (1H, dd, J_{10-8}=1.7 Hz, J_{10-9}=7.1 Hz, 10-H) 7.43 (5H, m, Hϕ).

Synthesis of 14.

Estimated yield = 55% (for the two diastereoisomers). Purification yield = 47% (for one diastereoisomer).

CI+MS : *m/z* 300 $[M+H]^+$ (BP) 364 $[M\text{-}Cl]^+$.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.39 (1H, dm, J_{3gem}=13.2 Hz, 3ax-H) 1.51 (1H, dm, J_{4gem}=13.0 Hz, 4eq-H) 1.69 (1H, tt, J_{4gem}=12.8 Hz, $J_{4ax-3eq}$=4.6 Hz, 4ax-H) 1.87 (1H, tq, J_{3gem}=13.0 Hz, $J_{3eq-4ax}$=4.3 Hz, 3eq-H) 2.10 (1H, ddm, J_{4a-5}=10.6 Hz, J_{4a-10b}=2.4 Hz, 4a-H) 3.74 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.4 Hz, $J_{2ax-3eq}$=2.6 Hz, 2ax-H) 4.10 (1H, s, 6-H) 4.11 (1H, dt, J_{2gem}=11.3 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.2 Hz, 2eq-H) 4.38 (1H, d, J_{10b-4a}=2.9 Hz, 10b-H) 4.71 (1H, d, J_{5-4a}=10.6 Hz, 5-H) 6.49 (1H, d, J_{7-8}=8.6 Hz, 7-H) 7.07 (1H, dd, J_{8-7}=8.5 Hz, J_{8-10}=2.5 Hz, 8-H) 7.24 (1H, d, J_{10-8}=2.5 Hz, 10-H) 7.40 (5H, m, Hϕ).

Synthesis of 15.

Estimated yield = 90% (for the two diastereoisomers). Purification yield = 53% (for the two diastereoisomers, one of them isolated pure).

CI+MS : *m/z* 338 $[M+H]^+$ (BP) 292 $[M-OCH_2CH_3]^+$.

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.39 (3H, J_{14-13}=7.1 Hz, 14-H) 1.43 (1H, m, 3ax-H) 1.52 (1H, m, 4eq-H) 1.71 (1H, tt, 4ax-H) 1.88 (1H, tq, 3eq-H) 2.10 (1H, dm, J_{4a-5}=10.8 Hz, 4a-H) 3.78 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.6 Hz, $J_{2ax-3eq}$=2.6 Hz, 2ax-H) 4.13 (1H, dt, J_{2gem}=11.6 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.2 Hz, 2eq-H) 4.34 (2H, q, J_{13-14}=7.1, 13-H) 4.45 (1H, d, J_{10b-4a}=2.7 Hz, 10b-H) 4.80 (1H, d, J_{5-4a}=10.8 Hz, 5-H) 6.52 (1H, d, J_{7-8}=8.5 Hz, 7-H) 7.40 (5H, m, Hϕ) 7.82 (1H, dd, J_{8-7}=8.6 Hz, J_{8-10}=2.1 Hz, 8-H) 7.98 (1H, d, J_{10-8}=2.0 Hz, 10-H).

Synthesis of 19.

Estimated yield = 90% (for the two diastereoisomers). Purification yield = 4% (for the two diastereoisomers).

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.22 (3H, d, J_{16-15}=6.8 Hz, CH_3) 1.25 (3H, d, J_{17-15}=6.8 Hz, CH_3) 1.50 (1H, dm, $J_{3ax-4ax}$=14.9 Hz, 3ax-H) 1.60 (1H, m, 4eq-H) 1.69 (1H, tt, J_{4gem}=13.7 Hz, $J_{4ax-3eq}$=4.7 Hz, 4ax-H) 1.90 (1H, tm, J_{3gem}=12.1 Hz, 3eq-H) 2.12 (1H, ddm, J_{4a-5}=11.0 Hz, J_{4a-10b}=2.3 Hz, 4a-H) 2.77 (1H, h, J_{15-16} =J_{15-17}=6.8 Hz, C<u>H</u>$(CH_3)_2$) 3.77 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.6 Hz, $J_{2ax-3eq}$=2.5 Hz, 2ax-H) 4.10 (1H, s, 6-H) 4.15 (1H, dt, J_{2gem}=11.2 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.3 Hz, 2eq-H) 4.44 (1H, d, J_{10b-4a}=2.7 Hz, 10b-H) 4.80 (1H, d, J_{5-4a}=11.0 Hz, 5-H) 6.70 (1H, dd, J_{9-8}=J_{9-10}=7.6 Hz, 9-H) 7.10 (1H, dd, J_{8-9}=7.7 Hz, J_{8-10}=1.4 Hz, 8-H) 7.20 (1H, dd, J_{10-9}=7.5 Hz, J_{10-8}=1.4 Hz, 10-H) 7.40 (5H, m, Hϕ).

Synthesis of 20.

Estimated yield = 85% (for the two diastereoisomers). Purification yield = 60% (for the two diastereoisomers).

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.41 (1H, dm, $J_{3ax-4ax}$=13.5 Hz, 3ax-H) 1.54 (1H, dm, J_{4gem}=14.0 Hz, 4eq-H) 1.71 (1H, tt, $J_{4ax-3ax}$=13.7 Hz, $J_{4ax-3eq}$=4.6 Hz, 4ax-H) 1.88 (1H, tq, J_{3gem}=12.8 Hz, $J_{3eq-4ax}$ = 4.3 Hz, 3eq-H) 2.17 (1H, ddm, J_{4a-5}=10.7 Hz, J_{4a-10b}=2.5 Hz, 4a-H) 3.77 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.4 Hz, $J_{2ax-3eq}$=2.5 Hz, 2ax-H) 3.84 (3H, s, OCH_3) 4.15 (1H, dt, J_{2gem}=11.2 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.4 Hz, 2eq-H) 4,40 (1H, s, 6-H) 4.48 (1H, d, J_{10b-4a}=2.8 Hz, 10b-H) 4.74 (1H, d, J_{5-4a}=10.8 Hz, 5-H) 6.72 (1H, dd, J_{9-8}=7.9 Hz, J_{9-10}=7.2 Hz, 9-H) 6.77 (1H, dd, J_{8-9}=8.2 Hz, J_{8-10}=1.9 Hz, 8-H) 6.94 (1H, dd, J_{10-9}=7.1 Hz, J_{10-8}=1.7 Hz, 10-H) 7.43 (5H, m, Hϕ).

Synthesis of 21.

Estimated yield = 60% (for the two diastereoisomers). Purification yield = 40% (for one diastereoisomer).

CI+MS : *m/z* 300 $[M+H]^+$ (BP).

Trans diastereoisomer : ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.43 (1H, m, 3ax-H) 1.57 (1H, dm, J_{4gem}=14.0 Hz, 4eq-H) 1.71 (1H, tt, J_{4gem}=13.7 Hz, $J_{4ax-3eq}$=4.6 Hz, 4ax-H) 1.90 (1H, tq, J_{3gem}=11.6 Hz, $J_{3eq-4ax}$=4.4 Hz, 3eq-H) 2.13 (1H, ddm, J_{4a-5}=10.9 Hz, J_{4a-10b}=2.6 Hz, 4a-H) 3.76 (1H, dt, J_{2gem}=$J_{2ax-3ax}$=11.4 Hz, $J_{2ax-3eq}$=2.6 Hz, 2ax-H) 4.13 (1H, dt, J_{2gem}=11.2 Hz, $J_{2eq-3eq}$=$J_{2eq-3ax}$=2.2 Hz, 2eq-H) 4.44 (1H, d, J_{10b-4a}=2.8 Hz, 10b-H) 4.67 (1H, s, 6-H) 4.78 (1H, d, J_{5-4a}=10.7 Hz, 5-H) 6.67 (1H, dd, J_{9-8}=J_{9-10}=7.8 Hz, 9-H) 7.19 (1H, dd, J_{8-9}=7.6 Hz, J_{8-10}=1.4 Hz, 8-H) 7.23 (1H, dd, J_{10-9}=7.9 Hz, J_{10-8}=1.5 Hz, 10-H) 7.44 (5H, m, Hϕ).

Analysis of 22.

Purification yield = 9% (for the two diastereoisomers, one of them isolated pure).

APCI+ : *m/z* 374 $[M+H]^+$ 356 $[M-OH]^+$ 313 $[M-DHP-OH]^+$ (BP).

^{1}H NMR (300 MHz, CD_3CN) : δ 1,16 (1H, m, C<u>H</u>$_2$CH$_2$O) 1.57 (2H, m, C<u>H</u>$_2$CH$_2$CH$_2$O) 1.75 (1H, m, C<u>H</u>$_2$CH$_2$O) 2.11 (1H, m, C<u>H</u>CHOH) 3.48 (1H, m, C<u>H</u>$_2$O) 3.89 (1H, m, C<u>H</u>$_2$O) 4.28 (1H, d, J_{HNCH}=3.0 Hz, N<u>H</u>) 4.66 (1H, m, C<u>H</u>OH) 5.10 (1H, m, C<u>H</u>NH) 6.60 (1H, b, O<u>H</u>) 6.61 (2H, d, J=9.3 Hz, Cϕ) 7.61 (2H, d, J=8.8 Hz, Cϕ) 7.96 (2H, d, J=9.4 Hz, Cϕ) 8.19 (2H, d, J=8.9 Hz, Cϕ).

^{13}C NMR (300 MHz, CD_3CN) : δ 21.86 (<u>C</u>H$_2$CH$_2$O) 25.66 (<u>C</u>H$_2$CH$_2$CH$_2$O) 45.30 (<u>C</u>HCHOH) 58.70 (<u>C</u>H$_2$O) 59.04 (<u>C</u>HOH) 90.62 (<u>C</u>HNH) 111.94 (Cϕ) 124.03 (Cϕ) 126.37 (Cϕ) 128.68 (Cϕ).

Results of the qualification of aldehydes.

Various substituants of aromatic aldehydes have been tested. *Ortho*, *meta* or *para* halogens (F, Cl, or Br) were well tolerated. It was the same with alkyl, biphenyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy and tetrafluoroethoxy groups in any position. Electron withdrawing substituants (nitro, cyano, esters) gave tetrahydroquinolines with high conversions, and naphtaldehydes too. Heterocycles as thiophenecarboxaldehydes, furaldehydes and 2-pyridinecarboxaldehydes were also selected for the library. However, 3 or 4-pyridinecarboxaldehydes, some other heterocycles (indole, pyrazole or pyrrolecarboxaldehydes) and electron enriched benzaldehydes did not react or gave poor conversions.

Results of the qualification of anilines.

Several aromatic anilines have been submitted to qualification. For stereochemical reasons, *meta* substituants were selected only if the aniline was symetrical or *ortho* substituted. Alkyl and phenyl groups at any position were selected, except *tert*-butyl groups in *ortho* position. Naphtylamines were also selected. *Ortho* methoxy and *ortho* thioether groups favoured the reaction. *Para* substituants as bromine,

sulfonamide or amide groups gave good results. Substituants as nitro, cyano, trifluoromethyl, trifluoromethoxy, sulfonamide or chloro groups gave good conversions but favoured the side reaction described in the article.

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