

## University of Groningen

### Enantioselective synthesis of almorexant via iridium-catalysed intramolecular allylic amidation

Fananas Mastral, Martin; Teichert, Johannes F.; Fernandez-Salas, Jose Antonio; Heijnen, Dorus; Feringa, Ben L.

*Published in:*  
Organic & Biomolecular Chemistry

*DOI:*  
[10.1039/c3ob40655e](https://doi.org/10.1039/c3ob40655e)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2013

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Fananas Mastral, M., Teichert, J. F., Fernandez-Salas, J. A., Heijnen, D., & Feringa, B. L. (2013). Enantioselective synthesis of almorexant via iridium-catalysed intramolecular allylic amidation. *Organic & Biomolecular Chemistry*, 11(27), 4521-4525. <https://doi.org/10.1039/c3ob40655e>

**Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

**Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

Enantioselective synthesis of almorexant *via* iridium-catalysed intramolecular allylic amidation†Cite this: *Org. Biomol. Chem.*, 2013, **11**, 4521

Martín Fañanás-Mastral,\* Johannes F. Teichert, José Antonio Fernández-Salas, Dorus Heijnen and Ben L. Feringa\*

Received 3rd April 2013,  
Accepted 17th May 2013

DOI: 10.1039/c3ob40655e

www.rsc.org/obc

An enantioselective synthesis of almorexant, a potent antagonist of human orexin receptors, is presented. The chiral tetrahydroisoquinoline core structure was prepared *via* iridium-catalysed asymmetric intramolecular allylic amidation. Further key catalytic steps of the synthesis include an oxidative Heck reaction at room temperature and a hydrazine-mediated organocatalysed reduction.

## Introduction

Almorexant (**1**)<sup>1</sup> (Fig. 1) is a potent non-peptide antagonist of human orexin receptors which plays an important role in controlling the sleep-wake cycle and related hypothalamic functions.<sup>2</sup> Developed by Actelion Pharmaceuticals,<sup>3</sup> it has been shown to significantly decrease wakefulness in rats, dogs and humans.<sup>4</sup>

Almorexant features a chiral C1-substituted tetrahydroisoquinoline core next to a chiral  $\alpha$ -phenyl-substituted amide. The published enantioselective route<sup>3</sup> relies on a Bischler-Napieralski cyclization followed by Noyori's ruthenium-catalysed asymmetric transfer hydrogenation<sup>5</sup> of the corresponding 3,4-dihydroisoquinoline. Later, this second step was improved by a hydrogenation reaction employing an Ir/TaniaPhos catalyst (Scheme 1a).<sup>6</sup>

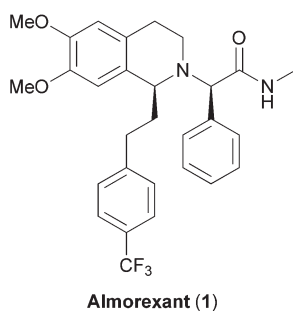
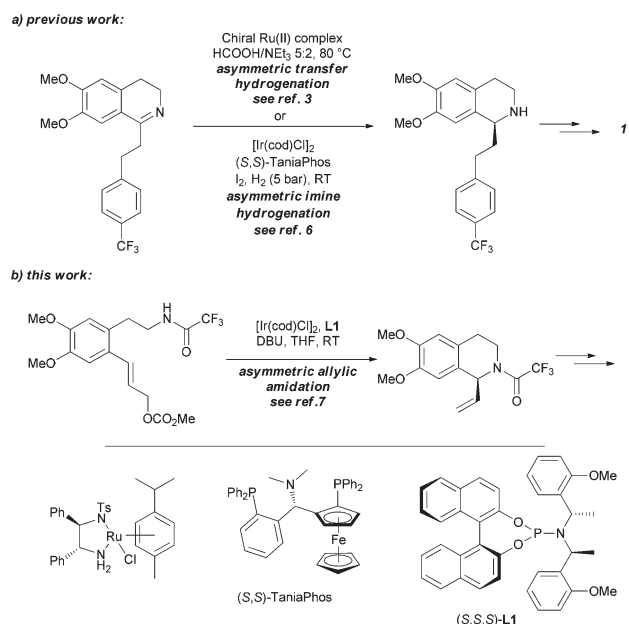


Fig. 1 Almorexant.

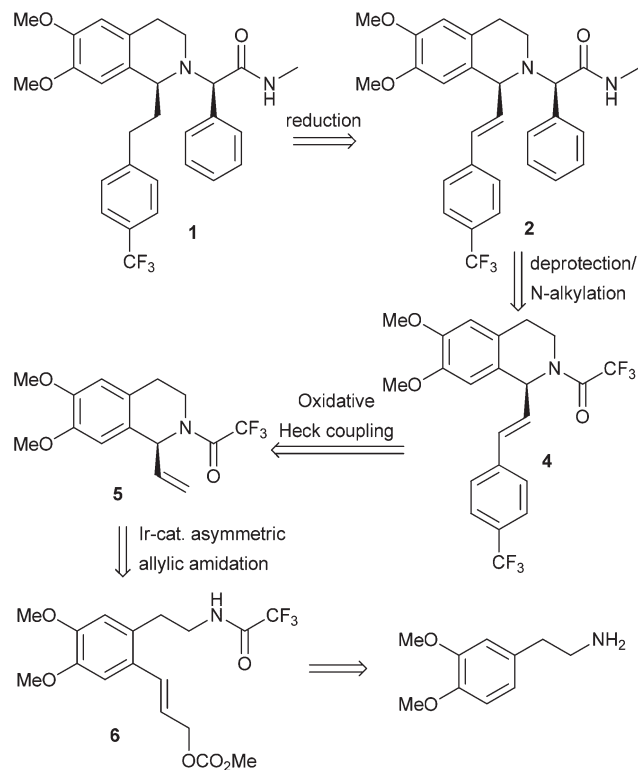
Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands. E-mail: b.l.feringa@rug.nl, m.fananas.mastral@rug.nl; Fax: +31 50 363 4296; Tel: +31 50 363 4278

† Electronic supplementary information (ESI) available: NMR spectra of all products. See DOI: 10.1039/c3ob40655e

Scheme 1 Key enantioselective steps for the synthesis of almorexant **1**.

We recently described a new catalytic enantioselective approach towards chiral 1-vinyltetrahydroisoquinolines and other chiral *N*-heterocycles based on an iridium-catalysed intramolecular asymmetric allylic amidation.<sup>7</sup> We envisioned that this protocol could be applied to the synthesis of the key chiral tetrahydroisoquinoline core of almorexant (Scheme 1b).

Our retrosynthetic analysis is depicted in Scheme 2. Compound **1** could be obtained by reduction of the double bond present in intermediate **2**, ideally without racemisation of the benzylic stereocentres. This reduction was expected to be cumbersome due to the facile racemisation of this kind of structure.<sup>8</sup> Compound **2** could be prepared by a sequential *N*-deprotection and *N*-alkylation with (*S*)-mandelate derivative



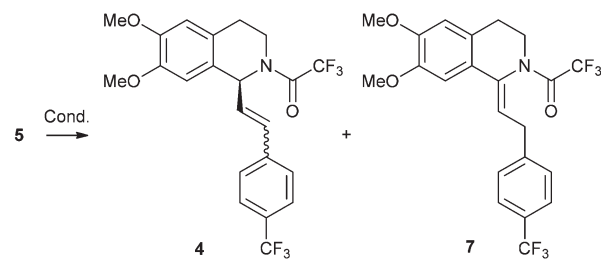
**Scheme 2** Retrosynthetic analysis of almoxerant.

3 (see Scheme 4). Key intermediate **4** could be obtained *via* an oxidative Heck type coupling reaction between (4-(trifluoromethyl)phenyl)boronic acid and chiral tetrahydroisoquinoline **5**, a key chiral intermediate which is accessible with excellent enantioselectivity through the iridium-catalysed intramolecular asymmetric allylic amidation of **6**.<sup>7</sup>

## Results and discussion

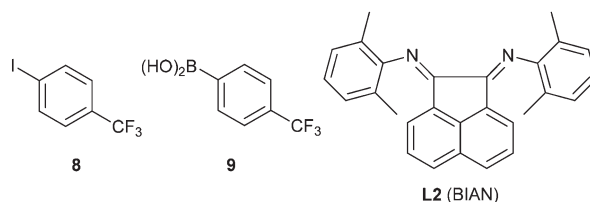
The synthetic route started with commercially available 3,4-dimethoxyphenethylamine which was converted into allyl carbonate **6** as described recently.<sup>7</sup> Iridium-catalysed intramolecular asymmetric allylic amidation afforded 1-vinyltetrahydroisoquinoline **5** in 97% yield with 95% ee, according to our previously reported procedure.<sup>7</sup> We then tried to install the (trifluoromethyl)phenyl moiety by cross-metathesis<sup>9</sup> between **5** and 4-trifluoromethyl styrene. However, all attempts using different ruthenium catalysts under different conditions failed. The fact that only homocoupled styrene and starting material were found in the reaction mixture is indicative that the reactivity of the terminal olefin moiety of **5** is relatively low. The same low reactivity was found when we attempted the hydroboration of **5** in order to perform a subsequent Suzuki coupling.<sup>10</sup>

The synthesis of compound **4** could however be achieved by employing a Heck reaction. The reaction between **5** and 1-iodo-4-(trifluoromethyl)benzene under the classical Heck



	Conditions	4:7	Yield (%) <sup>a</sup>
A	<b>8</b> (2 equiv), Pd(OAc) <sub>2</sub> 10 mol%, PPh <sub>3</sub> 20 mol%, NaOAc (4 equiv), NBu <sub>4</sub> Br (10 equiv), DMF, 100 °C, 16 h	2:1	77 <sup>b</sup>
B	<b>9</b> (1.5 equiv), Pd(OAc) <sub>2</sub> 5 mol%, <b>L2</b> 7 mol%, O <sub>2</sub> (1 atm), MeOH/H <sub>2</sub> O 9:1, RT, 16 h	1:0	88

<sup>a</sup>Isolated yield. <sup>b</sup>Combined yield.

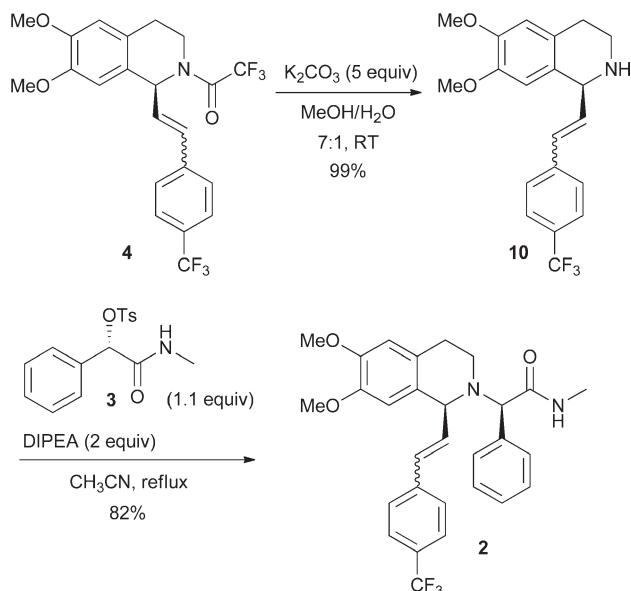


**Scheme 3** Heck vs. oxidative Heck reaction of **6**.

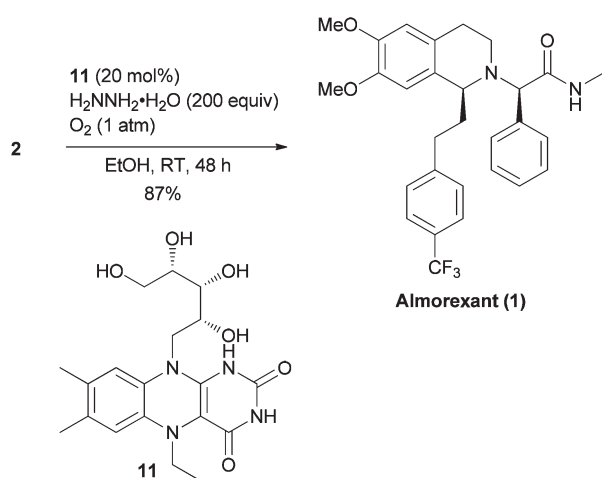
conditions<sup>11</sup> afforded a 2:1 mixture of compound **4** and the isomerized enamide **7** (Scheme 3). The high temperature required for this transformation might facilitate the isomerization possibly promoted by a palladium hydride species formed during the reaction. This problem in regioselectivity was overcome by the use of the milder Pd/BIAN catalysed oxidative Heck reaction,<sup>12</sup> developed in our laboratories,<sup>13</sup> which takes place at room temperature. Thus, reaction between tetrahydroisoquinoline **5** and (4-(trifluoromethyl)phenyl)boronic acid under these conditions afforded compound **4** as the only product of the reaction (*E/Z* 5:1) in 88% yield (Scheme 3).

Once the (trifluoromethyl)phenyl moiety was introduced, the trifluoroacetamide group was removed by treatment with K<sub>2</sub>CO<sub>3</sub> in MeOH–H<sub>2</sub>O<sup>7</sup> and the resulting secondary amine was alkylated in very good yield using enantiomerically pure (*S*)-mandelate derivative **3**<sup>3</sup> (Scheme 4).

The final step to accomplish the synthesis of almoxerant **1** relied on the reduction of compound **2**, which carries a stereogenic centre adjacent to the double bond. These and related structures often show isomerization of the double bond to an in-conjugation position with the tetrahydroisoquinoline aromatic group and thus loss of the stereogenic centre, when they are subjected to transition metal-catalysed hydrogenations.<sup>8</sup> Taking this into account, we decided to use the recently reported olefin reduction employing a riboflavin-based organo-catalyst and hydrazine in air which precludes any isomerisation (epimerisation).<sup>14,15</sup> Thus, reduction of **2** employing 20 mol% of riboflavin **11** and an excess of hydrazine gave rise



Scheme 4 N-Deprotection–N-alkylation sequence to **2**.



Scheme 5 Riboflavin-based organocatalysed reduction of **2**.

to almorexant **1** in excellent yield as a single enantiomer without any epimerisation (Scheme 5). Spectral data of **1** were identical to those previously reported.<sup>3</sup>

## Conclusions

In summary, we have presented a concise enantioselective synthesis of almorexant, a potent antagonist of human orexin receptors. Key steps are an iridium-catalysed intramolecular asymmetric allylic amidation, a catalytic oxidative Heck reaction under ambient conditions and a hydrazine-mediated riboflavin-catalysed reduction. The chiral tetrahydroisoquinoline starting material of known absolute configuration was readily accessible by iridium-catalysed intramolecular allylic amidation.

## Experimental

### General procedures

Chromatography: Merck silica gel type 9385 230–400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890; MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or an LTQ Orbitrap XL (ESI+). <sup>1</sup>H and <sup>13</sup>C NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using CDCl<sub>3</sub> as a solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl<sub>3</sub>: δ 7.26 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Carbon assignments are based on APT <sup>13</sup>C NMR experiments. Optical rotations were measured on a Schmidt+Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g per 100 mL). Solvents were used as received. [Ir(COD)Cl]<sub>2</sub> was purchased from Strem Chemicals, Inc. Hydrazine monohydrate, DBU, compounds **8** and **9**, and Pd(OAc)<sub>2</sub> were purchased from Aldrich, and used without further purification. Ligands **L1**<sup>16</sup> and **L2**<sup>13</sup> were prepared as reported in the literature.

(*E*)-3-(4,5-Dimethoxy-2-(2-(2,2,2-trifluoroacetamido)ethyl)-phenyl)allyl methyl carbonate **7** was synthesized from commercially available 3,4-dimethoxyphenethylamine according to our previously reported procedure.<sup>7</sup>

### (*S*)-1-(6,7-Dimethoxy-1-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone (**5**)<sup>7</sup>

[Ir(COD)Cl]<sub>2</sub> (2.5 mol%) and **L2** (5.0 mol%) were dissolved in dry THF (1.0 mL per 0.2 mmol) under an N<sub>2</sub> atmosphere. Then, DBU (1 equiv.) was added and the reaction mixture was heated at 50 °C for 30 min. Then, it was brought to room temperature and **6** (1 equiv.) was added. The reaction mixture was stirred until TLC showed full conversion. All volatiles were removed under reduced pressure to yield the crude product. Purification by column chromatography (SiO<sub>2</sub>, pentane–EtOAc 3 : 1) afforded **5** in 97% yield with 95% ee as a colourless oil as a mixture of two conformers in a 3.6 : 1 ratio (determined by <sup>1</sup>H NMR at 20 °C). Major conformer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.60 (s, 1H), 6.58 (s, 1H), 6.00–5.91 (m, 2H), 5.30 (dd, *J* = 9.9, 0.8 Hz, 1H), 5.12 (dd, *J* = 15.5, 0.8 Hz, 1H), 4.03–3.98 (m, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.53 (ddd, *J* = 13.8, 12.1, 3.9 Hz, 1H), 3.00–2.90 (m, 1H), 2.76–2.68 (m, 1H major). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 155.6 (q, *J* = 35.8 Hz), 148.3, 147.8, 135.6, 125.3, 124.7, 118.6, 116.8 (q, *J* = 287.9 Hz), 111.1, 110.6, 56.0, 55.9, 55.5, 40.0, 28.7. <sup>19</sup>F NMR: (376 MHz, CDCl<sub>3</sub>) δ = –69.4. HR-MS (APCI+, *m/z*): calculated for C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>3</sub> [M + H<sup>+</sup>]: 316.1155, found: 316.1140. [α]<sub>D</sub><sup>20</sup> = +168.3 (*c* = 0.85 in CHCl<sub>3</sub>). Enantiomeric excess was determined by chiral HPLC (Chiralpak OJ-H: *n*-heptane–2-propanol 90 : 10, 40 °C, 210 nm), retention times: 19.7 min (*S*), 24.7 min (*R*).

**(S,E)-1-(6,7-Dimethoxy-1-(4-(trifluoromethyl)styryl)-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (4)**

To a stirred solution of Pd(OAc)<sub>2</sub> (5 mol%) and BIAN (L2) (7 mol%) in a 9 : 1 mixture MeOH–H<sub>2</sub>O (2 mL per 1 mmol), (S)-1-(6,7-dimethoxy-1-vinyl-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone **5** (1 equiv.) and (4-(trifluoromethyl)phenyl)boronic acid **9** (3 equiv.) were added at room temperature. An oxygen balloon was fitted to the reaction vessel, and the reaction mixture was stirred at room temperature overnight. After TLC analysis showed completion of the reaction, all volatiles were removed under reduced pressure to afford the crude product. Purification by flash column chromatography on silica gel afforded the pure product **4** in 88% yield as a colourless oil and as a mixture of two conformers in a 4.5 : 1 ratio (determined by <sup>1</sup>H NMR at 20 °C). *Major conformer*: <sup>1</sup>H NMR (201 MHz, CDCl<sub>3</sub>) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 3H), 6.58 (s, 1H), 6.56 (s, 1H), 6.44–6.25 (m, 2H), 6.06 (d, *J* = 5.1 Hz, 1H), 4.08–3.90 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.65–3.43 (m, 1H), 3.06–2.83 (m, 1H), 2.80–2.62 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 155.8 (q, *J* = 36.4 Hz) 148.6, 148.1, 139.4, 132.6, 129.9 (q, *J* = 32.6 Hz), 129.6, 126.9 (2C), 125.5 (q, *J* = 3.7 Hz, 2C), 125.4, 124.5, 111.2, 110.6, 56.1, 55.9, 55.1, 29.7, 28.7. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –62.6, –69.3.

**(S)-6,7-Dimethoxy-1-(4-(trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline (10)**

To a solution of **4** (1 equiv.) in MeOH–H<sub>2</sub>O (7 : 1), K<sub>2</sub>CO<sub>3</sub> (3 equiv.) was added and the reaction mixture was stirred for 16 h. Volatiles were removed under reduced pressure, and the resulting mixture was diluted in water (10 mL) and washed with ethyl-acetate (3 × 5 mL). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure, to yield the product **10** as a colourless solid (99% yield) as a 5 : 1 mixture of *E/Z* isomers. Compound **10** was used in the next step without further purification. *E* isomer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.56 (s, 1H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.50 (s, 1H), 6.37 (dd, *J* = 15.8, 7.8 Hz, 1H), 4.57 (d, *J* = 7.8 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.24–3.16 (m, 1H), 3.04–2.97 (m, 1H), 2.82–2.70 (m, 2H).

**(R)-2-((S)-6,7-Dimethoxy-1-(4-(trifluoromethyl)styryl)-3,4-dihydroisoquinolin-2(1H)-yl)-N-methyl-2-phenylacetamide (2)**

To a solution of **10** (1 equiv.) and DIPEA (2 equiv.) in acetonitrile, (S)-2-(methylamino)-2-oxo-1-phenylethyl 4-methylbenzenesulfonate (**3**) (1.1 equiv.) was added. The reaction mixture was stirred at reflux overnight. When the reaction was judged complete using TLC analysis, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with sodium carbonate. The organic layer was dried using Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (AcOEt–pentane 2 : 1) to yield **2** as a colourless oil (82% yield). *E* isomer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H),

7.34–7.29 (m, 5H), 6.91 (q, *J* = 4.9 Hz, 1H), 6.64 (s, 1H), 6.50 (dd, *J* = 15.9, 7.1 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.37 (s, 1H), 4.42 (s, 1H), 4.40 (d, *J* = 7.1 Hz, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.07–2.98 (m, 2H), 2.91–2.85 (m, 1H), 2.88 (d, *J* = 4.9 Hz, 3H), 2.61–2.55 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 172.0, 148.2, 147.3, 140.1, 137.3, 132.8, 131.8, 129.5 (q, *J* = 32.2 Hz), 128.7 (2C), 128.5 (2C), 128.2, 126.8, 126.7 (2C), 126.5, 125.5 (q, *J* = 3.8 Hz, 2C), 124.1 (q, *J* = 271.9 Hz), 111.4, 111.2, 70.6, 61.3, 56.0, 55.9, 41.4, 26.2, 26.1. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –62.5. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –16.0 (*c* = 0.5, CHCl<sub>3</sub>).

**(R)-2-((S)-6,7-Dimethoxy-1-(4-(trifluoromethyl)phenethyl)-3,4-dihydroisoquinolin-2(1H)-yl)-N-methyl-2-phenylacetamide (almorexant, 1)**

To a solution of **2** (0.012 mmol, 1 equiv.) in EtOH (1 mL), an atmosphere of oxygen was applied (balloon, 1 atm). A solution of the riboflavin catalyst **11** (0.0024 mmol, 0.2 equiv.) in EtOH (0.2 mL) was added. Then hydrazine hydrate (2.4 mmol, 200 equiv.) was added dropwise and the mixture was stirred at room temperature during 48 h. CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added and the mixture was washed with water (3 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 2 mL), and the organic layers were combined and dried over Na<sub>2</sub>SO<sub>4</sub>. All volatiles were removed *in vacuo* to yield the crude product which was purified by column chromatography on silica gel (EtOAc–pentane 2 : 1) to afford pure almorexant as a single stereoisomer as a colourless oil (87% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52 (d, *J* = 8.0 Hz, 3H), 7.28–7.23 (m, 5H), 7.14 (d, *J* = 8.0, 2H), 6.84 (q, *J* = 4.8 Hz, 1H), 6.58 (s, 1H), 6.04 (s, 1H), 4.25 (s, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.40–3.30 (m, 2H), 3.16–3.04 (m, 2H), 2.98–2.85 (m, 1H), 2.88 (d, *J* = 4.9, 3H), 2.71–2.61 (m, 1H), 2.51–2.42 (m, 1H), 2.18–2.06 (m, 1H), 1.85–1.75 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 172.4, 147.8, 147.3, 146.3, 137.1, 129.1, 128.7, 128.6, 128.5, 128.3, 128.1 (q, *J* = 32.1 Hz), 125.3 (q, *J* = 4.0 Hz, 2C), 125.0, 124.2 (q, *J* = 271.2 Hz), 111.4, 110.1, 70.1, 57.1, 55.9, 55.8, 40.7, 37.7, 33.4, 26.1, 21.8. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ –62.3. HRMS (ESI+, *m/z*): calcd for C<sub>29</sub>H<sub>32</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 513.23595; found: 513.23539. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –27.6 (*c* = 0.21, CHCl<sub>3</sub>). Chiral HPLC analysis: Chiralcel OD column, *n*-heptane–i-PrOH 95 : 5, 40 °C, 210 nm, retention time: 22.5 min.

**Acknowledgements**

We thank the Netherlands Organization for Scientific Research (NWO-CW) and the National Research School Catalysis (NRSC-C) for financial support.

**Notes and references**

- 1 R. T. Owen, R. Castañer, J. Bolós and C. Estivill, *Drugs Future*, 2009, **34**, 5.
- 2 T. Sakurai, A. Amemiya, M. Ishii, I. Matsuzaki, R. M. Chemelli, H. Tanaka, S. C. Williams, J. A. Richardson, G. P. Kozlowski, S. Wilson, J. R. S. Arch,



- R. E. Buckingham, A. C. Haynes, S. A. Carr, R. S. Annan, D. E. McNulty, W.-S. Liu, J. A. Terrett, N. A. Elshourbagy, D. J. Bergsma and M. Yanagisawa, *Cell*, 1998, **92**, 573.
- 3 T. Weller, R. Koberstein, H. Aissaoui, M. Clozel and W. Fischli, *WO*, 2005/118548, 2005.
- 4 C. Brisbare-Roch, J. Dingemanse, R. Koberstein, P. Hoever, H. Aissaoui, S. Flores, C. Mueller, O. Nayler, J. van Gerven, S. L. de Haas, P. Hess, C. Qiu, S. Buchmann, M. Scherz, T. Weller, W. Fischli, M. Clozel and F. Jenck, *Nat. Med.*, 2007, **13**, 150.
- 5 N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916.
- 6 M. A. H. de Vries, D. Domin, M. Helms, C. Imboden, R. Koberstein, Z. Nazir, W. Skranc, M. Stanek, W. Tschibull and M. G. K. Verzijl, *WO*, 2009/083903, 2009.
- 7 J. F. Teichert, M. Fañanás-Mastral and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2011, **50**, 688.
- 8 For some representative examples, see: (a) K. Mori, T. Ohtaki, H. Ohruji, D. R. Berkebile and D. A. Carlson, *Eur. J. Org. Chem.*, 2004, 1089; (b) A. N. Parvulescu, P. A. Jacobs and D. E. de Vos, *Chem.-Eur. J.*, 2007, **13**, 2034.
- 9 (a) S. J. Connon and S. Blechert, *Angew. Chem., Int. Ed.*, 2003, **42**, 1900; (b) A. H. Hoveyda and A. R. Zhugralin, *Nature*, 2007, **450**, 243; (c) C. Samojlowicz, M. Bieniek and K. Grela, *Chem. Rev.*, 2009, **109**, 3708; (d) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746.
- 10 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
- 11 (a) R. F. Heck, *Acc. Chem. Res.*, 1979, **12**, 146; (b) S. Bräse and A. de Meijere, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, ch. 5, vol. 1.
- 12 For a recent review on the oxidative Heck reaction, see: B. Karimi, H. Behzadnia, D. Elhamifar, P. F. Akhavan, F. K. Esfahani and A. Zamani, *Synthesis*, 2010, 1399.
- 13 A. L. Gottumukkala, J. F. Teichert, D. Heijnen, N. Eisink, S. van Dijk, C. Ferrer, A. van den Hoogenband and A. J. Minnaard, *J. Org. Chem.*, 2011, **76**, 3498.
- 14 (a) C. Smit, M. W. Fraaije and A. J. Minnaard, *J. Org. Chem.*, 2008, **73**, 9482; (b) J. F. Teichert, T. den Hartog, M. Hanstein, C. Smit, B. ter Horst, V. Hernandez-Olmos, B. L. Feringa and A. J. Minnaard, *ACS Catal.*, 2011, **1**, 309.
- 15 For other different diimide based reductions, see: (a) D. J. Pasto and R. T. Taylor, *Org. React.*, 1991, **40**, 91; (b) E. Montenegro, B. Gabler, G. Paradies, M. Seemann and G. Helmchen, *Angew. Chem., Int. Ed.*, 2003, **42**, 2419; (c) C. Welter, R. M. Moreno, S. Streiff and G. Helmchen, *Org. Biomol. Chem.*, 2005, **3**, 3266.
- 16 K. Tissot-Croset, D. Polet, S. Gille, C. Hawner and A. Alexakis, *Synthesis*, 2004, 2586.