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Enantioselective Synthesis of Ozanimod, the Active Pharmaceutical Ingredient of a New Drug for Multiple Sclerosis

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This paper is dedicated to Professor Franco Cozzi on his 70th Birthday.

We report here a short enantioselective synthesis of Ozanimod, a potent modulator of the enzyme Sphingosine-1-phosphate receptor ($S1P_R$), recently approved by FDA and EMA for the treatment of relapsing-remitting multiple sclerosis. Amongst different synthetic approaches explored, we achieved the best result introducing the stereogenic centre in the last step through imine asymmetric transfer hydrogenation (ATH) using Wills' catalysts. Besides the reduced numbers of enantiomeric purity controls required, this process culminates in an exceptionally high enantioselective reductive amination obtained with commercially available tethered Ru catalysts. Starting from commercially available 4-cyano-indanone, enantiomerically pure Ozanimod was obtained in 5 steps in 62% overall yield and 99% ee.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS), characterized by demyelination and variable degrees of axonal loss. It is one of the most common causes of non-traumatic neurological disability in young adults.[1] Because of the obscure etiology of MS, finding a cure has been challenging so far.[2] With over 2.5 million patients worldwide, MS is subdivided in almost 4 sub-types, relapsing-remitting multiple sclerosis (RRMS) being the most populate with approx. 85% of all cases.[3]

The disease is characterized by several neurological dysfunctions dominated by the trafficking and accumulation of lymphocytes T and B in inflamed tissues. Sphingosine-1-phosphate (S1P) is a signaling molecule involved in a wide range of immunological, cardiovascular and neurological processes, such as the control of lymphocyte trafficking and regulating heart rate, rhythm and vascular tone. These activities are mediated through interaction with the sphingosine-1-phosphate receptor ($S1P_R$), a G-coupled receptor expressed by dendritic cells, lymphocytes, cardiomyocytes, and vascular endothelial cells.[4] S1PR has five receptor subtypes, ubiquitous expressed in multiple organs and systems, and thus involved in several immune-mediated disorders, including RRMS.[5] Pharmacological modulation of S1P receptors can be considered a suitable therapy for RRMS therapeutic intervention. In early 2020, FDA and EMA approved a potent S1P modulator named Ozanimod (brand name ZEPOSIA), to treat adult patients with active RRMS disease. Ozanimod is also under phase III clinical trials for treatment of ulcerative colitis and Crohn's disease.[6]

Yet, despite its importance, in the scientific literature, there is no description of Ozanimod synthesis, most of them located in patent's publications.[7–12] The most representative retrosynthetic approach is outlined in Scheme 1. The oxadiazole central ring is broken into two fragments (**A** and **B**) and the chiral 1-amino-indane fragment **B** is always obtained from the simplest 4-cyano-1-aminoindane (*S*)-**2** (Scheme 1a).[9]

The standard synthesis of this key intermediate depends on a 4-step process starting from 4-cyano indanone (**3**) that is converted into the corresponding *tert*-butylsulfinyl imine **5** through condensation with chiral auxiliary sulfinamide **4**. Diastereoselective reduction at −78 °C with $NaBH_4$, followed by acid hydrolysis of the auxiliary, gives the key amine in good yields and good enantiomeric purity (*S*)-**2** (Scheme 1b). Further elaboration of the ethanolamine arm and oxadiazole condensation gave the final product **1** in an 8-steps overall synthetic scheme. To our knowledge, the best complete synthesis of Ozanimod based on the Ellmann's chiral auxiliary gave the final product in 23% overall yield over 8 steps.[10] The process relies on the use of low temperature requiring cryogenic liquids, use of dangerous solvents and extensive application of protective groups. Recently, Gröger and co-workers described an alternative route to amine (*S*)-**2** based on enzymatic catalysis.[13] Transaminase derived from *Vibrio fluvialis* (VF-TA) worked on carboxymethyl indanone (**7**), in the presence of L-Ala as amine donor, to give the corresponding amino indanone carboxylate

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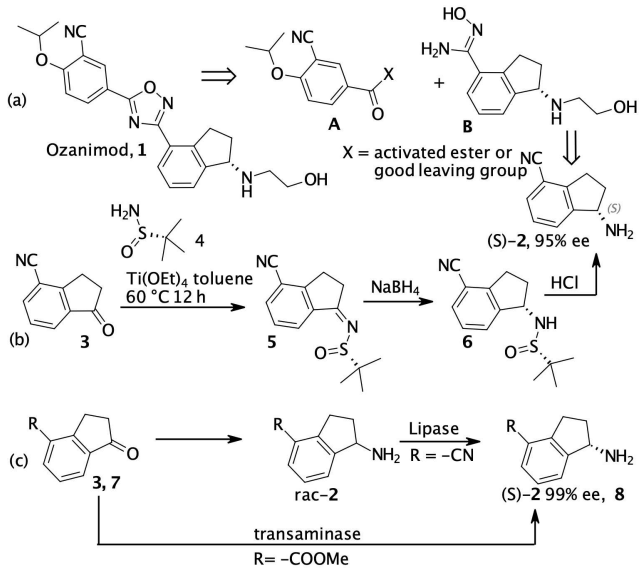


Scheme 1. **(a)** Common retrosynthetic approach to Ozanimod. **(b)** Synthesis of key intermediate (*S*)-**2** reported in patents (ref. 10–12). **(c)** Enzyme catalyzed enantioselective synthesis of (*S*)-**2** (ref. 13). (S)-**2**, rac-(**2**) and **3**: R = CN; **7** and **8**: R = −COOMe.

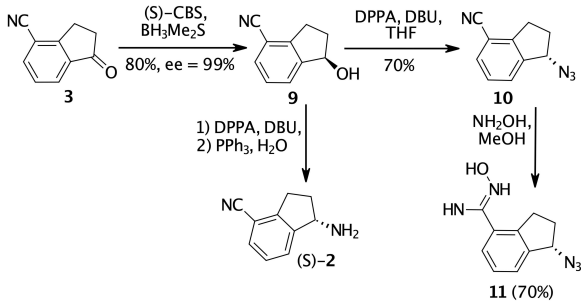
(**8**) in good conversion and ee. Alternatively, acylation of the racemic amine *rac*-(**2**) with lipase B from *Candida antarctica* (CAL–B) and isopropyl methoxy acetate as the acyl donor, gave amine (*S*)-**2** with modest overall yield 19%) although with excellent ee (99%).

Following our interest in optimizing the synthesis of API for important medicines,[14–16] we tried to design a new approach to Ozanimod **1** based on catalytic introduction of the stereogenic center, reduction of unrequired steps and limited use of protective groups and dangerous solvents.

Results and Discussion

Due to the relatively simple structure, the general retrosynthesis was not altered, and the chiral amine (in azide form) was our first key intermediate. Due to the "phenone" nature of indanone **3**, it was reduced with (S)-(+)-2-methyl-CBS-oxazaborolidine, (*S*)-CBS (10%), and stoichiometric $BH_3{\cdot}SMe_2$ in DCM at −20 °C.[17] With this procedure, we obtained the alcohol **9** in good yield and almost complete control of the configuration of the newly formed stereogenic center after crystallization from ethyl acetate/hexane (Scheme 2).

The absolute configuration was established transforming the alcohol **9** into amine (S)-2 through DPPA azidation, that proceeded with inversion of configuration, and in situ Staudinger reaction with PPh_3/H_2O. The product of this synthetic sequence had the same characteristic (NMR/chiral HPLC) of the amine (*S*)-**2** described in the original patent.[10] Alcohol **9** was transformed into azide **10** with DPPA and DBU in 70% yield and then hydroxylamine (free base) was added to the nitrile in refluxing ethanol to give the hydroxycarbamidoyl derivative **11**.

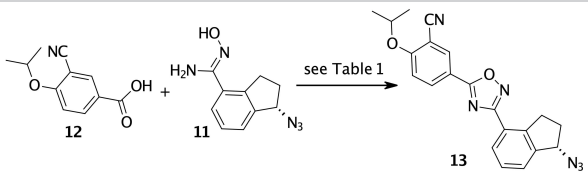


Scheme 2. First synthetic approach based on (*S*)-CBS oxaborolidine catalytic enantioselective reduction of ketone **3**. DPPA = diphenylphosphoryl azide. DBU = 1,8-Diazabicycloundec-7-ene.

Amidoximes are usually sufficiently stable compounds, and **11** was isolated after chromatography as a viscous waxy compound. A variety of different conditions were then screened for the synthesis of 1,2,4-oxadiazole ring, both for the activation of benzoic acid 11 and the aromatization towards the oxadiazole ring (Table 1).

The original cyclisation proceeded in the presence of EDC and HOBT for the activation of the carboxylate of compound **12**.[18] This is an "atom expensive" reagent to achieve oxadiazole formation, as a MW of 291.8 is waste just to remove two molecules of H_2O. At first, we tried to activate the benzoic acid **11** as acyl chloride with oxalyl chloride, followed by addition of **11** and final aromatization promoted by heating to 80 °C. Unfortunately, we observed a very poor reactivity, and most of the benzoic acid was recovered. Attempts to use, $POCl_3$ or PCl_5 to generate the acyl chloride still gave unsatisfactory results. Therefore, to avoid the use of acyl chloride, we tried a method involving the use of propyl phosphonic anhydride (T3P®), a highly reactive cyclic anhydride coupling reagent, with broad functional group tolerance and easy work-up.[19] Benzoic acid **12**, amidoxime **11** and T3P® were mixed in DMF but, after heating to 80 °C, we did not observe the formation of oxadiazole **13**. Poor results were also obtained with *i*-BuOCOCl

Table 1. Attempts to 1,2,4-oxadiazole ring formation.

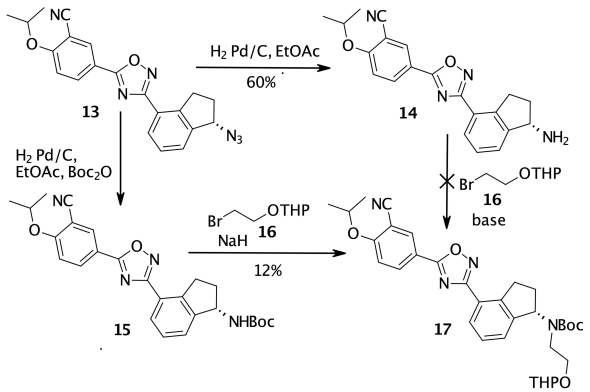


Entry	Reaction conditions[a]	13 Yield[b]
1	**12** + $(COCl)_2$, 5 h, then **11** in DMF at 80 °C.	25%
2	**12** + $POCl_3$ then **11** neat at 80 °C	12%
3	**12** + **11** + T3P in DMF at 80 °C	nd
4	**12** + CDI then **11** in DMF followed by CDI, 110 °C	49%
5	**12** + CDI then **11** in DMF followed by TBAF, 110 °C.	69%

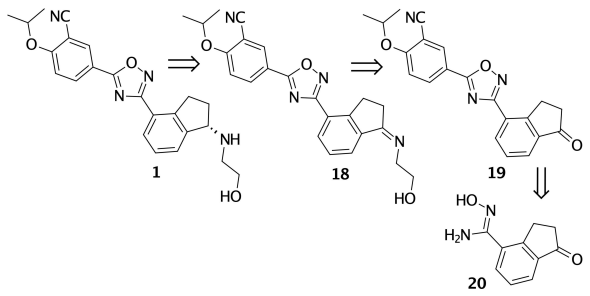
[a] Reaction conditions: Acid 12 (0.5 mmol) was mixed at 0 °C with the activation reagent (0.6 mmol) and stirred at rt for 2–8 h. **11** (0.6 mol) was added in the suitable solvent (1 mL) and the vial heated for 12 h. After cooling the solvent was evaporated and product **13** isolated by flash chromatography on silica gel. [b] Isolated yields.

of triazine based coupling agents. Thus, **12** was activated with an equivalent of CDI[20] at 0 °C and added to amidoxime **11**. After the formation of the linear intermediate (LC-MS analysis), another equivalent of CDI was added and the mixture was heated to 115 °C to promote dehydration. After aqueous workup oxadiazole **13** was isolated in 49% yield. To increase the yield, the last cyclisation step was attempted using TBAF[21] and effectively yields in compound **13** were increased to 69%. Pleased to have found a procedure more efficient than that reported in the original patent, we approached the elaboration of the lateral aminoethanol chain. The original report described the amidation with benzyloxy acetic acid and further amide reduction and deprotection,[10] another sequence that produced high amount of wastes, we thus tried to explore the direct alkylation of the amine.

The azide of **13** was reduced with catalytic hydrogenation, and on amine **14** directed alkylation with different bromoethanol derivatives was attempted but the expected product was never obtained (Scheme 3). Amine **14** was consequently protected with Boc anhydride in a one-pot reaction, with the formation of **15** in an unoptimized 60% yield. Unluckily, the use of NaH to deprotonate the NHBoc group for the further nucleophilic substitution on 2-bromoethanol THP-ether **16** gave the required compound **17** in very low yield (12%) together with a complex mixture of unknown by-products derived from the cleavage of oxadiazole ring. When other strong bases (LiHMDS, BuLi) were employed, it was evident that the oxadiazole ring was unstable in presence of such strong bases and we were never able to obtain compound **17** following these conditions (Scheme 3).



Scheme 3. Attempted Ozanimod via direct alkylation of amine **13** or its Boc derivative **15**.



Scheme 4. New retrosynthetic approach based of enantioselective reduction of ethanolamine.

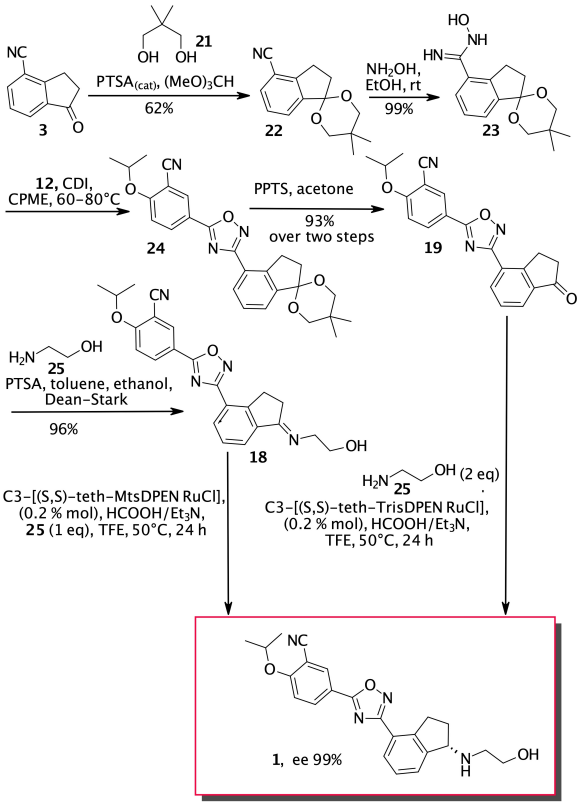
At this point, the next sequence of events in the retrosynthesis was apparent. For example, alkylation of amine (S)-**2** with bromoethanol THP ether **16** could be possible without affecting the overall number of synthetic steps of the synthesis. However, this approach might have also some drawbacks, not least the tiresome feature of carrying the stereocenter through the remaining process. We decided therefore to investigate the possibility to introduce the stereocenter in the last step through an enantioselective reduction of the imine **18** obtained from ketone **19** (Scheme 4).

Ketone **19** must be consequently synthesized and, after oxadiazole retrosynthetic cleavage, amidoxime ketone **20** became the key intermediate (Scheme 4). As the use of NH_2OH required to transform the nitrile into amidoxime is not compatible with the presence of a free carbonyl, this function must be protected. We explored two ways: the formation of an acetal or the reduction to -OH followed by reoxidation after oxadiazole synthesis. The first approach resulted the more efficient and only this one is reported here for brevity.

Commercially available ketone **3** was then submitted to different acetalysation attempts using diverse alcohols.

Amongst several trials, we chose 2,2-dimethyl-1,3-propanediol **21** that provided **22** as a solid compound, using trimethyl orthoformate as a dehydrating agent in the presence of a catalytic amount of PTSA. The optimized yield for acetalysation (62%) was the lowest of the overall process, but, being at the first step, the impact on the synthesis efficiency was not too high (Scheme 5). Acetal **22** was submitted to reaction with hydroxylamine (free base) in ethanol at rt to give amidoxime **22** in almost quantitative yield. Cyclisation to oxadiazole occurred using our previously explored procedure with CDI at 60–80 °C (Scheme 5). Optimized condition employed only 1.5 eq of CDI respect to the reagents and TBAF was not required for increase yield, as cyclisation occurred slowly at 80° (12 h) in cyclopentyl methyl ether (CPME). Without further purification, the acetal of **24** was hydrolyzed with PTSA in wet acetone to give ketone **19** in 93% yield over 2 steps.

The introduction of unprotected ethanolamine **25** on ketone **19** required a lengthy optimization of reaction conditions. Best results were obtained mixing the two reagents under acid catalysis and heating gently in benzene with contemporary evaporation of the azeotropic mixture formed (rotary evaporator or Dean-Stark apparatus). Unfortunately, the use of different solvents ((DCM, CPME, THF, EtOH) gave unsatisfactory results. Although soluble in benzene, compound **19** was insoluble in toluene, thus preventing the use of this solvent in the reaction. Finally, we found the solution using a mixture of toluene/ethanol 4/1 v/v in order to obtain a homogenous solution and prevent the formation of the diethoxy acetal. The toluene/water/ethanol azeotrope was removed using a rotary evaporator in small scale and a Dean-Stark apparatus on a larger scale. After a long optimization, imine **18** was obtained as a solid in 96%.



Scheme 5. Final 5-step enantioselective synthesis of Ozanimod.

Having the imine in hand, we explored the possibility to carry out the enantioselective hydrogenation asymmetric hydrogen transfer reaction (ATH)[22–25] a technology widely applied in industry for the asymmetric reduction of carbonyl and imine groups. Wills' ruthenium diamine tethered chiral catalyst C3-[(*R,R*)-teth-TsDPEN RuCl][24] was employed at first to establish the reaction conditions and several solvents were tested at different temperatures (Table 2). Good conversion in amine **1** was obtained at 70 °C using HCOOH/Et_3N as the hydrogen source in almost all solvents, but the best ees were obtained using MeOH (79% conv., 54% ee, entry 1, Table 2) and trifluoroethanol, TFE (91% conv., 86% ee, entry 7, Table 2). Then different tethered and untethered transfer hydrogenation catalysts were explored under these conditions. From data collected in Table 2, it is clear that better results were obtained with tethered catalysts.

With the *S,S* configuration of the catalyst, amine **1** was formed with the correct stereochemistry. This can be attributed to the higher stability of the tethered catalysts structure, less likely to undergo deactivation in the presence of the amine product. Using C3-[(*S,S*)-teth-MtsDPEN RuCl] and C3-[(*S,S*)-teth-TrisDPEN RuCl][26] 99% ee was reached, together with a good conversion (84%), although 16% of ketone **19** was formed (entries 12 and 13 in Table 2). After checking that the ketone was not present in the starting material, reaction conditions were modified, finding that a further improvement could be obtained increasing to some extent the amount of Et_3N.

Table 2. Optimization of enantioselective hydrogenation of imine **18** into amine **1**.[a]

Ent.	Catalyst	Solvent	**1**, Yield [%]	*ee* [%][b]
1	C3-[(*R,R*)-teth-TsDPEN RuCl]	MeOH	79	54 (*R*)
2	C3-[(*R,R*)-teth-TsDPEN RuCl]	2-PrOH	57	15
3	C3-[(*R,R*)-teth-TsDPEN RuCl]	THF	64	0
4	C3-[(*R,R*)-teth-TsDPEN RuCl]	MeCN	65	44
5	C3-[(*R,R*)-teth-TsDPEN RuCl]	DMF	63	12
6	C3-[(*R,R*)-teth-TsDPEN RuCl]	Toluene	73	2
7	C3-[(*R,R*)-teth-TsDPEN RuCl]	TFE	91	86 (*R*)
8	(*S,S*)-F5DPEN	TFE	53	96
9	(*S,S*)-TsDACH RuCl(p-cym)	TFE	23	10
10	(*S,S*)-MsDPEN RuCl(mesityl.)	TFE	46	90
11	C3-[(*S,S*)-teth-MsDPEN RuCl]	TFE	93	84
12	C3-[(*S,S*)-teth-MtsDPEN RuC]l	TFE	86	99 (*S*)
13	C3-[(*S,S*)-teth-TrisDPEN RuCl]	TFE	86	99 (*S*)
14	C4-[(*S,S*)-teth-MsDPEN RuCl]	TFE	89	68
15	C4-[(*S,S*)-teth-TrisDPEN RuCl]	TFE	90	89
16	C3-[(*S,S*)-teth-TrisDPEN RuCl][c]	TFE	86	99 (*S*)

[a] Reaction conditions: 50 mg of imine **18**, catalyst (2 mol%), HCO_2H/Et_3N 5:2 complex (5 equiv. respect to imine) and 1 mL solvent were added to a glass vial and the resulting mixture was stirred at 70 °C overnight. The vial was cooled and then diluted with MeOH. A 20 μL aliquot was removed and added to an HPLC vial containing MeOH (1 mL) and were analyzed by HPLC (for conditions see SI). [b] Determined via HPLC analysis, see SI. [c] 1 eq of ethanolamine added to the reaction mixture.

However, as during the reaction the amount of formic acid decreases, the corresponding increment of pH promotes the imine hydrolysis. The same problem occurred when the amount of formic acid was increased. However, the addition of 1 eq of ethanolamine to the reaction mixture had a positive effect on the reaction. In this case, almost full conversion without decrease of the ee (99% conv, 99% ee) was observed (entry 16 in Table 2).

Based on this encouraging result, we decided to explore the possibility of a direct reductive amination of ketone **19**. There are scattered examples of direct reductive amination of ketones under transfer hydrogenation conditions[27] but no general method is established. The same tethered Ru catalysts used on imine **19** were explored and, in this case, C3-[(*S,S*)-teth-TrisDPEN RuCl] proved to be the most efficient, even lower conversions were obtained, possibly a result of less favorable reaction pH or catalysts inhibition.

In order to force the reaction to completion, the HCOOH/Et_3N mixture was slowly added to the reaction mixture containing the catalyst and the reagent in TFE at 50 °C. After 24 h, the Ozanimod amine was obtained in 92% conversion and 99% ee. The dosing procedure presumably gives improved conditions for both imine formation and imine reduction, with better control of reaction pH. Ultimately, reduction of imine **19** with C3-[(*S,S*)-teth-MtsDPEN RuCl with HCOOH/Et_3N (5/2 (5 eq) plus 1 equivalent of ethanolamine, producing amine **1** in 99% yield and 99% ee, was the best possible outcome. Pure Ozanimod was isolated through the formation of the corresponding HCl salt that showed spectral data in accordance with literature.[10] The determination of ruthenium in the final product by atomic absorption spectrophotometry showed a residual Ru contents below 10 ppm.

Conclusions

In conclusion, we developed an enantioselective synthesis of the RMS drug Ozanimod in just 5 steps in 55% overall yield and 99% ee, an impressive result compared with 23% yield in 8 steps of the patented route. The key step is one of the more efficient examples of ATH enantioselective reductive amination described so far, based on commercially available ruthenium catalysts. This result reiterates that, with the correct choice of the catalyst, imine hydrogenation is still the privileged access to enantiomerically pure amines. Use of environmentally sustainable conditions without unnecessary loss of chemical materials and overall shortness are the other strength of the process. Moreover, the introduction of the stereogenic center at the end of the synthesis simplify the overall procedure reducing the analytical efforts required for complete characterization enantiomerically pure intermediates employed for the preparation of a chiral drug.

Experimental Section

(*R*)-1-Hydroxy-2,3-dihydro-1H-indene-4-carbonitrile 9. (*S*)-(+)-2-Methyl-CBS-oxazo-borolidine (3 mL of a 1 M solution in toluene, 3 mmol) and borane-dimethylsulfide (300 μL, 3 mmol) were mixed into a three-neck round-bottom flask equipped with an addition funnel under magnetic stirring and nitrogen atmosphere. The reaction was stirred at rt for 10′ and then dry DCM (50 mL) was added followed by the remaining part of borane-dimethylsulfide (5.4 mL, 59.88 mmol in total). The reaction was then cooled to −20 °C and through the addition funnel was added dropwise a solution of ketone **3** (4.70 g, 29.94 mmol) over 20′. The reaction was stirred at −20 °C for 2 h and then quenched at −20 °C with the slowly addition of water since complete evolution of gas; the resulting mixture was then warmed to room temperature and stirred for additional 30′. The phases were separated, and the aqueous phase extracted with DCM (3×30 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to provide a pale-yellow oil, that was recrystallized from EtOAc (10 mL) and hexane (50 mL). The precipitate was filtered on a Buchner funnel and washed with hexane to provide compound **9** (3.83 g, 24.1 mmol) as a white solid (yield 80%). MS (ESI) for $C_9H_{10}NNaO$ 183 $(M+Na)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J=7.6, 1H), 7.42 (d, J=7.6, 1H), 7.25 (t, J=7.6, 1H), 5.16 (t, J=6.4, 1H), 3.38 (1H, bs, OH), 3.08 (ddd, J=17.2, 8.4, 4.4, 1H), 2.85 (dt, J=16.8, 7.8 Hz, 1H) 2.46 (m, 1H), 1.91 (m, 1H), ppm [10] ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.8, 146.0, 131.3, 128.5, 127.1, 117.1, 108.5, 75.47, 34.92, 28.97 ppm.

(S)-1-Azido-N′-hydroxy-2,3-dihydro-1H-indene-4-carboximidamide 11 To a solution of alcohol **9** (0.5 g, 3.1 mmol) in THF (5 mL) and toluene (5 mL), diphenylphosphoryl azide (1.04 g, 3.8 mmol) was added at 25 °C. DBU (0.62 g, 4.1 mmol) was added, monitoring that internal temperature does not exceed 25 °C. The reaction was maintained under stirring at 25 °C until complete conversion (about 10 hours). A 20% (w/w) aqueous solution of sodium carbonate was added followed by toluene (50 mL). The phases were separated, and the organic layer was washed with water. The organic phase was evaporated under reduced pressure providing 0.57 g of crude azide **10** which was dissolved in ethanol (10 mL). Hydroxylamine hydrochloride (118 mg, 1.7 mmol) and sodium carbonate (180 mg, 1.7 mmol) were added under stirring and the mixture was refluxed for about 12 hours, then cooled to 25 °C and filtered. The filtrate was evaporated under reduced pressure and the crude purified by silica gel flash chromatography (petroleum ether: ethyl acetate 4:6 (V/V)) to provide 531 mg of the title compound (yield: 79%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (bm, 1H), 7.46 (m, 2H), 7.29 (t, J=7.2, 1H), 5.92 (bs, 1H), 4.85 (bs, 3H), 3.27 (m, 1H), 3.08 (m, 1H), 2.46 (m, 1H), 2.12 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 141.9, 131.4, 128.6, 127.2, 116.6, 108.8, 65.1, 31.4, 29.8 ppm. HRMS (ESI) calcd for $C_{10}H_{12}N_5O$ $(M+1)^+$ 218.1042; found 218.10417.

(*S*)-(1-Amino-2,3-dihydro-1H-indene-1-yl)-4-carbonitrile (*S*)-2. To a solution of alcohol **9** (0.5 g, 3.1 mmol,) in THF (5 mL) and toluene (5 mL), diphenylphosphoryl azide (0.104 g, 3.77 mmol) was added at 25 °C. DBU (0.62 g, 4.08 mmol) was added monitoring that internal temperature does not exceed 25 °C. The reaction was maintained under stirring at 25 °C until complete conversion into azide **10** (about 10 hours). Triphenyl phosphine (1.09 g, 4.15 mmol) was added and, after complete N_2 evolution (about 10 hours), water (75 mL) was added. The reaction was maintained under stirring at 50 °C until complete conversion (about 15 hours), then a 32% (w/w) aqueous solution of sodium hydroxide was added up to obtain a pH >12. The phases were separated, and the organic layer was washed with water. Formic acid and water were added up to achieve a pH between 3.5–4, then the phases were separated. The aqueous phase was washed with toluene. 2-Methyltetrahydrofuran and a 32% (w/w) aqueous solution of sodium hydroxide were added to the aqueous phase up to obtain a pH >10. The phases were separated, and the organic layer was washed with water. The organic phase was evaporated under reduced pressure and crude amine was purified by crystallization as the hemitartrate in methanol (0.76 g, 52% yield). The final product showed the same properties described in literature.[10]

(*S*)-5-(3-(1-Azido-2,3-dihydro-1H-inden-4-yl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile 13. To a solution of 3-cyano-4-isopropoxybenzoic acid **12** (132 mg, 0.64 mmol) in DMF (3 ml) maintained at 0 °C, 1,1′-carbonyldiimidazole (115 mg, 0.71 mmol) was added portionwise. The mixture was maintained under stirring at the same temperature for about 30 minutes, then a solution of **11** (140 mg, 0.64 mmol) in DMF (2 mL) was added. The mixture was maintained under stirring at 25 °C for 3 hours, then additional 1,1′ carbonyldiimidazole (115 mg, 0.71 mmol) was added. The flask was heated to 115 °and stirred 24 h at this temperature. After cooling to 25 °C, ethyl acetate (20 mL) was added. The mixture was washed with an aqueous saturated solution of $NaHCO_3$, 1 N HCl, water and brine. After drying, the organic layer was evaporated under reduced pressure and the crude purified by silica gel chromatography (petroleum ether : ethyl acetate 7:3 (V/ V), yielding 170 mg of the title compound as a colorless oil (yield: 69%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J=1.6, 1H), 8.24 (dd, J=8.8, 2.0, 1H), 8.07 (d, J=7.6, 1H), 7.48 (d, J=7.2, 1H), 7.36 (t, J=7.6, 1H), 7.06 (d, J=8.8, 1H), 4.89 (t, J=4.8, 1H), 4.77-4.71 (m, 1H), 3.31 (dddd, J=72.4, 14.4, 8.0, 5.6, 2H), 2.53-2.44 (m, 1H), 2.20-2.11 (m, 1H), 1.43 (d, J=6.0, 6H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.6, 168.2, 162.3, 143.0, 141.9, 133.5, 133.4, 128.7, 126.9, 126.7, 123.1, 116.3, 114.8, 113.2, 103.4, 72.3, 65.1, 31.7, 31.5, 21.3 ppm. HRMS (ESI) calcd for $C_{21}H_{18}N_6NaO_2$ $(M+Na)^+$ 409.1389; found 409.13882.

(*S*)-*tert*-Butyl-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-inden-1-ylcarbamate 15. Azide **13** (150 mg, 0.39 mmol) was dissolved in EtOH (5 mL) in a round-bottom flask under magnetic stirring. Pd/C 10% (8.3 mg corresponding to 0.83 mg of Pd, 0.0078 mmol) was added to the solution followed by Boc_2O (94 mg, 0.43 mmol) and the resulting mixture was stirred at room temperature for 16 h under an atmosphere of H_2 (balloon). The solution was then filtered over celite to remove Pd/C and evaporated. The crude was dissolved in CH_2Cl_2 (10 mL) and washed with HCl 1 N (3×5 mL), water (3×5 mL) and brine (5 mL); the organic phase was dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified by silica gel flash chromatog-

raphy (heptane:EtOAc 4:1) to provide compound **15** (108 mg, 0.23 mmol) as a white solid (yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$,): δ 8.28 (s, 1H), 8.22 (d, J=8.0, 1H), 7.96 (d, J=8.0, 1H), 7.41 (d, J=7.6, 1H), 7.28 (t, J=7.6, 1H), 7.03 (d, J=9.2, 1H), 5.16 (d, J=7.2, 1H), 4.85 (t, J=6.4, 1H), 4.75–4.69 (m, 1H), 3.38–3.32 (m, 1H), 3.10–3.01 (m, 1H), 2.58–2.56 (m, 1H), 1.82–1.73 (m, 1H), 1.43–1.39 (m, 15H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.9, 168.8, 162.7, 155.7, 145.3, 142.9, 134.0, 133.8, 128.2, 127.2, 126.8, 123.1, 116.8, 115.2, 113.6, 103.9, 72.7, 55.7, 33.8, 31.5, 28.4, 28.2, 21.7 ppm. HRMS (ESI) calcd for $C_{26}H_{28}N_4NaO_4$ $(M+Na)^+$ 483.2008; found 483.20082.

5′,5′-Dimethyl-2,3-dihydrospiro[indene-1,2′-[1,3]dioxane]-4-carbonitrile 22. To a solution of ketone **3** (30 g, 0.19 mol) in toluene (200 mL), neopentyl glycol (19.6 g, 0.19 mol) and PTSA (0.72 g, 0.0038 mol) were added under stirring at 25 °C. Trimethyl orthoformate (26.4 g, 0.24 mol) was added and the mixture was maintained under stirring at 20–25 °C until complete conversion (about 12 hours). The reaction was cooled to 5 °C, then a 10% aqueous solution of Na_2CO_3 (150 mL) and toluene (100 mL) were added. The resulting phases were separated, and the aqueous layer was extracted with toluene (80 mL). The collected organic phases were evaporated under reduced pressure up to obtain a residue which was triturated in 2-PrOH (130 mL) for 1 hour. The resulting solid was filtered, washed with 2-propanol and dried at 40 °C under reduced pressure yielding 28.6 g of the title compound (yield: 62%). ^{1}H NMR (300 MHz, DMSO-d6): δ 7.78 (dd, J=25.6, 7.6, 2H), 7.47 (t, J=7.7, 1H), 3.73 (d, J =11.2, 2H), 3.49 (d, J =11.2, 2H), 3.04 (t, J=6.9, 2H), 2.46 (d, J=6.9, 2H), 1.25 (s, 3H), 0.80 (s, 3H) ppm. MS (ESI) 266 $(M+Na)^+$ $C_{15}H_{17}NO_2$ (243.30): calcd C 74.05, H 7.04, N 5.76; found C 74.06, H 7.07, N 5.78.

N′-Hydroxy-5,5-dimethylspiro[1,3-dioxane-2,1′-2,3-dihydroindene]-4′-carboximidamide 23. To a dispersion of hydroxylamine hydrochloride (20.3 g, 292.2 mmol) in ethanol (490 mL), triethylamine (31.5 g, 311.7 mmol) was added. The mixture was maintained under stirring at 25 °C for 1 hour, then acetal **22** (23.7 g, 97.4 mmol) was added. The reaction was maintained under stirring at the same temperature until complete conversion (about 48 hours). The resulting solid was filtered, washed with ethanol and dried at 40 °C under reduced pressure, yielding 20 g of the title compound (quantitative yield). An analytical sample was prepared through recrystallisation with EtOAc. ^{1}H NMR (500 MHz, DMSO-d6): δ 9.55 (s, 1H), 7.47 (dd, J=7.6, 1.2, 1H), 7.41(dd, J=7.6, 1.2, 1H), 7.28 (dd, J=8.0, 7.3, 1H), 5.72 (s, 2H), 3.71 (d, J=11.1, 2H), 3.47 (dt,J=11.3, 1.1, 2H), 3.02 (t, J=6.9, 2H), 2.34 (dd, J=7.4, 6.5, 2H), 1.26 (s, 3H), 0.78 (s, 3H) ppm. MS (ESI) 275 $(M-H)^-$ $C_{15}H_{20}N_2O_3$ (276.33): calcd C 65.20, H 7.30, N 10.14; found C 65.17, H 7.29, N 10.12.

2-Isopropoxy-5-(3-(1-oxo-2,3-dihydro-1H-inden-4-yl)-1,2,4-oxadiazol-5-yl)benzonitrile 19. To a dispersion of 3-cyano-4-isopropoxybenzoic acid **12** (17 g, 82.8 mmol) in cyclopentyl methyl ether (300 mL) heated to 55 °C, 1,1′-carbonyldiimidazole (20.8 g, 128.3 mmol) was added portionwise. The mixture was maintained under stirring at the same temperature until complete conversion (about 1 hour), then amidoxime **23** (22.9 g, 82.8 mmol) was added. The reaction was heated to 80 °C and maintained under stirring at the same temperature until complete conversion (about 12 hours). After cooling to 60 °C, cyclopentyl methyl ether (200 mL) and a 0.5 M aqueous solution of sodium hydroxide (200 mL) were added. The resulting phases were separated at 50 °C and the organic layer was washed with water (200 mL) at the same temperature. The organic phase was evaporated under reduced pressure to obtain a solid which was dispersed in acetone (400 ml) containing PTSA (1.28 g, 6.73 mmol). The mixture was maintained under stirring at 25 °C until complete conversion (about 2 hours), then the resulting solid was filtered, washed with acetone and dried at 45 °C under reduced pressure, thus yielding 22.6 g of the title compound (yield: 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (dd, J=7.6, 1.2, 1H), 8.47 (d, J=2.2, 1H), 8.38 (dd, =8.9, 2.2, 1H), 7.96 (dd, J=7.6, 1.1, 1H), 7.60 (tt, J =7.6, 0.8, 1H), 7.16 (d, J=9.0, 1H), 4.88–4.79 (m, 1H), 3.61–3.55 (m, 2H), 2.86–2.80 (m, 2H), 1.51 (d, J=6.1,6H) ppm.[28] MS (ESI) 382 $(M+Na)^+$

Ozanimod (1) through hydrogen transfer reduction of imine 18. To a dispersion of ketone **19** (500 mg, 1.39 mmol) in a 4:1 (*V/V*) mixture of toluene and ethanol (60 mL), PTSA (4.7 mg, 0.0247 mmol) and 2-aminoethanol (340 mg, 5.54 mmol) were added. The mixture was maintained under reflux conditions and the formed water distilled out using a Dean-Stark condenser containing activated 4 A molecular sieves. The formation of a precipitate was observed during the course of the reaction. After complete conversion (about 12 hours), the mixture was cooled to 20 °C and the solid filtered, washed with toluene and dried at 40 °C under reduced pressure, thus yielding 540 mg of the crude imine **18**, yield: 96%; ES/MS 403 $(M+H)^+$, 827, $(2\,M+Na)^+$. An aliquot of 50 mg of **18** (0.12 mmol), dispersed in 2,2,2-trifluoroethanol (1 mL), was mixed with C3-[(*S,S*)-teth-MtsDPEN RuCl] (1.6 mg, 0.0024 mmol), 2-aminoethanol (7.6 mg, 0.12 mmol) and formic acid triethylamine complex 5:2 (53.7 mg, 0.62 mmol), under stirring at 25 °C. The mixture was maintained under stirring at 50 °C until complete conversion (about 24 hours), then it was cooled to 20 °C and diluted with methanol. An aliquot of the mixture was analysed by HPLC according to the method described in literature[10] showing an enantiomeric excess (ee)=99%. To this methanolic solution a 10% (w/w) solution of hydrogen chloride in methanol (0.13 g, 0.36 mmol) was added. The mixture was gently heated to 45 °C and maintained under stirring for 2 hours. After cooling, the resulting solid was filtered, washed with methanol and dried under reduced pressure to provide 46.5 mg of Ozanimod.HCl (yield 96%) with chiral HPLC and spectral data in accordance with those reported in literature.[10]

Ozanimod (1) via reductive amination of ketone 19. To a dispersion of compound **19** (50 mg, 0.14 mmol) in 2,2,2-trifluoroethanol (1 mL), C3-[(*S,S*)-teth-TrisDPEN RuCl] (2.0 mg, 0.0028 mmol), heated to 50 °C, 2-aminoethanol (17.0 mg, 0.28 mmol) and formic acid triethylamine complex 5:2 (60.2 mg, 0.70 mmol) were slowly added under stirring. The mixture was maintained under stirring at 50 °C until complete conversion (about 24 hours), then it was cooled to 20 °C and diluted with methanol. An aliquot of the mixture was analysed by HPLC according to the method described literature showing an enantiomeric excess (ee)=99%. Purification through a shorth path of silica with EtOAc/heptane 5 :1, followed by evaporation of the solvent gave a pure sample of amine **1** (45 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ=8.44 (s, 1H), 8.36 (dd, J=8.9, 2.2, 1H), 8.10 (d, J=6.7, 1H), 7.57 (d, J=6.4, 1H), 7.41 (t, J=7.6, 1H), 7.14 (d, J=9.1, 1H), 4.82 (p, J=6.2, 1H), 4.38 (t, J=6.8, 1H), 3.80–3.66 (m, 2H), 3.54–3.42 (m, 1H), 3.28–3.16 (m, 1H), 3.02–2.89 (m, 2H), 2.61–2.51 (m, 1H), 2.26 (s, 2H), 2.01–1.90 (m, 1H), 1.50 (d, J=6.1, 6H). ^{13}C NMR (126 MHz, CDCl3) δ=173.04, 169.04, 162.76, 146.40, 143.59, 134.15, 133.89, 128.18, 126.99, 123.23, 116.93, 115.31, 113.57, 103.98, 72.76, 62.82, 61.24, 48.44, 33.25, 31.83, 21.76. MS (ESI) 405 $(M+H)^+$

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Conflict of Interest

The authors declare no conflict of interest.

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