Supporting Information

First scale-up synthesis of WAY-262398, a novel, dual-acting SSRI/5HT1a antagonist

Antonia Nikitenko, Asaf Alimardanov, Jay Afragola, Jean Schmid, Livia Kristofova, Deborah Evrard, Nicole T. Hatzenbuhler, Vasilios Marathias, Gary Stack, Steve Lenicek, and John Potoski

Wyeth Research, Pearl River, NY

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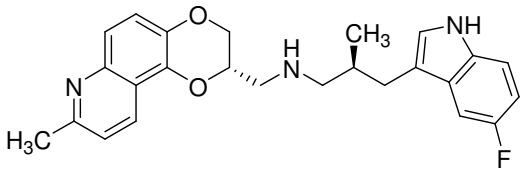
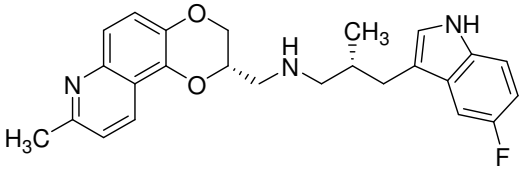
General Experimental Methods

^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ (compounds 17, 18) and DMSO-d6 (compounds 9, 12, 13, 16, 19, 1) using tetramethylsilane as a standard. Chiral HPLC analysis was performed on HP 1100-6 liquid chromatograph equipped with a Whelk O1 RR 4.6 x 250 mm column. Mobile phase composition: 60% heptane containing 0.02% TFA, 40% isopropyl alcohol, flow rate 1 mL/min.

Absolute configuration of the second chiral center in WAY-262398



WAY-262398



A

In order to approach the issue of the chiral center in the acid **6,** we needed to establish the absolute configuration of that chiral center. NMR along with the chiral alignment media PBLG, in $CDCl_3$, was used to determine the stereochemistry of the

chiral center containing the methyl group in **A**, a diastereomer of WAY-262398.[1] Compound **A** was used because of a better compound supply. The configuration of the chiral center containing the methyl group was determined as described in reference 1 and as described herein. Since the first chiral center present in the ring was known to be S, the stereochemistry for this center was left fixed and was used in determining the chirality of the second center. Seven NOE's and nine residual dipolar coupling constants (RDCs) were obtained from the second chiral center (the chiral carbon containing the methyl group) of **A**. Of the nine RDCs obtained from **A**, six RDCs were carbon-proton couplings and three were carbon-carbon couplings. The NOEs and RDCs were obtained using one dimensional and two dimensional homo and heteronuclear NMR experiments both under isotropic and anisotropic conditions as described in the experimental section. The structure of compound **A** was built using Molecular Orbital Environment (MOE) and the structure was minimized to obtain lowest energy conformers in a simulated PBLG/$CDCl_3$ environment. The structure of the averaged lowest energy conformer was then imported in the program PALES[2]. By using PALES and the approach outlined by Griesinger et al.[3] the lowest energy structure of **19** was used to back-calculate the carbon-proton and carbon-carbon RDCs. Back-calculated and experimental RDCs were then plotted as described in reference 1. A good fit between experimental and back-calculated RDCs was observed. In all instances, the configuration of the first stereocenter present in the ring of **A** was fixed as S. The results described below only pertain to the second stereocenter containing the methyl group. The linear curve fit of D_{calc} to D_{obs} was found to be $D_{calc} = D_{obs} + 0.4$ Hz with a Pearson's correlation factor of $R^2 = 0.921$ for when the second stereocenter is R. The high correlation factor and very small offsets, in each case, indicate that the experimental RDCs and associated structure fit very well and are significantly accurate. To determine the chirality of the unknown stereocenter, the configuration of the compound **A** model was changed from R to S. A recalculation using PALES was conducted and a new set of RDCs were back-calculated based on the epimerized structure and re-plotted verse the experimental RDCs. In this case, the D_{calc} to D_{obs} linear fit was substantially lowered. This produced a correlation factor $R^2 = 0.742$ and $D_{calc} = 0.58D_{obs} + 1.7$ Hz for the S. These results indicate the chirality was correct in the first set of calculations. Absolute configuration of the chiral centers in **A** was then determined to be "S" and "R", "S" being the known chiral center from quinaldine dioxane brozylate. Therefore, WAY-262398 would be "S" and "S", and our aim is (2S)- 3-(5-fluoro-1H-indol-3-yl)-2-methylpropanoic acid.

REFRENCES:

1. Vasilios M. Marathias *, Gregory J. Tawa , Igor Goljer , Alvin C. Bach II Stereochemical identification of (*R*)- and (*S*)-ibuprofen using residual dipolar couplings, NMR, and modeling. Chirality 2007: 19, Pages 741 – 750.

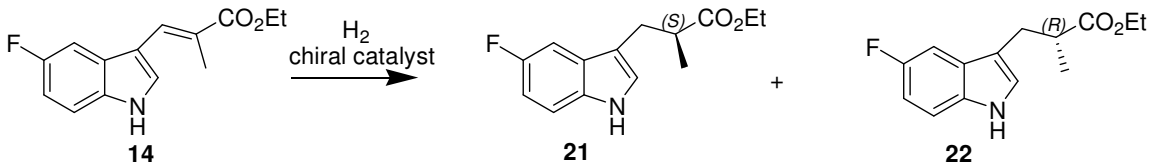
2. Bax A, Zweckstetter M. Prediction Of Sterically Indiced Alignmnet in a Diluted Liquid Crystalline Phase: Aid to Protein Structure Determination by NMR. J Am Soc 2000; 122: 3791-3792.

3. Verdier L, Sakhaii P, Zweckstetter M, Griesinger C. Measurment of Long Range H,C couplings in Natural Products in Orientaion Media: A tool for Structure elucidation of Natural Products. JMR 2003; 163:353-359.

Salt Screening for the Chiral Resolution of Acid 6

Base	acetonitrile/ methanol	acetonitrile	EtOAc	iPrOH	Comments
R-methylbenzylamine	-	-	-	-	
D-(+)-2-aminobutanol	-	-	-	-	
(+)-dehydroabiethylamine	-	+			Racemic salt
(-)-ephedrine	-	-	-	-	
(-)-pseudoephedrine	-	-	-	-	
(-)-norephedrine	+	+			Enantiomer ratio 72:28
(-)-cinchonidine	-	+			Enantiomer ratio 38:62
brucine	-	-	-	-	
(+)-benzylphenetylamine	-	-	-	-	
(-)-benzylphenetylamine	-	-	-	-	
(-)-a-phenylpropylamine	-	-	-	-	
(+)-2-aminomenthol	-	-	-	-	
quinidine	-	-	-	-	

Conditions and results for the Chiral Reduction of Ester 14

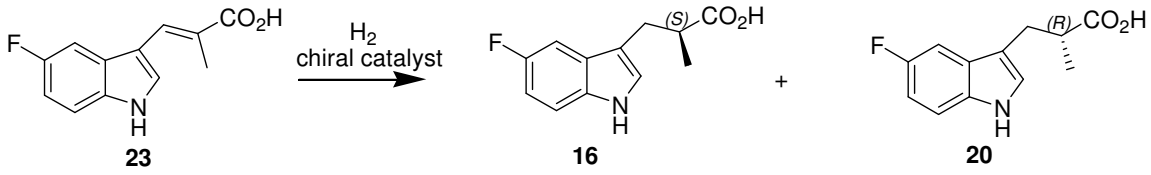


450 psi, 18 h, EtOH, different ligands + $Rh(cod)_2BF_4$

SM/C molar ratio = 100
L/MP molar ratio = 1:1 = 0.002mmol
Solvent: 2 mL of EtOH (HPLC grade, sparged for 30 min with N_2 prior reaction)
Metal Precursor: $Rh(cod)_2BF_4$ (AA44031)/ MW=406.08/ 0.82 mg per reaction
Stock solution of 6.8 mg in 500µL MeOH was prepared.
60 µL per reaction was used. (low solubility in EtOH)
Catalyst preparation: Solid ligand weighed into reac. liners, MP solution added, 500µL EtOH added, sealed and shacked for two hours.

#	Ligand	Catalyst	T [C]	Chiral HPLC [%]		
				RT=7.1 min, SM	RT=9.6 min	RT=12.6 min
1	Josiphos R,S-DPP-F- EDtBP	$Rh(cod)_2BF_4$	60	nd	51.1	48.9
2	Josiphos R,S-Bis-DDPP-F-EDCP	$Rh(cod)_2BF_4$	30	1.3	25.5	73.2
3	Josiphos R,S-Bis-DDPP-F-EDCP	$Rh(cod)_2BF_4$	60	nd	28.7	71.3
4	Josiphos R,S-Bis-TMPP-F-EDtBP	$Rh(cod)_2BF_4$	60	nd	49.5	50.5
5	Josiphos R,S-Di-BTMPP-F-EDCP	$Rh(cod)_2BF_4$	60	21.9	40.5	37.6
6	Josiphos R,S-Di-BTMPP-F-EDPP	$Rh(cod)_2BF_4$	60	15.4	43.3	41.3
7	Josiphos R,S-DCP-F-EDtBP	$Rh(cod)_2BF_4$	30	4.5	66.7	28.8
8	Josiphos R,S-DCP-F-EDtBP	$Rh(cod)_2BF_4$	60	0.8	76.9	22.4
9	Josiphos R,S-DCP-F-EDCP	$Rh(cod)_2BF_4$	60	nd	62.0	38.0
10	Josiphos S,R-DFP-F-EDXP	$Rh(cod)_2BF_4$	60	nd	46.4	53.6
11	S-BINAP	$Rh(cod)_2BF_4$	30	22.7	27.3	50.0
12	S-BINAP	$Rh(cod)_2BF_4$	60	64.1	11.6	24.3
13	Mandyphos S,S-Bis-R-DMAPM-bis-DPP-F	$Rh(cod)_2BF_4$	60	0.6	74.1	25.3
14	Mandyphos S,S-Bis-R-DMAPM-di-bis-DMMPP-F	$Rh(cod)_2BF_4$	60	1.1	59.1	39.8
15	S,S-Me-BPE	$Rh(cod)_2BF_4$	60	100	nd	nd
16	S,S-Me-DuPhos	$Rh(cod)_2BF_4$	60	14.4	49.7	35.9

Conditions and results for the Chiral Reduction of Acid 23



23 **16** **20**

#	Ligand's STREM Cat.No.	Ligand (Solvias No.)	L:MP molar ratio	S/C molar ratio	MP	Solvent	T [°C]	pres [psi]	Chiral HPLC [%]		
									RT=8.0 min,SM	RT=36 .4 min	RT=39 .0min
1	26-0975 191-8	Josiphos R,S-DCP-F-EdtBP SL-J009	1:1	100	Rh	MeOH	60	80	nd	27.5	72.5
2	26-0975 189-1	Josiphos R,S-DCP-F-EdtBP SL-J009	1:1	100	Rh	MeOH	60	400	nd	27.5	72.5
3	26-1000 189-2	Josiphos R,S-DCP-F-EDCP SL-J003	1:1	100	Rh	MeOH	60	400	nd	47.8	52.2
4	26-1150 191-6	Josiphos R,S-Bis-DDPP-F-EDCP SL-J007	1:1	100	Rh	MeOH	60	80	nd	66.0	44.0
5	26-1150 187-7	Josiphos R,S-Bis-DDPP-F-EDCP SL-J007	1:1	100	Rh	MeOH	60	400	nd	68.2	31.8
6	26-1150 189-3	Josiphos R,S-Bis-DDPP-F-EDCP SL-J007	1:2	100	Rh	MeOH	60	400	nd	61.0	39.0
7	26-0240 191-2	Mandyphos S,S-Bis-R-DMAPM-bis-DCHPP-F SL-M002	1:1	100	Rh	MeOH	25	80	nd	44.1	55.9
8	26-0240 191-1		1:1	100	Rh	MeOH	60	80	nd	44.1	55.9
9	26-0240 191-3		1:1	500	Rh	MeOH	60	80	nd	44.7	55.3
10	26-0240 187-2		1:1	100	Rh	MeOH	60	400	nd	44.9	55.1
11	26-0240 191-4		1:2	100	Rh	MeOH	60	80	nd	45.8	54.2
12	26-0240 189-4		1:2	100	Rh	MeOH	60	400	nd	55.36	44.7
13	26-0252 191-5	Mandyphos S,S-Bis-R-DMAPM-bis-DPP-F SL-M001	1:1	100	Rh	MeOH	60	80	nd	24.1	75.9
14	26-0252 187-4		1:1	100	Rh	MeOH	60	400	nd	25.6	74.4
15	193.1	Mandyphos S,S-Bis-R-DMAPM-di-bis-DMMPP-F SL-M004	1:1	100	Rh	MeOH	25	50	nd	8.0	92.0
16	26-0248 187-5		1:1	100	Rh	MeOH	60	400	nd	9.8	90.2
17	193-2		1:1	100	Rh	EtAc	60	400	nd	15.3	84.7
18	193-3		1:1	100	Rh	Hex	60	400	nd	n/a	n/a
19	193-4		1:1	100	Rh	Tol	60	400	nd	18.1	81.9
20	193-5		1:1	100	Rh	TFE	60	400	nd	13.8	86.2
21	193-6		1:1	100	Rh	THF	60	400	nd	n/a	n/a
22	26-0244 187-6	Mandyphos S,S-Bis-R-DMAPM-bis-TFMPP-F SL-M003	1:1	100	Rh	MeOH	60	400	nd	26.7	73.3
23	26-1310 191-7	Walphos R,R-DPPP-F-EDP, SL-W003	1:1	100	Rh	MeOH	60	80	nd	25.4	74.6
24	26-1310 187-8		1:1	100	Rh	MeOH	60	400	nd	28.1	71.9
25	26-1120 193-7	Walphos R,R-DCHPP-F-EDTFMPP SL-W008-1	1:1	100	Rh	MeOH	60	400	nd	36.2	63.8
26	26-1130 193-8	Walphos R,R-DDMMPPP-F-EDTFMPP SL-W005-1	1:1	100	Rh	MeOH	60	400	nd	32.2	67.5
27	15-0098 189-5	S,S-Et-DuPhos	1:1	100	Rh	MeOH	60	400	nd	72.2	27.8
28	15-0098 189-6	S,S-Et-DuPhos	1:1	100	Ru	MeOH	60	400	nd	44.1	55.9
29	26-1155 187-3	TANIAPHOS	1:1	100	Rh	MeOH	60	400	nd	46.8	53.2
30	15-0152 189-7	R-Tol-BINAP	1:1	100	Ru	MeOH	60	400	nd	35.8	64.2