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Synthesis of Tetracyclic Heterocompounds as Selective Estrogen Receptor Modulators. Part 3. Development of an Acid-Catalyzed Racemization Process for (*S*)-2,8-(Dimethoxy)-5-{4-[2-(1-piperidinyl)ethoxy]-phenyl}−11,12-dihydro-*5H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene

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Abstract:

A novel and economical process was developed for recycling the undesired enantiomer, (*S*)-2,8-dimethoxy-5-{4-[2-(1-piperidinyl)-ethoxy]phenyl}-11,12-dihydro-*5H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene (1b) obtained from chiral chromatographic separation, by refluxing 1b with HCl (4.0 equiv) in EtOH for 76 h, or with H_2SO_4 (2.0 equiv) in water for 68 h to afford a near racemic mixture ((*R*)-1a/(*S*)-1b = 41−42%/49−53%, chiral HPLC area%) in >96% isolated yield and good chemical purity (87−95%).

Introduction

The scale-up preparation of 2,5,8-substituted 11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalene derivatives as selective estrogen receptor modulators (SERMs) has been reported recently,[1] where racemate **1** was prepared via an eight-step nonchromatographic linear synthetic process in 17% overall yield with 99.5% chemical purity (RPHPLC, area %). Chiral HPLC separation of **1** afforded (*R*)-enantiomer **1a** and the corresponding (*S*)-enantiomer **1b** (Scheme 1). Furthermore, the advanced *in vitro* and *in vivo* biological studies determined that (*R*)-**1a** was the most active compound with the desired SERM activity, while (*S*)-**1b** was the enantiomer with weak SERM activity. Because attempts for either enantioselective asymmetric synthesis of (*R*)-**1a** or the enantiomeric resolution of the racemate **1** with chiral acids were unfruitful,[2] the optically pure (>99% ee) (*R*)-**1a** was obtained on kilogram scale by the chiral chromatographic separation of racemate **1**. The conversion of (*S*)-**1b** back to the racemic **1** would help in a higher yield of (*R*)-**1a** within a short time cycle. Herein, we report an acid-catalyzed racemization process for recycling (*S*)-**1b**.

Results and Discussion

A review of the literature showed no published results on the racemization of a tetracyclic compound like (*R*)-**1a**/(*S*)-**1b**, although it was known that the very similar (*R*)-3-(4-hydroxyphenyl)-4-methyl-2-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2*H*-chromen-7-ol (**2a**, Scheme 2), a 2,3,4,7-substituted coumarin derivative, could be easily converted to a racemic mixture in 92% yield, after treatment with 5% LiOH in DMF at 80 °C for 3 h.[3] Due to the similarity, compound (*R*)-**3a** (99.0% ee),[4] the 2,8-dihydroxy analogue of (*R*)-**1a**, was first subjected to these known base-catalyzed conditions (5% LiOH in DMF at 80 °C) to produce a 63.3% (*R*)-**3a** enriched mixture after 60 h. The rate slowed unacceptably toward the end of the reaction, and no further optimization was conducted with LiOH-catalyzed racemization of (*R*)-**3a**.

When the above LiOH-catalyzed conditions were applied to pure 2,8-dimethoxy (*R*)-**1a** enantiomer (99.8% ee), however, no product (*S*)-**1b** was detected in the reaction mixture as analyzed by chiral HPLC. In addition, the treatment of (*R*)-**1a** separately with other bases (such as KOH, piperidine, and 4-(*N*,*N*-dimethyl)pyridine) in different refluxing solvents (such as MeOH, EtOH, and MeCN) also did not result in (*S*)-**1b**. It seemed that a base deprotonation of 2- and/or 8-phenolic hydroxyl group (calculated pK_as of 2-OH and 8-OH = 10.19 and 9.88, respectively)[1] of (*R*)-**3a** was the driving force for this base-catalyzed racemization. The enantiomer (*R*)-**1a** was unable to be racemized under investigated basic conditions because of having 2,8-dimethoxy groups on the molecule.

The unsuccessful racemizations of (*R*)-**1a**/(*S*)-**1b** under basic conditions led us to explore other possible chemistries. For instance, (*R*)-**1a**/(*S*)-**1b** could possibly be racemized under acid-catalyzed conditions[5] when more than one equivalent of an acid was used, due to the presence of the piperidine ring on the side

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(2) Unpublished internal communications.

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(4) The optically pure (99.0% ee) (*R*)-enantiomer **3a** was obtained from a preparative chiral HPLC separation of its racemate **3**, which was prepared in-house and described as compound **11** in ref 1a of this publication.

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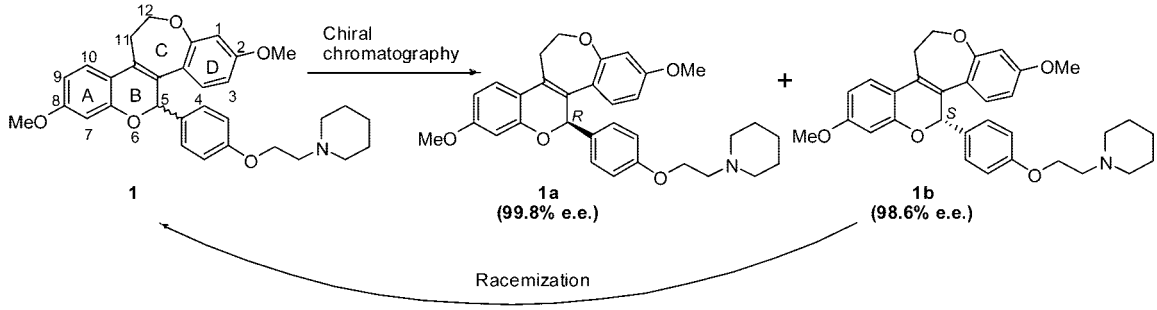
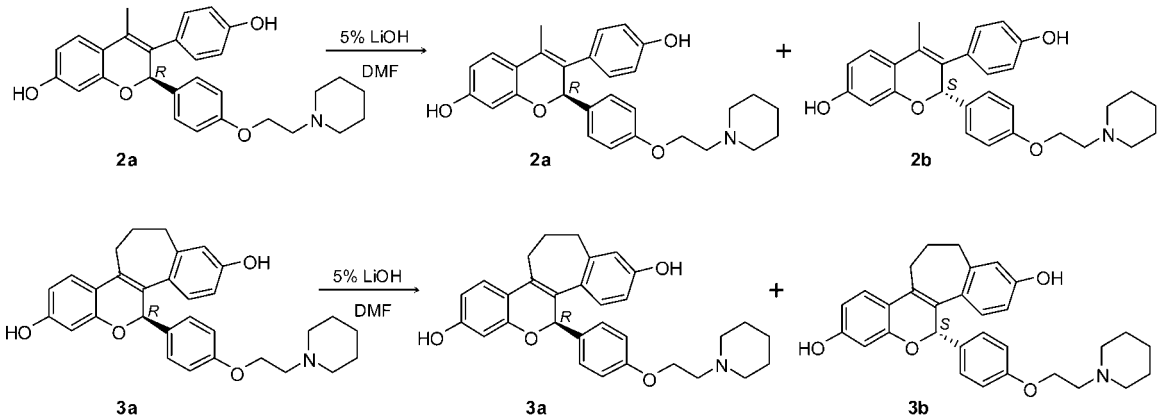
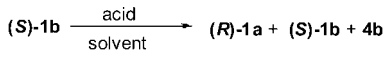
Scheme 1



Scheme 2



Scheme 3



chain of (*R*)-**1a** or (*S*)-**1b**. The excess acid could protonate the molecule on oxygen, preferably the 6-oxygen, to form a delocalized oxonium species, which might cause the C_5 stereogenic center to be racemized.[5a]

To test this hypothesis, (*S*)-**1b** (98.6% ee) was treated with a slight excess (1.13 equiv) of either (1*R*)-(−)- or (1*S*)-(+)-10-camphorsulfonic acid ((−)-/(+)-CSA) ($pK_a = -2.17$)[6a] in refluxing EtOH for 60 h; both reactions gave very similar (*S*)-**1b**-enriched (∼68.5%, chiral HPLC area %) mixtures with the formation of (*R*)-**1a** (∼29%) and a detectable level of byproduct **4b** (∼2.3%)[7] (Scheme 3, entries 1 and 2 of Table 1). Other solvents (such as CH_2Cl_2, MeCN, THF, and MeOH) were screened before EtOH was selected, which showed either no racemization (for example, in CH_2Cl_2 and MeCN) or less than 10% formation (in THF and MeOH) of (*R*)-**1a**, after (*S*)-**1b** (1.0 equiv) was refluxed with (1*R*)-CSA (1.13 equiv) in each tested solvent for 60 h, respectively. Among all acids tested, the best result (42.0% of (*R*)-**1a**) was achieved when only HCl (4.0 equiv, 1 M solution in EtOH) ($pK_a = -6.0$ and -6.1)[6b,c] was used after 76 h (entry 8 of Table 1), extending the reaction time to 96 h did not change the product profile. Of interest, (*R*)-**1a** was also converted to a near racemic mixture with the presence of **4b** (7.5%) under the above-described HCl-catalyzed conditions (entry 9 of Table 1). On the other hand, although the reaction of (*S*)-**1b** with 4.0 equiv of aqueous HCl (37% solution) in refluxing water for about three days that resulted in only trace amount (<1%) of (*R*)-**1a** (entry 13 of Table 1), H_2SO_4 (2.0 equiv) ($pK_a = -3.0$)[6c] still accomplished a near racemic mixture under the same reaction conditions (entry 14 of Table 1). Considering HCl is a very strong Brønsted acid, other commonly used Lewis acids such as $BF_3 \cdot Et_2O$, $MgBr_2 \cdot Et_2O$, $SnCl_4$, and $TiCl_4$ were also examined for catalyzing the racemization of (*S*)-**1b**, all which, however, resulted in less than 10% of the desired enantiomer (*R*)-**1a** under the investigated conditions (entries 15−20 of Table 1). The above HCl-catalyzed reaction conditions were found to be reproducible on 1-, 10-, and 30-g scale of (*S*)-**1b**, which set the stage for racemization on larger scale. This acid-catalyzed process was not conducted on multikilogram scale because the project was unforeseeably terminated before the scale-up campaign.

A proposed reaction mechanism for this acid-catalyzed racemization of (*S*)-**1b** is shown in Scheme 4. After the 6-oxygen of (*S*)-**1b** was protonated to the oxonium intermediate **5**, the positive charge could delocalize the electron density on C_5-O_6 bond via *path a* that led to the stabilized 4,5,8-trisubstitued-2,3-dihydrobenzo[*b*]oxepine carbocation intermediate **4a**,[8a] of which the 4-substituted phenol hydroxyl group could approach to the sp^2 hybridized carbocation carbon[8b] from either the top or bottom side and reclose the B-ring to achieve a racemic (*R*)-**1a**/(*S*)-**1b** mixture.[5] On the other hand, the syn-

(7) The structure of the byproduct **4b** was confirmed by comparing its ^1H NMR, LC/MS ($MH^+ = 514$), and HPLC analytical data with an in-house prepared authentic compound **4b**.

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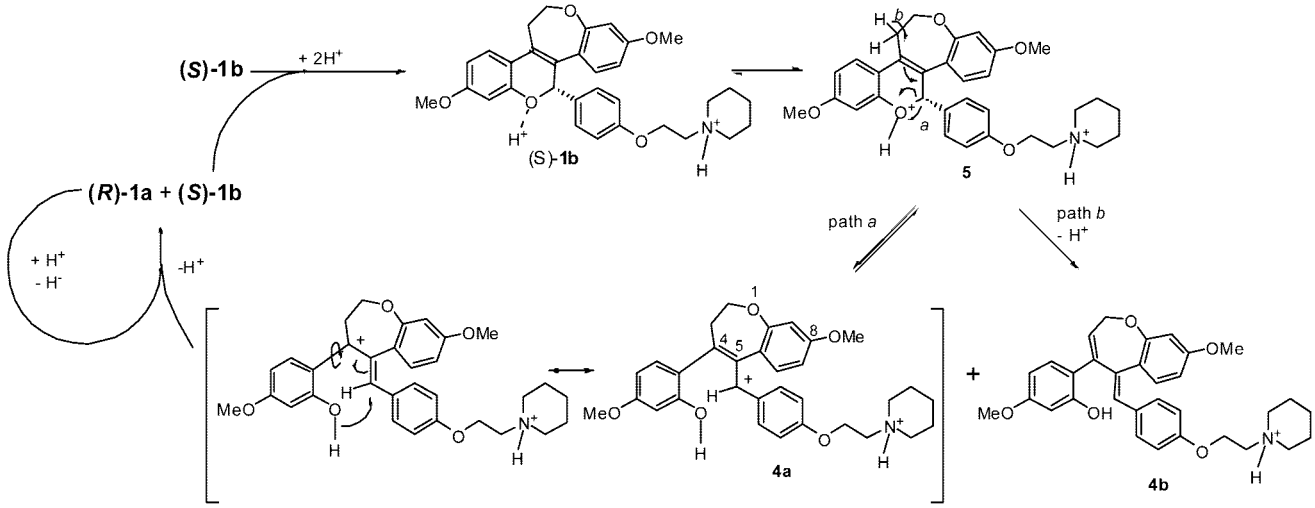
Table 1. **Results of acid-catalyzed racemization of (R)-1a and (S)-1b enantiomers with different acids in the selected solvents**

entry	cmpd	acid (equiv)	solvent	temp (°C)	time (h)	(*R*)-**1a**/(*S*)-**1b**/**4b**[a](chiral HPLC, area %)
1	(*S*)-**1b** (98.6% ee)	(1*R*)-CSA (1.13)	EtOH	78	60	28.9/68.5/2.4
2	(*S*)-**1b**	(1*S*)-CSA (1.13)	EtOH	78	60	28.8/68.7/2.3
3	(*S*)-**1b**	(1*R*)-CSA (2.3)	EtOH	78	80	37.1/58.9/3.8
					150	39.7/57.5/2.8
4	(*S*)-**1b**	TFA (2.3)	EtOH	70	60	5.3/94.5/0.28
5	(*S*)-**1b**	$MeSO_3H$ (4.0)	EtOH	75	68	38.3/61.7/ND[e]
6	(*S*)-**1b**	(1*R*)-CSA (1.0) + HCl (3.0)[b]	EtOH	78	70	40.0/56.5/3.6
7	(*S*)-**1b**	(1*R*)-CSA (1.0) + HCl (4.0)[b]	EtOH	78	60	41.1/53.8/5.1
8	(*S*)-**1b**	HCl (4.0)[b]	EtOH	78	76	42.0/53.1/4.8
9	(*R*)-**1a** (99.8% ee)	HCl (4.0)[b]	EtOH	78	72	47.6/42.5/7.5
10	(*S*)-**1b**	HCl (4.0)[c]	EtOH	75	68	26.6/73.4/ND[e]
		HCl (20.0)[c]		75	68	42.1/57.9/ND
11	(*S*)-**1b**	$MeSO_3H$ (4.0)	H_2O:EtOH (1:1)	75	68	24.5/75.5/ND
12	(*S*)-**1b**	HCl (4.0)[c]	H_2O:EtOH (1:1)	75	68	20.7/79.3/ND
		HCl (20.0)[c]		55	68	0.9/99.1/ND
13	(*S*)-**1b**	HCl (4.0)[c]	H_2O	95	68	0.8/99.2/ND
14	(*S*)-**1b**	H_2SO_4 (2.0)[d]	H_2O	95	68	41.0/49.0/2.5
15	(*S*)-**1b**	$BF_3 \cdot Et_2O$ (1.0)	CH_2Cl_2	20	72	0.5/99.5[f]
16	(*S*)-**1b**	$BF_3 \cdot Et_2O$ (3.0)	THF	20	12	0.5/99.5[g]
17	(*S*)-**1b**	$MgBr_2 \cdot Et_2O$ (3.0)	CH_2Cl_2	40	12, 66	7.5/92.5[h], 9.0/91.0[i]
18	(*S*)-**1b**	$SnCl_4$	CH_2Cl_2 (3.0)	20	12	0.5/99.5[j]
19	(*S*)-**1b**	$TiCl_4$ (1.0)	CH_2Cl_2	20	12	3.5/96.5[k]
20	(*S*)-**1b**	$TiCl_4$ (4.0)	THF	68	48	multiple products[l]

[a] The retention times of the byproducts **4b** = 8.1 min, (*R*)-**1a** = 11.4 min, and (*S*)-**1b** = 22.3 min as determined by chiral HPLC. [b] A 1.0 M solution in EtOH. [c] A 37% solution in H_2O. [d] A 96% solution. [e] Not determined. [f] Recovered 80% of (*S*)-**1b** plus the rest of uncharacterized byproducts. [g] Recovered 93% of (*S*)-**1b** plus the rest of uncharacterized byproducts. [h] Recovered 91% of (*S*)-**1b** plus the rest of uncharacterized byproducts. [i] Recovered 61% of (*S*)-**1b** plus the rest of uncharacterized byproducts. [j] Recovered 95% of (*S*)-**1b** plus the rest of uncharacterized byproducts. [k] Recovered 91% of (*S*)-**1b** plus the rest of uncharacterized byproducts. [l] The mixture was uncharacterized.

Scheme 4. **Proposed mechansism of acid-catalyzed racemization of (*S*)-enantiomer 1b**



chronous elimination of an allylic proton from the 11-position of **5** via *path b* would result in the olefin byproduct **4b**.

Conclusions

The optically pure (*R*)-**1a** (99.8% ee) was unable to be converted to the racemic mixture **1** using basic conditions; this result was attributed to the absence of 2,8-phenolic protons on the molecule. In contrast, when the optically pure (*S*)-**1b** (98.6% ee) was treated with CSA in refluxing EtOH for 60−80 h, it produced an (*S*)-**1b** enriched mixture (∼29%/69% to ∼37%/59%; (*R*)-**1a**/(*S*)-**1b**). The addition of HCl to CSA further increased the yield of (*R*)-**1a** to greater than 40% of the mixture. The best reaction conditions were found with using HCl (4 equiv, 1.0 M in EtOH) to afford a near racemic mixture of (*R*)-**1a**/(*S*)-**1b** (42.0%/53.1%) in 99% isolated yield with high chemical purity (>95%). When water was the solvent, 96% H_2SO_4 (2 equiv) also produced a near racemic mixture of (*R*)-**1a**/(*S*)-**1b** (41.0%/49.0%) in 96% isolated yield with good chemical purity (86.9%). Other Lewis acids displayed very weak (or no) catalytical effect to racemize (*S*)-**1b**. A new and economical process was developed for the reproducible recycling of the undesired (*S*)-**1b** isomer, which could be a useful method for the racemization of other enantiomerically pure 2,5,8-substituted 11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalene derivatives whenever it is needed.

Experimental Section

The starting materials (*R*)-**1a** and (*S*)-**1b** were prepared in-house, while the other reagents and solvents were obtained from commercial suppliers and were used without further purification.

^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance-300 instrument, and mass spectra were recorded on an Agilent series 180 LC/MS instrument (positive/negative modes). The chemical purity was determined on an Agilent series 1100 system at UV_{max} = 254 and 340 nm, using a ZORBAX Eclipse XDB-phenyl column (4.6 mm i.d. × 50 mm, 3.5 micron) at 40 °C with flow rate of 1.0 mL/min and run time of 10.0 min. Solvent system: A - 80% H_2O + 0.1% TFA; B - 20% CH_3CN. Gradient: B 20% → 80%/0.0 min →10.0 min, B 80% → 90%/10.0 min → 11.0 min, B 90%/6.0 min, B 90% → 20%/17.0 min → 20.0 min. The retention times of the byproduct **4b** is 4.01 min and racemate **1** is 4.51 min. The optical purity/racemic ratio of (*R*)-**1a**/(*S*)-**1b** were determined on an Agilent series 1100 system at UV_{max} = 210 and 254 nm, using a Chiralpak AD column (Chiral Technologies, Inc.) (4.6 mm ID × 250 mm, 10 micron) at 20 °C with flow rate of 1.0 mL/min and run time of 33.0 min with 100% 2-propanol as the mobile phase. The retention time of the byproduct **4b** is 8.1 min, (*R*)-**1a** is 11.4 min, and (*S*)-**1b** is 22.3 min. Preparative chiral HPLC separation of (*R*)-**1a**/(*S*)-**1b** was conducted on a Chiralpak AD column (5.0 cm i.d. × 150 mm, 10 μm), at 20 °C with flow rate of 50 mL/min and run time of 25.0 min, with 100% 2-propanol as the mobile phase.

A Typical Acid-Catalyzed Racemization Procedure in EtOH for (*S*)-Enantiomer 1b. A four-neck 500-mL round-bottom flask (RBF) equipped with a thermocouple controller, a mechanical stirrer, a condenser, a pressure-equalization dropping funnel, a septum, and a nitrogen inlet adapter was charged with (*S*)-**1b** (10.0 g, 0.0195 mol; 98.6% ee) and EtOH (120.0 mL, 190 proof), and the suspension was stirred under nitrogen. A solution of HCl (77.8 mL, 0.0778 mol; 1.0 M in EtOH) was added over a 10-min period (this addition was a mildly exothermic process, the internal temperature was 28 °C after the addition), and the reaction was heated to reflux (78 °C, internal temperature) for 76 h. The progress of the racemization was determined by chiral HPLC analysis (authentic racemate **1** (>99.5%) was used as a standard reference). After the reaction time, the reaction was cooled to 20 °C, and the solvent was concentrated at 60 °C under house vacuum (~120 mmHg). The resulting nearly racemic HCl salt was a dark-cherry, foamy solid, which was dissolved in D.I. H_2O (100 mL) and cooled to 0 °C in an ice−water bath, and the pH of the solution was adjusted to ≥12.0 with 5 N NaOH solution (~40 mL). The alkaline solution was extracted with EtOAc (150 mL × 3), and the combined organic phase was washed with brine (100 mL). The solvent was concentrated at 60 °C under house vacuum to afford 10.56 g (105.6% isolated yield) of the near-racemic **1** free base as a yellow-brown, foamy solid. The identity and purity of this material was confirmed by comparing the analytical data of its ^{1}H NMR, LC/MS, the retention times on reverse phase HPLC (97%, area %) and chiral HPLC (>95%, total area %) with that of an in-house prepared authentic racemate **1**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (m, 2 H), 1.58 (m, 4 H), 2.46 (m, 4 H), 2.71 (t, J = 6.0, 2 H), 2.89 (t, J = 5.8, 2 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 4.03 (t, J = 6.1, 2 H), 4.69 (t, J = 5.5, 2 H), 6.06 (s, 1 H), 6.36 (d, J = 1.0, 2 H), 6.48 (dd, J = 0.9, 8.3, 1 H), 6.58 (dd, J = 0.9, 8.2, 1 H), 6.68 (d, J = 9.1, 2 H), 7.02 (d, J = 8.4, 1 H), 7.17 (d, J = 8.3, 1 H), 7.36 (d, J = 9.0, 2 H). LC/MS m/z 514 (MH^+), 536 (MNa^+).

A Typical Acid-Catalyzed Racemization Procedure in H_2O for (*S*)-Enantiomer 1b. Into a four-neck 500 mL RBF were charged (*S*)-**1b** (10.8 g, 0.021 mol, 93.2%) and water (250 mL). After the yellowish suspension was warmed to 60 °C, a solution of 96% H_2SO_4 (2.24 mL, 0.042 mol) was added dropwise, and the formed yellow-orange suspension was heated further to 95 °C (which became a clear, yellowish solution at 80 °C) and stirred for 68 h. After the reaction was cooled to 80 °C, toluene (100 mL) was added to the brownish mixture, and then the pH was adjusted to ~10 by addition of 50% aqueous NaOH (4 mL) with intensive stirring. The resulting mixture was cooled to 50 °C, diluted with THF (50 mL), and further cooled to 20 °C with intensive stirring. The two phases were then separated, and the organic layer was evaporated to afford 10.4 g (96.3% isolated yield; 87%, HPLC area %) of the near-racemic **1** free base as a sticky, brown, foamy solid.

Chiral chromatographic purification of the above obtained near-racemic **1** free base (8.0 g) afforded: 3.31 g (41% recovery yield; 95.9%, RPHPLC, area %; 99.9% ee, chiral HPLC) of the desired (*R*)-**1a** containing 1.55% (RPHPLC, area %) of **4b** and the rest of uncharacterized byproduct; plus 3.92 g (49% recovery yield; 96.6%, RPHPLC, area %; 99.2% ee, chiral HPLC) of the undesired (*S*)-**1b**, which also contained 0.95% (RPHPLC, area %) of **4b**.

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