JOC The Journal of Organic Chemistry

Article

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Organocatalytic Enantioselective Pictet–Spengler Reactions for the Syntheses of 1-Substituted 1,2,3,4-Tetrahydroisoquinolines

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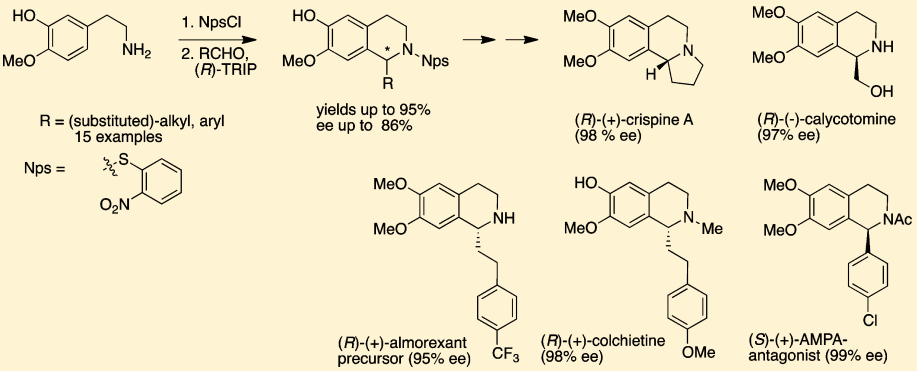
Supporting Information



ABSTRACT: A series of 1-substituted 1,2,3,4-tetrahydroisoquinolines was prepared from *N*-(*o*-nitrophenylsulfenyl)-phenylethylamines through BINOL-phosphoric acid [(*R*)-TRIP]-catalyzed asymmetric Pictet–Spengler reactions. The sulfenamide moiety is crucial for the rate and enantioselectivity of the iminium ion cyclization and the products are readily recrystallized to high enantiomeric purity. Using this methodology we synthesized the natural products (*R*)-crispine A, (*R*)-calycotomine and (*R*)-colchietine, the synthetic drug (*R*)-almorexant and the (*S*)-enantiomer of a biologically active (*R*)-AMPA-antagonist.

INTRODUCTION

Natural and synthetic 1-substituted tetrahydroisoquinolines (e.g., norcoclaurine, emetine and solifenacin) and their more complicated biosynthetic derivatives such as morphine (Figure 1) have received broad attention in medicinal and synthetic chemistry.[1,2] The diverse pharmaceutical applications of alkaloids of this class have stimulated the development of several synthetic methods, of which catalytic approaches are obviously most attractive. Transition metal-catalyzed asymmetric hydrogenation reactions of isoquinolines and their 3,4-dihydro analogues with, e.g., iridium, rhodium and ruthenium catalysts are frequently used and often provide high ee values with an expanding number of substrates (Scheme 1).[3] However, metal-free catalytic approaches may be more desirable in view of the pharmaceutical applications. The most direct approach would be the biomimetic Pictet–Spengler condensation reaction starting from a suitably functionalized phenylethylamine such as dopamine and a range of aldehydes (Scheme 1).[2]

Recently, several remarkable publications described racemic Pictet–Spengler syntheses of tetrahydroisoquinolines. Stambuli and co-workers reported the use of calcium hexafluoroisopropoxide as a very effective catalyst for condensation of 3-hydroxyphenylethylamines, not only with aldehydes but also with unactivated ketones.[4] Inorganic phosphates played an essential role in a tetrahydroisoquinoline synthesis directly from dopamine in aqueous solutions.[5] Norcoclaurine synthase (NCS) was identified as a Pictet–Spenglerase that catalyzes the enantioselective condensation of dopamine with *p*-hydroxyphenylacetaldehyde.[6a] Optimization of this biocatalytic reaction produced (*S*)-norcoclaurine on gram scale,[6b] and the scope was extended to several benzyl-substituted tetrahydroisoquinolines.[6c,d]

An increasing number of enantioselective Pictet–Spengler reactions mediated by organocatalysts such as BINOL- and SPINOL-phosphoric acids and functionalized thioureas are reported in the literature, although the amine precursors have been restricted to tryptamines and derivatives thereof.[7] The highly nucleophilic indole system in combination with the hydrogen bonding properties of the indole N–H make this aromatic ring system an ideal reaction partner in many organocatalytic conversions. The phenylethylamine counterpart, required for tetrahydroisoquinoline synthesis, has no clear examples in the enantioselective Pictet–Spengler condensation yet. One closely related example is a ruthenium-catalyzed isomerization combined with an enantioselective organocatalyzed Pictet–Spengler type cyclization reaction described by Toda and Terada.[8]

Received: May 19, 2014
Published: July 21, 2014

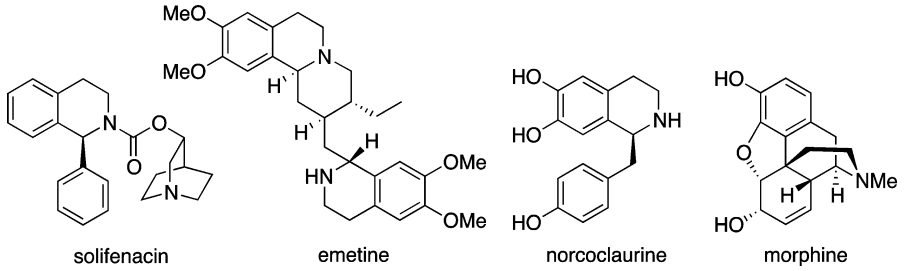
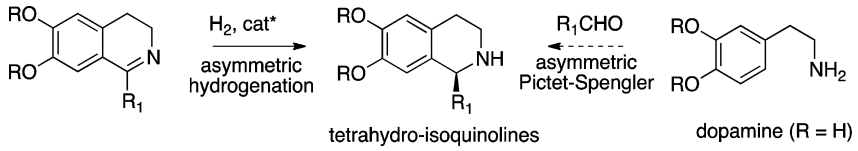


Figure 1. Pharmaceutically relevant 1-substituted tetrahydroisoquinolines.

Scheme 1. Catalytic Synthetic Approaches to 1-Substituted Tetrahydroisoquinolines



Scheme 2. Preparation of *N*-Substituted Phenylethylamines

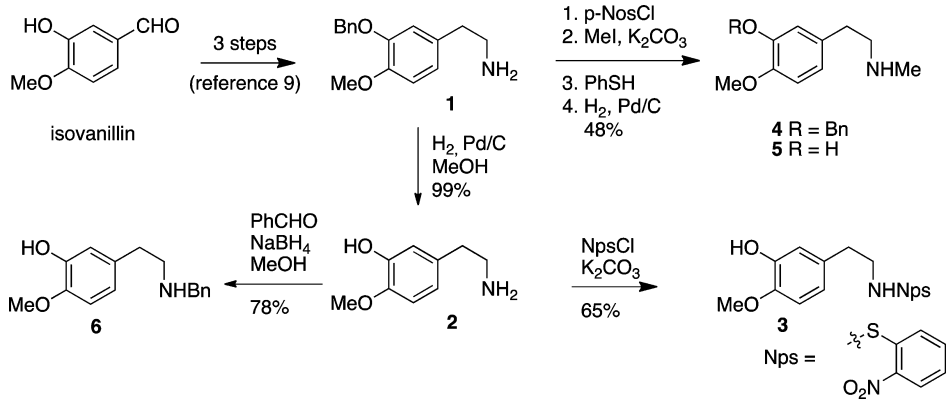
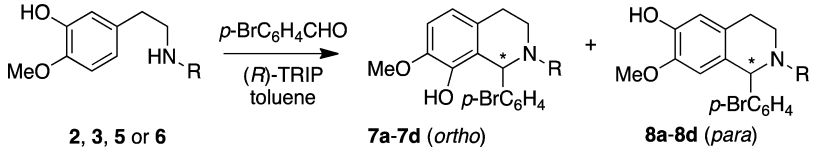


Table 1. Influence of the *N*-Substituent on the Pictet–Spengler Cyclization[a]



entry	R	product, yield (%)	*T* (°C), time	*ortho*/*para*[b]	ee *para*[c] (%)
1	H (**2**)	**7a**/**8a**, 79	110, 48 h	52/48	0
2	methyl (**5**)	**7b**/**8b**, 94	rt, 36 h	15/85	4
3	benzyl (**6**)	**7c**/**8c**, 74	rt, 36 h	30/70	29
4	Nps[d] (**3**)	**7d**/**8d**, 84	90, 48 h	<5/95	49

[a]Reaction conditions: amine (0.02 mmol), *p*-bromobenzaldehyde (0.03 mmol), (*R*)-TRIP (5 mol %, see Table 2 for its structure), toluene (0.2 mL). [b]Determined by ^{1}H NMR. [c]Determined by HPLC. [d]Nps = *o*-nitrophenylsulfenyl.

In this account we will describe successful enantioselective Pictet–Spengler condensations to interesting 1-substituted tetrahydroisoquinolines catalyzed by enantiopure biarylphosphoric acids. Key issues to attain success are the substitution pattern of the aromatic ring in the phenylethylamine starting material and the ancillary substituent on nitrogen.

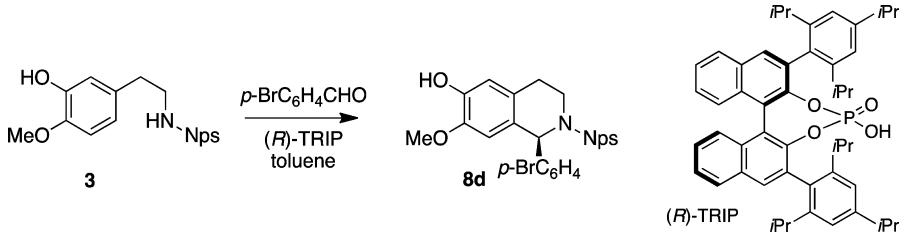
RESULTS AND DISCUSSION

Previous studies in our group on Pictet–Spengler reactions with BINOL-phosphoric acids as catalyst have shown that the electron-donating 3-methoxy substituent in, e.g., 3,4-dimethoxyphenylethylamine is not sufficiently activating the *para*-position for ring closure to occur. A 3-hydroxy substituent as in **2** (Scheme 2) makes the aromatic ring considerably more reactive, while the methyl on *O*-4 protects the catechol part of dopamine against air oxidation.[4,8] Furthermore, it was clear from our tryptamine research and other work that the presence of an appropriate *N*-substituent is crucial for the formation of an iminium intermediate with suitable reactivity.[7d–f]

Our synthetic efforts started with the preparation of the amines for the Pictet–Spengler reactions. Thus, *β*-(3-benzyloxy-4-methoxyphenyl)ethylamine (**1**) was prepared from isovanillin in three steps (Scheme 2) according to a literature procedure.[9] Hydrogenolysis of the benzyl ether

dx.doi.org/10.1021/jo501099h | J. Org. Chem. 2014, 79, 7380–7390

Table 2. Optimization of the Reaction Conditions with 3[a]



entry	cocatalyst	additive	T (°C)	conv (%)	ee (%)
1	–	–	105	40 (3 h)	49
2	(*R*)-BINOL	–	105	40 (3 h)	62
3	(*S*)-BINOL	–	105	70 (3 h)	70
4	(*S*)-BINOL	3 Å MS	105	50 (3 h)	48
5	(*S*)-BINOL	4 Å MS	105	40 (3 h)	44
6	(*S*)-BINOL	argon[b]	105	90 (3 h)	72
7	(*S*)-BINOL	argon	90	100 (18 h)	73[c]

[a]Reaction conditions: Nps-amine **3** (0.02 mmol), *p*-bromobenzaldehyde (0.03 mmol), (*R*)-TRIP (5 mol %), BINOL (20 mol %), toluene (0.2 mL). [b]Slow argon flow to remove water. [c]10 mol % (*R*)-TRIP. Nps = *o*-nitrophenylsulfenyl.

produced primary amine **2**, which was converted into *o*-nitrophenylsulfenamide **3** and *N*-(benzyl)phenylethylamine **6** in single steps. *N*-Methyl derivative **5** was prepared from **1** via *N*-nosylation followed by alkylative methylation to give **4** and subsequent hydrogenolytic debenzylation.

The primary amine **2** quickly formed the corresponding imine when heated with *p*-bromobenzaldehyde under BINOL-phosphoric acid catalysis in toluene (Table 1, entry 1). However, subsequent Pictet–Spengler cyclization was rather slow to provide a remarkable 1:1 mixture of *ortho*/*para* regioisomers without any enantioselectivity. On the other hand the secondary *N*-methyl and *N*-benzyl amines **5** and **6** showed good Pictet–Spengler condensation already at room temperature (Table 1, entries 2 and 3). Moderate *ortho*/*para* regioselectivity was observed, with low ee for the desired *para*-isomer. Apparently, iminium ion formation between the secondary amine and an aldehyde occurred readily, requiring only a weakly acidic catalyst such as, e.g., a phenolic OH. To increase the contribution of the BINOL-phosphoric acid catalyst to iminium ion formation, the substituent on nitrogen had to become more electron-withdrawing. Terada et al. have shown that *N*-Boc and *N*-phosphinyl substituted phenylethylamines prevent formation of the iminium ion with aldehydes and only marginal Pictet–Spengler reaction occurred.[8]

We then turned our attention to sulfenyl substituents on nitrogen, which have electron-withdrawing properties in between *N*-alkyl and *N*-carbonyl substituents. The tritylsulfenyl (Ph_3CS) substituent, a nitrogen protecting group that previously showed good results in the synthesis of β-carbolines from tryptamines, was not stable enough under the required Pictet–Spengler conditions.[10] It eventually appeared that the *ortho*-nitrophenylsulfenyl substituent (Nps, see **3**) was the group of choice. *o*-Nitrophenyl-sulfenamides have excellent properties with respect to stability and crystallinity (bright yellow colored), although their NMR spectra often suffer from broad signals due to hindered rotation about the NS-bond.[11] The Nps group has been used as an *N*-protecting group in, e.g., peptide chemistry and as an activating group in Friedel–Craft reactions.[12] The Nps-group was readily introduced by use of commercially available *o*-nitrophenylsulfenyl chloride. Removal of this protecting/activating Nps-group is known to occur in high yield through treatment with dilute hydrochloric acid.

In the event (Table 1, entry 4) Nps-amine **3** cyclized in good yield at 90 °C. This temperature is probably required to generate the *N*-sulfenyliminium ion. A first screening with **3** and *p*-bromobenzaldehyde showed that (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL-phosphoric acid [(*R*)-TRIP] was the optimal catalyst. In all reactions the amount of the "*ortho*"-cyclization product was reduced to less than 5%. Further optimization of the ee was accomplished by using (*S*)-BINOL as a cocatalyst (Table 2). Water formed during the reaction might have a negative effect on the reaction, but addition of drying agents such as molecular sieves or sodium sulfate to the reaction mixture had a negative effect on both the conversion and the ee. Reproducible results could be obtained by passing a slow argon flow over the solution at 90 °C, thereby azeotropically removing water that is formed during the condensation.

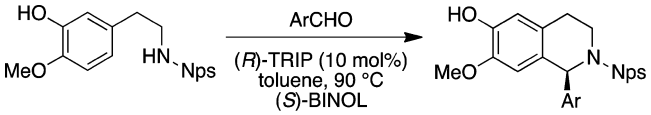
Next the scope in the aldehyde was examined. A series of aromatic aldehydes revealed that substituent have a strong influence on the ee (Table 3). Benzaldehydes with an electron-withdrawing substituent at the *para*-position gave good ee's (entries 4, 5, 7, 9), while benzaldehyde itself and its *p*-methoxy analogue gave considerably lower values (entries 1 and 6). This could be a result of a more intimate ion pair in the ring closing transition state derived from electron-deficient aldehydes, inducing a stronger interaction with the (*R*)-TRIP counterion. Apparently, *meta*- and *ortho*-substituents fit less well in the transition state with (*R*)-TRIP and require further catalyst optimization (entries 2, 3, 8, 10, 11).

The enantiomeric purity of a number of Pictet–Spengler products could be readily increased by making use of the crystallization properties of the Nps-substituent. Both the *p*-Cl and *p*-Br derivatives **9d** and **8d** completely crystallized as racemates from dichloromethane/petroleum ether solutions, leaving the virtually pure (*S*)-enantiomer in the filtrate. To prove its absolute configuration the former *p*-chlorophenyl-tetrahydroisoquinoline (**9d**) was converted to **11** ($[\alpha]_D^{20}$ = +224) in three simple steps (Scheme 3). This confirmed the (*S*)-configuration of **11**, as the (*R*)-enantiomer of **11** ($[\alpha]_D^{20}$ = −206, 98% ee) is well-known as an AMPA receptor antagonist.[3c]

Aliphatic aldehydes appeared to be more reactive in the Pictet–Spengler condensation than the aromatic aldehydes so

dx.doi.org/10.1021/jo501099h | J. Org. Chem. 2014, 79, 7380–7390

Table 3. Pictet–Spengler with Aromatic Aldehydes[a]



3 8d, 9a-9j

entry	ArCHO	product	yield (%)[b]	ee (%)	ee refined (%)[c]
1	PhCHO	**9a**	75	26	–
2	2-ClC_6H_4CHO	**9b**	83	0	–
3	3-ClC_6H_4CHO	**9c**	75	47	–
4	4-ClC_6H_4CHO	**9d**	83	71 (*S*)	99
5	4-BrC_6H_4CHO	**8d**	79	73 (*S*)	99
6	4-$MeOC_6H_4CHO$	**9e**	62	0	–
7	4-$CF_3C_6H_4CHO$	**9f**	79	86 (*S*)	–
8	3-$NO_2C_6H_4CHO$	**9g**	85	28	–
9	4-$NO_2C_6H_4CHO$	**9h**	51	68	–
10	3,4-$(MeO)_2C_6H_4CHO$	**9i**	79	24	
11	2-naphthylCHO	**9j**	80	64	–

[a]Reaction conditions: Nps-amine **3** (0.2 mmol), aldehyde (0.3 mmol), (*R*)-TRIP (10 mol %), (*S*)-BINOL (20 mol %), toluene, 90 °C, slow argon flow, 18 h. [b]Isolated yield. Nps = *o*-nitrophenylsulfenyl. [c]ee of the product in the filtrate after removal of the crystalline racemate.

that the reactions were conducted at a somewhat lower temperature of 80 °C with 5 mol % catalyst (Table 4). *n*-Hexanal was selected for optimization studies. Small improvements were obtained by using (*S*)-BINOL and acetic acid as cocatalysts. Again the use of molecular sieves as drying agents had a negative effect on both the yield and the ee. Acetoxyacetaldehyde (Tabel 4, entry 5) was so reactive that the reaction could be carried out at room temperature, but this did not result in a higher ee. The product **16** had the opposite configuration as the major enantiomer in comparison with the products **12**–**15** (note that all compounds are designated *R* because of a change in substituent priorities). The products from the four functionalized aldehydes (Table 4, entries 2–5) could be obtained in high enantiomeric purity via recrystallization and were then further converted into alkaloids and bioactive compounds (Schemes 4–7).

tert-Butyl 4-oxobutanoate (Table 4, entry 2) appeared to be a much more suitable precursor than the corresponding methyl ester for the synthesis of the popular target alkaloid crispine A (**19**),[13] both in terms of enantioselectivity and crystallization properties. The Pictet–Spengler product **13** (99% ee, after removal of the crystalline racemate) was first treated with dry HCl in ethanol (generated from acetyl chloride). The resulting mixture of the secondary amine and the ethyl sulfenate byproduct was heated in refluxing xylene to produce lactam **17**. The presence of the ethyl sulfenate byproduct in this cyclization process seemed to have some beneficial effect, as earlier removal of the sulfenate byproduct gave a much lower yield of the lactam and a considerable amount of oxidation to an isoquinoline. Subsequent *O*-methylation of purified **17** afforded **18** and removal of the carbonyl through treatment with $LiAlH_4$ then gave crispine A (**19**) as shown in Scheme 4.

For the synthesis of calycotomine (**21**)[14] a suitably protected 2-hydroxyacetaldehyde was required as the starting material. After comparing several protecting groups such as benzyl, TBDMS and pivaloyl, acetoxyacetaldehyde was selected as the most convenient with respect to deprotection and crystallization properties (Table 4, entry 5 and Scheme 5). The Pictet–Spengler product (58% ee) was *O*-methylated before the acetyl group was removed from the primary alcohol. The racemic **20** was allowed to crystallize, which left the virtually enantiopure product in the mother liquor. The sulfenamide NS-bond in **20** was then cleaved in the presence of thiophenol (in order to prevent partial intramolecular sulfenylation of the primary alcohol) providing the alkaloid calycotomine as a crystalline product.

(*R*)-(+)-Colchietine (**22**) was prepared in two steps by deprotection and *N*-demethylation of *p*-methoxyphenylethyltetrahydroisoquinoline (**14**, Scheme 6). This alkaloid was isolated from *Colchicum szovitsii* and its (*S*)-(+) configuration was assigned on the basis of comparison with other alkaloids.[15] In chloroform we measured a specific rotation of +8, but in methanol as a solvent we observed no significant rotation, although the literature reports a value of +8 in this solvent. A recent synthetic publication on the (*S*)-enantiomer of colchietine by Uenishi et al. describes a rotation of +1.9 in methanol (87% ee), which demonstrates the fluctuation of these values.[16] Better proof of the configuration was obtained by conversion of **14** into trimethoxytetrahydroisoquinoline **23**, of which the (*R*)-configuration has been confirmed by degradation studies.[17] Further support was inferred from HPLC-analysis, as on an AD-Chiralpak or ODH-Chiralcel column all of the tetrahydroisoquinoline (*S*)-enantiomers eluted before the (*R*)-enantiomers.[18,19] In agreement with these results, **15** was converted into almorexant precursor **24**, the (*R*)-(+)-enantiomer of the bioactive (*S*)-compound (Scheme 7).[20]

CONCLUSION

To achieve enantioselective Pictet–Spengler condensation of phenylethylamines to 1-substituted 1,2,3,4-tetrahydroisoquinolines, we introduced a moderately strong electron-withdrawing substituent on the nitrogen atom. The Nps (*o*-nitrophenylsulfenyl) substituent demonstrated excellent properties with respect to reactivity and stability. Recrystallization of the Pictet–Spengler products was strongly facilitated by the Nps-group and gave tetrahydroisoquinolines with high enantiopurity. In addition, the Nps substituent displayed protecting group properties that were required for the synthetic transformations

Scheme 3. Synthesis of an AMPA Receptor Antagonist

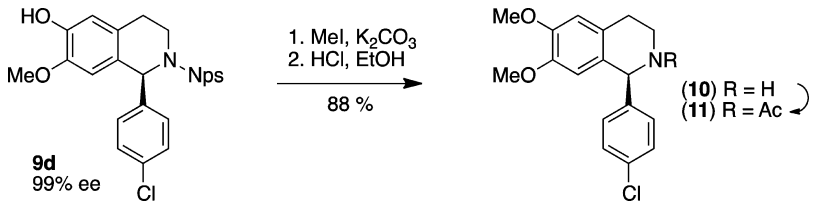


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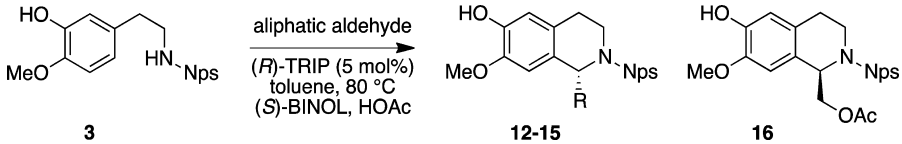
Table 4. Pictet–Spengler with Aliphatic Aldehydes[a]

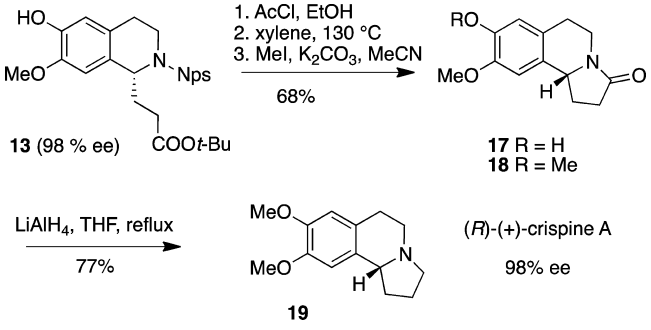


3 12-15 16

entry	RCHO	product	yield (%)[b]	ee (%)	ee refined (%)[c]
1	n-$C_5H_{11}CHO$	**12**	88	70 (*R*)	–
2	t-$BuO_2CCH_2CH_2CHO$	**13**	88	67 (*R*)	99
3	p-$MeOC_6H_4CH_2CH_2CHO$	**14**	84	72 (*R*)	99
4	p-$F_3CC_6H_4CH_2CH_2CHO$	**15**	75	33 (*R*)	95
5	$AcOCH_2CHO$	**16**	92[d]	58 (*R*)	97

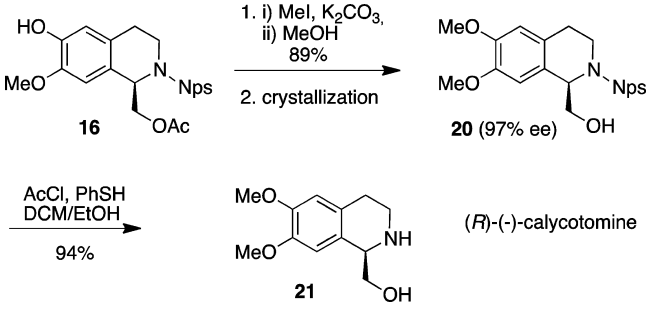
[a]Reaction conditions: Nps-amine **3** (0.2 mmol), aldehyde (0.3 mmol), (*R*)-TRIP (5 mol %), (*S*)-BINOL (20 mol %), HOAc (20–50 mol %), toluene, 80 °C, 18 h. [b]Isolated yield. [c]ee of the product in the filtrate after removal of the crystalline racemate, except for entry 3, in which case the virtually pure enantiomer crystallized. [d]Slow addition of the aldehyde; reaction at rt.

Scheme 4. Synthesis of (*R*)-Crispine A



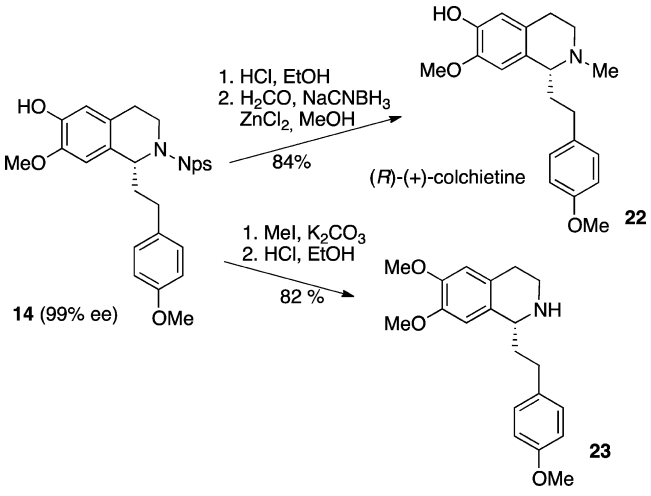
13 (98 % ee) 17 R = H 18 R = Me 19

Scheme 5. Synthesis of (*R*)-Calycotomine



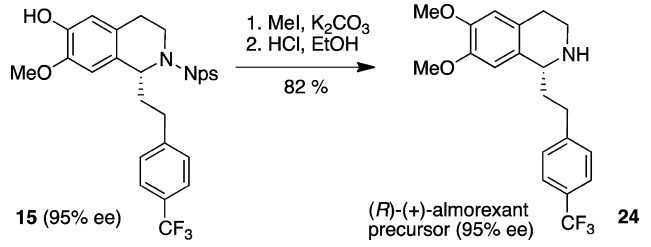
16 20 (97% ee) 21

Scheme 6. Synthesis of (*R*)-Colchietine and the Isomer 23



14 (99% ee)

Scheme 7. Synthesis of an (*R*)-Almorexant Precursor



15 (95% ee)

toward a series of biologically relevant alkaloids and bioactive compounds.

EXPERIMENTAL SECTION

General Information. All ^1H NMR and ^{13}C NMR spectra (APT) were recorded (^1H 400 MHz, ^{13}C 100 MHz) at room temperature in $CDCl_3$. Accurate mass measurements were performed with electrospray ionization (ESI). All reactions were carried out in oven-dried glassware with magnetic stirring under a nitrogen atmosphere. THF was freshly distilled from sodium and benzophenone. Toluene was distilled over calcium hydride and stored on 4 Å molecular sieves. Aldehydes were purified by recrystallization, distillation or chromatography on silica gel. (*R*)-3,3′-Bis(2,4,6-triisopropylphenyl)-BINOL-phosphoric acid [(*R*)-TRIP] was prepared according to a literature method.[21] All Nps-protected tetrahydroisoquinolines were bright yellow, stable compounds. The ^1H and ^{13}C NMR spectra, however, showed extreme line broadening for atoms in the vicinity of the nitrogen–sulfur bond.[11b]

***β*-(3-Hydroxy-4-methoxyphenyl)ethylamine (2).** A solution of *β*-(3-benzyloxy-4-methoxyphenyl)ethylamine **1**[9] (9.00 g, 35.0 mmol) in methanol (200 mL) was stirred with 10% Pd/C (0.9 g) under a balloon of hydrogen gas for 18 h at rt. After filtration of the catalyst and removal of the solvent compound **2** (5.85 g, 35.0 mmol, 100%) was obtained as a solid: mp 139–150 °C; IR (film) ν 3337, 3275, 2932, 1511 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.79 (d, J = 8.2 Hz, 1 H), 6.62 (d, J = 1.9 Hz, 1 H), 6.54 (dd, J = 8.2, 1.9 Hz, 1 H), 4.0 (broad, NH, OH, H_20), 3.71 (s, 3 H), 2.69 (m, 2 H), 2.49 (m, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.8, 146.2, 133.1, 119.2, 116.3, 112.5, 55.9, 39.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{14}NO_2$ 168.1025, found 168.1016.

***N*-(2-Nitrophenylsulfenyl)-*β*-(3-hydroxy-4-methoxyphenyl)-ethylamine (3).** Amine **2** (1.67 gr, 10.0 mmol) was dissolved in a mixture of $CHCl_3$ (100 mL), methanol (5 mL) and triethylamine (0.5 mL) in a 250 mL flask with stirring and heating until fully dissolved. The solution was cooled to 0 °C, 100 mL saturated K_2CO_3 solution in water was added, and after stirring for 5 min 2-nitrophenylsulfenyl chloride (2.28 gr, 12.0 mmol) was added in three portions. After vigorous stirring for 1 h TLC analysis [silica gel, ethyl acetate/

dx.doi.org/10.1021/jo501099h | J. Org. Chem. 2014, 79, 7380–7390

methanol/25% NH_4OH (v/v/v = 90/8/2) as eluent] confirmed full conversion. Extractive workup with $CHCl_3$, drying over $MgSO_4$ and removal of the solvents gave a crude mixture from which some solid Nps-dimer was removed by trituration with an ethyl acetate/petroleum ether mixture. The product was obtained in pure form by flash chromatography [silica gel, dichloromethane/petroleum ether/ethyl acetate (v/v/v = 50/50/2−50/50/6) as eluent]. Crystallization occurred after complete removal of residual ethyl acetate by coevaporation twice with dichloromethane. Dissolving the product in dichloromethane, addition of petroleum ether and cooling in ice gave **3** as yellow crystals (2.09 gr, 6.5 mmol, 65%): mp 77−78 °C; IR (film) ν 3488, 3350, 2935, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, J = 8.3, 2.0 Hz, 1 H), 7.81 (dd, J = 8.3, 1.2 Hz, 1 H), 7.59 (m, 1 H), 7.25 (m, 1 H), 6.85−6.82 (m, 2 H), 6.75 (m, 1 H), 5.63 (s, 1 H), 3.91 (s, 3 H), 3.22 (m, 2 H), 2.85 (m, 2 H), 2.72 (t, J = 5.7 Hz, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 145.4, 145.1, 142.3, 133.5, 131.8, 125.5, 124.3, 124.1, 120.2, 114.8, 110.7, 55.8, 52.4, 36.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_4S$, 321.0909, found, 321.0895. Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.22; H, 5.18; N, 8.68.

***N*-Methyl-β-(3-benzyloxy-4-methoxyphenyl)ethylamine (4).** 4-Nitrophenylsulfonyl chloride (6.65 g, 30.0 mmol) was added in three portions to a solution of β-(3-benzyloxy-4-methoxyphenyl)ethylamine **1**[9] (6.17 g, 24.0 mmol) and triethylamine (5.7 mL, 40 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 °C. The ice bath was removed, and after stirring for 2 h water (100 mL) was added. Extractive workup and flash chromatography [silica gel, petroleum ether/ethyl acetate (v/v = 75/25−40/60) as eluent] yielded crude *N*-4-nitrophenylsulfonyl-β-(3-benzyloxy-4-methoxyphenyl)ethylamine (8.85 g, 20.0 mmol, as a glass, which was immediately dissolved in anhydrous DMSO (75 mL) and stirred with K_2CO_3 (13.8 g, 100 mmol) and iodomethane (1.56 mL, 25.0 mmol) for 90 min at rt. Thiophenol (5.65 mL, 55 mmol) was added, and stirring was continued for 4 h. Extractive workup with ethyl acetate and chromatographic purification [silica gel, petroleum ether/ethyl acetate (v/v = 75/25−0/100) and ethyl acetate/methanol/triethylamine (v/v/v = 93/5/2) as eluent] gave **4** (3.03 g, 11.2 mmol, 56%) as a syrup: IR (film) ν 2932, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2 H), 7.38 (m, 2 H), 7.33 (m, 1 H), 6.85 (m, 1 H), 6.77 (m, 2 H), 5.17 (s, 2 H), 3.89 (s, 3 H), 2.77 (m, 2 H), 2.72 (m, 2 H), 2.40 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 147.8, 137.0, 132.4, 128.3, 127.6, 127.2, 121.1, 114.7, 111.8, 70.8, 55.9, 53.1, 36.2, 35.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{22}NO_2$, 272.1651, found, 272.1658.

***N*-Methyl-β-(3-hydroxy-4-methoxyphenyl)ethylamine (5).** A solution of **4** (0.50 g, 1.84 mmol) in methanol (20 mL) was stirred with 10% Pd/C (0.15 g) under a balloon of hydrogen gas for 16 h at rt. After filtration of the catalyst and removal of the solvent compound **5** (0.33 g, 1.82 mmol, 99%) was obtained as a glass: IR (film) ν 2500−3200 (broad), 1501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, 1 H, J = 8.2 Hz, 6.68, (d, 1 H, J = 2.0 Hz), 6.61 (dd, 1 H, J = 8.2, 2.0 Hz), 5.42 (broad, 2 H, OH, NH), 3.81 (s, 3 H), 2.83 (m, 2 H), 2.71 (m, 2 H), 2.40 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 146.1, 132.0, 118.8, 115.8, 111.3, 55.6, 52.4, 35.4, 34.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{16}NO_2$, 182.1181, found, 182.1178.

***N*-Benzyl-β-(3-hydroxy-4-methoxyphenyl)ethylamine 6.** A solution of β-(3-hydroxy-4-methoxyphenyl)ethylamine **2** (0.816 g, 4.0 mmol) and benzaldehyde (0.45 mL, 4.4 mmol) in methanol (50 mL) was stirred at rt for 18 h. After cooling in an ice bath sodium borohydride (0.228 g, 6.0 mmol) was added in three portions, and stirring was continued at rt for 1 h. Most of the methanol was removed by evaporation, and the residue was quenched with dilute aqueous sodium carbonate and extracted with ethyl acetate. Flash chromatography [silica gel, ethyl acetate and ethyl acetate/methanol/triethylamine (v/v/v = 92/5/3) as eluent] and recrystallization from ethyl acetate/petroleum ether gave **6** (0.903 g, 3.51 mmol, 78%) as needles: mp 87−88.5 °C; IR (film) ν 2934, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5 H), 6.79 (d, J = 8.2, 1 H), 6.76 (m, 1 H), 6.68 (dd, J = 8.2, 2.0 Hz, 1 H), 3.88 (s, 3 H), 3.82 (s, 2 H), 2.90 (m, 2 H), 2.76 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 145.7, 139.2, 132.3, 128.3, 128.1, 126.9, 119.3, 115.5, 111.0, 55.7, 53.4, 49.9, 34.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{20}NO_2$, 258.1494, found, 258.1506.

1-(4-Bromophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (7a) and 1-(4-Bromophenyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (8a). A solution of β-(3-hydroxy-4-methoxyphenyl)ethylamine **2** (68.4 mg, 0.40 mmol), 4-bromobenzaldehyde (82.5 mg, 0.50 mmol) and (*R*)-TRIP (15.0 mg, 5 mol %) in toluene (4 mL) was heated at 110 °C under a slow argon flow to remove water. After 30 min the vessel was stoppered, and heating was continued for 48 h. Chromatographic separation [silica gel, ethyl acetate/methanol/25% NH_4OH (v/v = 94/4/2) as eluent] gave **7a** as a glass (*ortho* isomer, 54.5 mg, 0.163 mmol, 41%) with 24% ee [Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, 0.5 mL/min, t (minor) = 22.37 min, t (major) = 26.26 min]; IR (film) ν 2932, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 2 H), 7.07 (m, 2 H), 6.81 (d, J = 8.3 Hz, 1 H), 6.72 (d, J = 8.3 Hz, 1 H), 5.30 (s, 1 H), 3.85 (s, 3 H), 2.70−2.95 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 143.3, 142.2, 131.1, 129.9, 128.9, 123.1, 120.6, 119.7, 109.6, 56.0, 54.8, 38.4, 28.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$, 334.0443, found, 334.0431.

8a: glass, *para* isomer, 50.5 mg, 0.151 mmol, 38%, with 0% ee [Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, 0.5 mL/min, t = 16.70 min, t = 22.44 min); IR (film) ν 2920, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.20) d, 2 H), 6.71 (s, 1 H), 6.23 (s, 1 H), 5.06 (s, 1 H), 3.71 (s, 3 H), 3.25 (m, 1 H), 3.10 (m, 1 H), 2.96 (m, 1 H), 2.75 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 144.4, 144.0, 131.5, 130.7, 128.5, 128.4, 121.2, 114.6, 110.1, 99.9, 60.8, 55.9, 41.7, 28.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$, 334.0443, found, 334.0439.

***N*-Methyl-1-(4-bromophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (7b) and *N*-Methyl-1-(4-bromophenyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (8b).** A solution of *N*-methyl-β-(3-hydroxy-4-methoxyphenyl)ethylamine **5** (72.4 mg, 0.40 mmol), 4-bromobenzaldehyde (82.5 mg, 0.50 mmol) and (*R*)-TRIP (15.0 mg, 5 mol %) in toluene (4 mL) was stirred at rt for 36 h. Chromatography [silica gel, ethyl acetate/petroleum ether (v/v = 20/80−50/50) as eluent] gave **7b** as a glass (*ortho* isomer, 23.4 mg, 0.068 mmol, 17%) with 24% ee [Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, 0.5 mL/min, t (minor) = 10.49 min, t (major) = 18.77 min]; ^1H NMR (400 MHz, $CDCl_3$, selected signals taken from an *ortho*/*para* mixture) δ 6.77 (d, J = 8.3 Hz, 1 H, 6.71 (d, J = 8.3 Hz, 1 H), 4.84 (bs, 1 H), 3.77 (s, 3 H), 2.37 (s, 3 H). **8b** (glass, *para* isomer, 106.8 mg, 0.307 mmol, 77%) with 7% ee [Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, 0.5 mL/min, t (minor) = 8.93 min, t (major) = 12.19 min]; IR (film) ν 2948, 2786, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2 H), 7.17 (m, 2 H), 6.66 (s, 1 H), 6.05 (s, 1 H), 4.20 (m, 1 H), 3.60 (s, 3 H), 3.06−3.15 (m, 2 H), 2.55−2.75 (m, 2 H), 2.23 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 144.1, 131.3, 130.6, 127.1, 121.0, 119.0, 113.9, 110.4, 70.2, 55.8, 51.8, 44.0, 28.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{19}BrNO_2$, 348.0599, found, 348.0600.

***N*-Benzyl-1-(4-bromophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (7c) and *N*-Benzyl-1-(4-bromophenyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (8c).** A solution of *N*-benzyl-β-(3-hydroxy-4-methoxyphenyl)ethylamine **1c** (102.8 mg, 0.40 mmol), 4-bromobenzaldehyde (82.5 mg, 0.50 mmol) and (*R*)-TRIP (15.0 mg, 5 mol %) in toluene (4 mL) was stirred at rt for 36 h. Chromatography with ethyl acetate/petroleum ether mixtures gave **7c** as a glass (*ortho* isomer, 37.8 mg, 0.089 mmol, 22%) with 24% ee [Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, 0.5 mL/min, t (minor) = 10.49 min, t (major) = 18.77 min]; IR (film) ν 3524, 2926, 1493, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.42 (m, 7 H), 7.10 (m, 2 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.74 (d, J = 8.3 Hz, 1 H), 5.52 (s, 1 H), 5.02 (s, 1 H), 3.87 (s, 3 H), 3.73 (d, J = 13.4 Hz, 1 H), 3.65 (d, J = 13.4 Hz, 1 H), 2.9−3.05 (m, 2 H), 2.65−2.75 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 142.6, 141.4, 139.4, 131.1, 130.6, 128.9, 128.4, 128.2, 127.0, 122.8, 120.5, 119.4, 109.4, 59.9, 57.7, 56.0, 43.1, 25.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{23}BrNO_2$, 424.0912, found, 424.0930.

dx.doi.org/10.1021/jo501099h | J. Org. Chem. 2014, 79, 7380−7390

8c: glass, *para* isomer, 88.2 mg, 0.208 mmol, 52%, with 29% ee [Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, 0.5 mL/min, *t* (minor) = 9.94 min, *t* (major) = 11.33 min]; IR (film) ν 3524, 2931, 1511, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2 H), 7.24−7.35 (m, 7 H), 6.70 (s, 1 H), 6.17 (s, 1 H), 5.53 (br, 1 H, OH), 4.54 (m, 1 H), 3.79 (d, *J* = 13.6 Hz, 1 H), 3.67 (s, 3 H), 3.32 (d, *J* = 13.6 Hz, 1 H), 3.05 (m, 1 H), 2.94 (m, 1 H), 2.70 (m, 1 H), 2.53 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 144.0, 143.7, 139.2, 131.3, 131.2, 131.1, 130.6, 128.9, 128.6, 128.2, 127.8, 126.9, 120.9, 113.9, 110.7, 67.4, 58.6, 55.9, 46.8, 28.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}BrNO_2$, 424.0912, found, 424.0924.

Pictet−Spengler Reactions of *p*-Bromobenzaldehyde with 2-Nitrophenylsulfenyl Substituted Phenylethylamine 3: Optimization Studies. The reactions were performed with amine **3** (0.02 mmol) and *p*-bromobenzaldehyde (0.03 mmol) in 0.2 mL of toluene. The conversion of the bright yellow Nps-derivatives was conveniently followed using TLC [silica gel, ethyl acetate/petroleum ether (v/v = 20/80−50/50) or dichloromethane/petroleum ether/ethyl acetate (v/v/v = 50/50/2−50/50/4) as eluent]. HPLC samples for ee-determination were prepared by scratching the yellow product spot (**8d**) from the TLC-plate, followed by extraction of the silica gel with a mixture of *n*-heptane/*i*-propanol (v/v = 85/15, ca. 0.1 mL), filtration and direct analysis.

General Procedure for the Pictet−Spengler Reaction of Aromatic Aldehydes with *N*-2-Nitrophenylsulfenyl Substituted Phenylethylamine 3. In a dry argon flushed flask Nps-protected amine **3** (64.1 mg, 0.2 mmol), (*R*)-TRIP (15.0 mg, 10 mol %) and (*S*)-BINOL (11.4 mg, 20 mol %) were dissolved in toluene (5 mL) and stirred for 10 min under argon. The mixture was heated to 90 °C, and the (substituted) benzaldehyde (0.30 mmol) added. The mixture was stirred overnight at 90 °C while the azeotropic toluene/water mixture was removed by a slow argon flow. The remaining solvent was removed by rotary evaporation, and the crude mixture was purified by flash chromatography [silica gel, dichloromethane/petroleum ether/ethyl acetate (v/v/v = 50/50/2−50/50/4) as eluent]. Removal of the solvent and coevaporation with dichloromethane (2−3 times to remove residual ethyl acetate) leads to the pure products. If required, recrystallization of the product to high enantiopurity was performed by precipitation of the racemate from concentrated dichloromethane solutions with petroleum ether. All Nps-protected tetrahydroisoquinolines were bright yellow, stable and readily purified. The ^1H and ^{13}C NMR spectra, however, showed extreme line broadening for atoms in the vicinity of the nitrogen−sulfur bond. The (*S*)-configuration was assigned to the aryl-substituted tetrahydroisoquinolines in analogy with **9d**[3b] and is based on the (+) rotation and on the elution order in chiral HPLC. Chiral HPLC: Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, flow 0.5 mL/min, 254 nm. (*S*)-**8d** (4-Br): yellow glass, 79% yield, 72% ee; after removal of the crystalline racemate: 52% yield, >99% ee; t_R (major) = 16.5 min, t_R (minor) = 22.2 min. Data: $[\alpha]_D^{20}$ = +107 (*c* = 1.04, $CHCl_3$); IR (film) ν 3526, 2929, 1510, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.3 Hz, 1 H), 7.92 (d, *J* = 8.3 Hz, 1 H), 7.55 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1 H), 7.39 (broad d, *J* = 7.9 Hz, 2 H), 7.23 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1 H), 7.08 (broad d, *J* = 8.0 Hz, 2H), 6.79 (s, 1 H), 6.25 (s, 1 H), 5.59 (s, 1 H), 5.16 (broad s, 1 H), 3.71 (s, 3 H), 3.53−3.34 (m, 1 H), 3.21−3.05 (m, 2 H), 2.95−2.85 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 145.0, 133.9, 131.4, 131.1, 127.5, 126.1, 125.0, 124.8, 121.8, 114.4, 110.4, 56.1, 49.3; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}BrN_2O_4S$, 487.0327, found, 487.0327.

(*S*)-**9a** (Ph): yellow glass, 75% yield, 26% ee; t_R (major) = 15.1 min, t_R (minor) = 19.8 min; $[\alpha]_D^{20}$ = +18 (*c* = 0.5, $CHCl_3$); IR (film) ν 3519, 2931, 1504, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.1 Hz, 1 H), 8.01 (d, *J* = 8.1 Hz, 1 H), 7.57 (m, 1 H), 7.18−7.36 (m, 6 H), 6.82 (s, 1 H), 6.34 (s, 1 H), 5.63 (broad s, 1 H, OH), 5.25 (broad, 1 H), 3.73 (s, 3 H), 2.8−3.7 (broad, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 144.7, 142.1, 133.7, 129.3, 128.1, 127.5, 127.3, 125.8, 125.1, 124.5, 114.2, 110.4, 55.9, 48.9; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}N_2O_4S$, 409.1222, found, 409.1218.

(*S*)-**9b** (2-Cl): yellow glass, 83% yield, 0% ee; t_R = 14.3 min, t_R = 16.8 min; IR (film) ν 3521, 2930, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.3, 1.2 Hz, 1 H), 7.97 (broad d, *J* = 8.3 Hz, 1 H), 7.55 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.25−7.14 (m, 2 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 6.93 (broad s, 1 H), 6.78 (s, 1 H), 6.26 (s, 1 H), 5.77 (broad s, 1 H), 5.57 (s, 1 H), 3.71 (s, 3 H), 3.43 (broad, 1 H), 3.19 (broad, 1 H), 3.07 (broad, 1 H), 2.86 (broad, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 144.7, 141.8, 140.7, 135.4, 133.5, 130.9, 129.6, 128.7, 127.6, 126.4, 125.6, 125.4, 124.5, 114.2, 110.0, 65.7, 55.9, 47.7, 26.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}ClN_2O_4S$, 443.0832, found, 443.0833.

(*S*)-**9c** (3-Cl): yellow glass, 75% yield, 47% ee; t_R (major) = 26.4 min, t_R (minor) = 42.5 min; $[\alpha]_D^{20}$ = +42.5 (*c* = 1.0, $CHCl_3$); IR (film) ν 3526, 2929, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.56 (t, *J* = 7.7 Hz, 1 H), 7.27−7.06 (m, 5 H), 6.79 (s, 1 H), 6.27 (s, 1 H), 5.61 (broad s, 1 H, OH), 5.18 (s, 1 H), 3.72 (s, 3 H), 2.8−3.7 (broad, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 144.7, 142.0, 134.0, 133.7, 129.3, 129.2, 127.7, 127.5, 125.8, 124.9, 124.6, 114.3, 110.2, 55.9, 49.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}ClN_2O_4S$, 443.0832, found, 443.0832.

(*S*)-**9d** (4-Cl): yellow glass, 83% yield, 71% ee; after removal of the crystalline racemate 57% yield, > 99% ee; t_R (major) = 15.7 min, t_R (minor) = 20.9 min; $[\alpha]_D^{20}$ = +104 (*c* = 1.0, $CHCl_3$); IR (film) ν 3525, 1505, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.3 Hz, 1 H), 7.94 (d, *J* = 8.2 Hz, 1 H), 7.56 (t, *J* = 7.7 Hz, 1 H), 7.23 (broad, 3 H), 7.15 (broad, 2 H), 6.79 (s, 1 H), 6.27 (s, 1 H), 5.66 (broad s, 1 H, OH), 5.19 (s, 1 H), 3.71 (s, 3 H), 3.44 (broad, 1 H), 3.29−3.04 (broad, 2 H), 2.99−2.83 (broad, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 144.7, 142.0, 133.8, 133.4, 130.6, 128.2, 127.2, 125.8, 124.8, 124.6, 114.2, 110.2, 55.9, 49.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}ClN_2O_4S$, 443.0832, found, 443.0821.

(*S*)-**9e** (4-OMe): yellow glass, 62% yield, 0% ee; t_R = 19.2 min, t_R = 26.2 min; IR (film) ν 3507, 2920, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.3 Hz, 1 H), 8.00 (d, *J* = 8.3 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 7.12 (broad d, 2 H), 6.80 (broad d, 2 H), 6.78 (s, 1 H), 6.31 (s, 1 H), 5.17 (s, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.50 (broad, 1 H), 3.13 (m, 2 H), 2.87 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 145.2, 144.6, 142.1, 133.7, 130.7, 130.5, 127.2, 125.7, 125.1, 124.4, 114.1, 113.9, 113.5, 113.4, 110.4, 55.9, 55.2, 48.7; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}N_2O_5S$, 439.1328, found, 439.1336.

(*S*)-**9f** (4-CF_3): yellow glass, 79% yield, 86% ee; t_R (major) = 14.5 min, t_R (minor) = 21.2 min; $[\alpha]_D^{20}$ = +70 (*c* = 0.87, $CHCl_3$); IR (film) ν 3530, 2928, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (m, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 7.56 (m, 3 H), 7.20−7.40 (m, 3 H), 6.83 (s, 1 H), 6.28 (broad, 1 H), 5.64 (broad, 1 H), 5.31 (m, 1 H), 3.73 (s, 3 H), 3.46 (broad, 1 H), 3.10−3.30 (m, 2 H), 2.95−3.05 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 144.9, 142.1, 133.8, 127.3, 127.0, 125.9, 125.15, 125.1, 125.0, 124.7, 124.1 (q, *J* = 273 Hz, CF_3), 114.3, 110.1, 55.9, 49.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}F_3N_2O_4S$, 477.1096, found, 477.1097.

(*S*)-**9g** (3-NO_2): yellow glass, 85% yield, 28% ee; t_R (major) = 28.4 min, t_R (minor) = 51.1 min; $[\alpha]_D^{20}$ = +33 (*c* = 1.0, $CHCl_3$); IR (film) ν 3530, 2928, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (m, 1 H) 8.2 (m, 2 H), 8.0 (m, 1 H), 7.64 (m, 2 H), 7.5−7.2 (m, 2 H), 6.87 (s, 1 H), 6.30 (s, 1 H), 5.7, (broad, 1 H, OH), 5.38 (s, 1 H), 3.75 (s, 3 H), 3.6−3.05 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 148.0, 145.4, 144.9, 135.3, 133.9, 133.4, 131.2, 129.3, 129.0, 128.3, 127.3, 127.2, 125.7, 124.8, 124.6, 124.4, 122.6, 117.7, 114.5, 111.0, 110.7, 55.9, 52.5, 49.9, 36.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_3O_6S$, 454.1073, found, 454.10669.

(*S*)-**9h** (4- NO_2): yellow glass, 51% yield, 68% ee; t_R (major) = 32.7 min, t_R (minor) = 50.2 min; $[\alpha]_D^{20}$ = +74 (*c* = 0.98, $CHCl_3$); IR (film) ν 3503, 2933, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (m, 1 H), 8.17−8.05 (m, 2 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.56 (m, 1 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 7.25 (m, 1 H), 6.81 (s, 1 H), 6.21 (broad, 1 H), 5.64 (broad, 1 H), 5.31 (broad, 1 H), 3.70 (s, 3 H), 2.9−3.5 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 145.4, 145.0, 133.9, 130.0, 127.1, 126.0, 124.9, 124.5, 123.5, 114.4, 110.0, 55.9, 49.8; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_3O_6S$, 454.1073, found, 454.1071.

dx.doi.org/10.1021/jo501099h | J. Org. Chem. 2014, 79, 7380−7390

(*S*)-**9i** [3,4-$(MeO)_2$]: yellow glass, 79% yield, 24% ee; t_R (major) = 24.0 min, t_R (minor) = 34.2 min; $[\alpha]_D^{20}$ = +5 (*c* = 0.52, $CHCl_3$); IR (film) ν 3476, 2919, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.1 Hz, 1 H), 8.02 (broad d, *J* = 7.3 Hz, 1 H), 7.54 (m, 1 H), 7.22 (m, 1 H), 6.60−6.80 (m, 3 H), 6.32 (s, 1 H), 5.58 (broad, 1 H, OH), 5.16 (broad, 1 H), 3.85 (s, 3 H), 3.74 (broad, 3 H), 3.71 (s, 3 H), 3.51 (broad, 1 H), 3.06−3.21 (m, 2 H), 2.83−2.95 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 148.4, 145.1, 144.6, 133.6, 127.2, 125.9, 125.1, 124.1, 121.8, 114.1, 112.4, 110.6, 110.4, 56.2, 55.9, 55.8, 48.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_6S$, 469.1433, found, 469.1436.

(*S*)-**9j** (2-naphthyl): yellow glass, 80% yield, 64% ee; t_R (major) = 18.7 min, t_R (minor) = 22.8 min; $[\alpha]_D^{20}$ = +75 (*c* = 1.0, $CHCl_3$); IR (film) ν 3526, 2915, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (m, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.76−7.82 (m, 3 H), 7.78 (d, *J* = 8.2 Hz, 2 H), 7.57−7.54 (m, 2 H), 7.53−7.45 (m, 2 H), 7.44−7.7 (m, 8 H), 7.22 (m, 1 H), 6.86 (s, 1 H), 6.37 (s, 1 H), 5.64 (broad, 1 H), 5.41 (s, 1 H), 3.69 (s, 3 H), 3.40−3.60 (m, 1 H), 3.20 (m, 2 H), 2.92−3.04 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 144.6, 142.1, 133.7, 132.9, 132.8, 128.3, 128.1, 127.9, 127.5, 127.3, 126.1, 126.0, 124.5, 114.2, 110.5, 55.9, 48.8, 29.7, 27.1; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_4S$, 459.1379, found, 459.1382.

(*S*)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10). A mixture of **9d** (39.6 mg, 0.11 mmol, >99% ee), iodomethane (20 μL, 0.32 mmol) and K_2CO_3 (60 mg, 0.43 mmol) in acetonitrile (1.5 mL) was stirred overnight in a stoppered flask at 80 °C. The product obtained after extractive workup (water/CH_2Cl_2) was dissolved in a mixture of CH_2Cl_2 (1 mL) and EtOH (1 mL) at 0 °C, and concentrated HCl (100 μL) was added. The reaction was stirred at this temperature for 3 h and quenched by addition of a semisaturated Na_2CO_3 solution (20 mL). Extraction with ethyl acetate and purification by flash chromatography [silica gel, petroleum ether/ethyl acetate (v/v = 50/50−0/100) and ethyl acetate/methanol (v/v = 90/10) as eluent] gave tetrahydroisoquinoline **10** (23.6 mg, 0.080 mmol, 88%) as a white solid: mp 112−115 °C; $[\alpha]_D^{20}$ = −31 (*c* = 0.61, $CHCl_3$); IR (film) ν 2925, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 6.62 (s, 1 H), 6.19 (s, 1 H), 5.02 (s, 1 H), 3.87 (s, 3 H), 3.64 (s, 3 H), 3.23−3.14 (m, 1 H), 3.08−2.99 (m, 1 H), 2.96−2.87 (m, 1 H), 2.79−2.69 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 147.0, 143.3, 133.0, 130.1, 129.2, 128.4, 127.6, 111.4, 110.6, 60.7, 55.8, 55.7, 41.7, 29.1; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}ClNO_2$, 304.1104, found, 304.1117.

***N*-Acetyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (11).** A solution of **10** (46.1 mg, 0.15 mmol) and acetic anhydride (18 μL) was stirred in $CHCl_3$ (4 mL) at room temperature for 2 h. Extractive workup (aqueous Na_2CO_3/ethyl acetate) and chromatography (silica gel, petroleum ether/ethyl acetate (v/v = 50/50−0/100 as eluent) gave **6** (32.2 mg, 0.090 mmol, 61%) as a glass: $[\alpha]_D^{20}$ = +224 (*c* = 1.1, $CHCl_3$), [literature value for the (R)-enantiomer $[\alpha]_D^{20}$ = −206 (*c* = 1.02, $CHCl_3$), 98% ee][3c]; ^1H NMR (400 MHz, $CDCl_3$, 5/1 mixture of rotamers, the major rotamer is shown) δ 7.24 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 1H), 6.70 (s, 1H), 6.52 (s, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.73−3.80 (m, 1H), 3.38 (ddd, *J* = 16.0, 11.8, 3.3 Hz, 1H), 2.98 (ddd, *J* = 16.4, 11.8, 5.8, 1H), 2.72−2.83 (m, 1H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers, the major rotamer is shown, 2 aromatic carbon signals not observed, δ 168.9, 148.6, 148.2, 133.4, 130.1, 128.4, 126.8, 126.3, 111.7, 56.1, 56.05, 54.0, 40.3, 28.6, 21.5. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}ClNO_3$, 346.1210, found, 346.1208.

General Procedure for the Pictet−Spengler Reaction of Aliphatic Aldehydes with *N*-2-Nitrophenylsulfenyl Substituted Phenylethylamine 3. In a dry argon flushed flask Nps-protected amine **3** (64.1 mg, 0.2 mmol), (*R*)-TRIP (7.6 mg, 5 mol %) (*S*)-BINOL (11.4 mg, 20 mol %) and acetic acid (5.7 μL, 50 mol %) were dissolved in toluene (5 mL) and stirred for 10 min under argon before the aldehyde (0.30 mmol) was added. The mixture was stirred during the indicated time at 80 °C in a stoppered flask. The remaining solvent was removed by rotary evaporation, and the crude mixture was purified by flash chromatography [silica gel, dichloromethane/petroleum ether/ethyl acetate (v/v/v = 50/50/0.5−50/50/4) as eluent]. Removal of the solvent and coevaporation with dichloromethane (2−3 times to remove residual ethyl acetate) led to the pure products. Crystallization to high enantiopurity was performed by precipitation of the major enantiomer (**14**) or the racemate (**13** and **15**) from concentrated dichloromethane solutions with petroleum ether. Compound **16** was crystallized to high enantiopurity after conversion to **20**. All Nps-protected tetrahydroisoquinolines were bright yellow, stable compounds and readily purified. The ^1H and ^{13}C NMR spectra, however, showed extreme line broadening for atoms in the vicinity of the nitrogen−sulfur bond. Chiral HPLC: Chiralcel OD-H, *n*-heptane/isopropanol (v/v = 70/30) as eluent, flow 0.5 mL/min, 254 nm. The (*R*)-configuration of the alkyl-substituted tetrahydroisoquinolines was determined as described in Schemes 3−6 and is further supported by the negative rotation and the elution order in chiral HPLC.

(*R*)-**12**: yellow glass, 88% yield, 64% ee; t_R (minor) = 11.7 min, t_R (major) = 13.3 min; $[\alpha]_D^{20}$ = −7 (*c* = 1.3, $CHCl_3$); IR (film) ν 3508, 2929, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.2 Hz, 1 H), 7.24−8.24 (m, 3 H), 6.72 (s, 1 H), 6.52 (s, 1 H), 5.32 (broad, OH), 4.07 (m, 1 H), 3.89 (s, 3 H), 2.6−3.75 (m, 4 H), 1.75−1.87 (m, 2 H), 1.30 (m, 4 H), 0.88 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 133.7, 125.8, 124.8, 124.4, 114.5, 109.2, 66.6, 56.0, 31.5, 22.6, 14.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_4S$, 403.1692, found, 403.1697.

(*R*)-**13**: Prepared from *tert*-butyl 4-oxobutanoate,[22] yellow glass, 88% yield, 67% ee; after removal of the crystalline racemate 57% yield, 99% ee; chiral HPLC Chiralpak AD, *n*-heptane/isopropanol (v/v = 70/30) as eluent, flow 1.0 mL/min, 254 nm; t_R (minor) = 10.8 min, t_R (major) = 12.8 min; $[\alpha]_D^{20}$ = −13 (*c* = 0.76, $CHCl_3$); IR (film) ν 3495, 2930, 1722, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.2 Hz, 1 H), 7.2−8.2 (broad, 3 H), 6.73 (s, 1 H), 6.59 (s, 1 H), 5.58 (s, 1 H), 4.14 (broad, 1 H), 3.89 (s, 3 H), 2.5−3.7 (broad, 4 H), 2.25−2.50 (broad, 2 H), 2.0−2.3 (broad, 2 H), 1.39 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 145.1, 144.4, 133.8, 125.9, 124.5, 114.9, 109.2, 80.3, 56.0, 32.6, 27.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_6S$, 461.1746, found, 461.1747.

(*R*)-**14**: yellow glass, 84% yield, 72% ee; after crystallization of the major enantiomer 59% yield, >99% ee; t_R (minor) = 24.1 min, t_R (major) = 30.8 min; mp 143.5−145.5 °C; $[\alpha]_D^{20}$ = −42 (*c* = 1.0, $CHCl_3$); IR (film) ν 3514, 2932, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.0 Hz, 1 H), 6.7−8.3 (broad, 8 H), 6.75 (s, 1 H), 6.50 (s, 1 H), 5.67 (bs, OH), 4.17 (broad, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 2.6−3.7 (broad, 6 H), 2,2 (broad, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 145.0, 144.3, 133.9, 133.8, 129.1, 126.0, 124.7, 124.5, 114.5, 113.8, 109.1, 56.0, 55.2; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{27}N_2O_5S$, 467.1641, found, 467.1657. Anal. Calcd for $C_{25}H_{26}N_2O_5S$: C, 64.36; H, 5.62; N, 6.00. Found: C, 64.04; H, 5.76; N, 6.14.

(*R*)-**15**: yellow glass, 75% yield, 33% ee; after removal of the crystalline racemate 26% yield, 95% ee; chiral HPLC Chiralcel OD-H, *n*-heptane/isopropanol (v/v = 70/30) as eluent, flow 0.6 mL/min t_R (minor) = 14.5 min, t_R (major) = 17.4 min; $[\alpha]_D^{20}$ = −38 (*c* = 0.9, $CHCl_3$); IR (film) ν 3510, 2929, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.8 Hz, 1 H), 7.2−8.3 (broad, 8 H), 6.76 (s, 1 H), 6.50 (s, 1 H), 5.60 (s, 1 H, OH), 4.20 (broad, 1 H), 3.87 (s, 3 H), 2.2−3.75 (broad, 6 H), 2.19 (broad, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 144.4, 133.9, 128.6, 126.2, 125.3, 125.2, 124.6, 124.55, 114.5, 108.9, 56.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{24}F_3N_2O_4S$, 505.1409, found, 505.1413.

(*R*)-**16**: yellow glass; reaction conditions, rt, addition of the aldehyde over 6 h, 92% yield, 58% ee; removal of the crystalline racemate was performed with **20**, see below; chiral HPLC Chiralpak AD, *n*-heptane/isopropanol (v/v = 70/30) as eluent, flow 1.0 mL/min, 254 nm; t_R (minor) = 17.8 min, t_R (major) = 22.1 min; $[\alpha]_D^{20}$ = −14 (*c* = 0.71, $CHCl_3$); IR (film) ν 3460, 2925, 1737, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.1 Hz, 1 H), 7.2−8.3 (broad, 3 H), 6.74 (s, 1 H), 6.62 (s, 1 H), 5.71 (broad, OH), 4.25−4.5 (broad, 3 H), 3.87 (s, 3 H), 2.5−3.7 (broad, 4 H), 2.02 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 133.6, 127.6, 125.7, 124.6, 124.2, 114.7, 111.9,

dx.doi.org/10.1021/jo501099h | J. Org. Chem. 2014, 79, 7380−7390

109.3, 66.7, 65.8, 64.6, 55.9, 47.2, 25.7, 21.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_6S$, 405.1120, found, 405.1126.

Pyrrolo-tetrahydroisoquinolidone 17. Acetyl chloride (71.4 μL, 1.0 mmol) was added to dry ethanol (1.5 mL) at 0 °C. After 15 min this solution was added in one portion to a stirred solution of **13** (98% ee, 43.0 mg, 0.093 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The reaction was stirred at this temperature for 1 h and quenched by addition of a semisaturated Na_2CO_3 solution (20 mL). Extraction with ethyl acetate and evaporation gave crude product, which was cyclized in xylene (mixture of isomers, 5 mL) containing triethylamine (100 μL) for 16 h at 130 °C under argon. (Removal of the side product Nps-OEt before cyclization resulted in considerable tetrahydroquinoline oxidation!) Purification by flash chromatography [silica gel, petroleum ether/ethyl acetate (v/v = 50/50−0/100) and ethyl acetate/methanol (v/v = 90/10) as eluent] gave **17** (16.5 mg, 0.071 mmol, 76%) as a glass: $[\alpha]_D^{20}$ = +254 (c = 0.83, $CHCl_3$); IR (film) ν 3200 (broad), 2971, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1 H), 6.56 (s, 1 H), 5.88 (broad, OH), 4.73 (m, 1 H), 4.26 (ddd, J = 15.1, 6.0, 2.3 Hz, 1 H), 3.89 (s, 3 H), 3.02 (m, 1 H), 2.86 (m, 1 H), 2.4−2.7 (m, 4 H), 1.85 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 145.8, 144.5, 128.7, 126.3, 114.7, 106.9, 56.6, 56.0, 37.1, 31.8, 27.9, 27.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{16}NO_3$, 234.1130, found, 234.1138.

***O*-Methylation of 17 to 18.** A mixture of **17** (15.0 mg, 0.064 mmol), iodomethane (20 μL, 0.32 mmol) and K_2CO_3 (60 mg, 0.43 mmol) in acetonitrile (1.5 mL) was stirred overnight in a stoppered flask at 80 °C. Extractive workup (water/ethyl acetate) and chromatography [silica gel, ethyl acetate and ethyl acetate/methanol (v/v = 95/5) as eluent] gave **18** (14.1 mg, 0.057 mmol, 89%) as a glass: $[\alpha]_D^{20}$ = +216 (c = 0.6, $CHCl_3$); IR (film) ν 2926, 1664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1 H), 6.58 (s, 1 H), 4.74 (m, 1H), 4.31 (ddd, J = 14.8, 6.1, 2.2 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.02 (m, 1 H), 2.90 (m, 1 H), 2.4−2.7 (m, 4 H), 1.84 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 148.1, 147.9, 129.3, 125.5, 111.6, 107.6, 56.5, 56.0, 55.9, 37.0, 31.8, 28.1, 27.7.

***(R)*-(+)-Crispine A (19).** Lactam **18** (16.0 mg, 0.065 mmol) was reduced with lithium aluminum hydride (1 M in THF, 0.15 mL) as described in the literature[13f] to give (*R*)-(+)-crispine A (11.7 mg, 0.050 mmol, 77%) as a slowly solidifying oil: mp 53−57 °C; $[\alpha]_D^{20}$ = +93 (c = 0.19, $CHCl_3$), Lit. several values are reported between $[\alpha]_D^{20}$ +90 and $[\alpha]_D^{20}$ +100[13]; IR (film) ν 2925, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1 H), 6.58 (s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.42 (m, 1 H), 3.20 (ddd, J = 14.0, 6.3, 2.8 Hz, 1 H), 3.0−3.25 (m, 2 H), 2.75 (bd, J = 17.4 Hz, 1 H), 2.65 (ddd, J = 11.0, 10.4, 4.8 Hz, 1 H), 2.56 (m, 1 H), 2.34 (m, 1 H), 1.8−2.0 (m, 2 H), 1.74 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3, 147.25, 131.0, 126.2, 111.3, 108.8, 63.0, 56.0, 55.8, 53.1, 48.3, 30.4, 28.1, 22.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1494, found, 234.1505.

1-Hydroxymethyl-*N*-*Nps*-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20). Pictet−Spengler product **16** (from 0.10 mmol **3**) was without purification converted into **20** in two steps. First, product **16**, iodomethane (20 μL, 0.32 mmol) and K_2CO_3 (60 mg, 0.43 mmol) in acetonitrile (1.5 mL) were stirred overnight in a stoppered flask at 80 °C. The suspension was then cooled to rt, and additional K_2CO_3 (90 mg, 0.65 mmol) and methanol (3 mL) were added, and stirring was continued for 3 h. Extractive workup (water/ethyl acetate) and chromatography [silica gel, petroleum ether/ethyl acetate (v/v = 50/50) as eluent] gave **20** (33.3 mg, 0.089 mmol, 89% over three steps) as a glass. Crystallization to increase enantiopurity was achieved by coevaporation with dichloromethane followed by precipitation of the racemate from a concentrated dichloromethane solution by adding petroleum ether. Concentration of the filtrate in vacuo gave **20** as a yellow glass: 19.7 mg, 52% yield (over 3 steps), 97% ee; Chiralpak AD, *n*-heptane/isopropanol (v/v = 70/30) as eluent, flow 1.0 mL/min, 254 nm; t_R (minor) = 10.7 min, t_R (major) = 13.5 min; $[\alpha]_D^{20}$ = −14 (c = 0.71, $CHCl_3$); IR (film) ν 3511, 2934, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.2 Hz, 1 H), 7.3−7.7 (broad, 3 H), 6.69 (s, 1 H), 6.64 (s, 1 H), 42.4 (m, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.7−4.0 (broad, 6 H), 1.92 (broad, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 147.6, 134.1, 127.0, 126.1, 124.7, 111.6, 109.8, 56.0, 55.9.

***(R)*-(−)-Calycotomine (21).** Acetyl chloride (71.4 μL, 1.0 mmol) was added to dry ethanol (1.5 mL) at 0 °C. After 15 min this solution was added in one portion to a stirred solution of **20** (97% ee, 18.0 mg, 0.048 mmol) and thiophenol[23] (15 μL, 0.15 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. After stirring at this temperature for 20 min the reaction was quenched by the addition of triethylamine (0.2 mL), and the solvents were evaporated. Chromatography [silica gel, ethyl acetate−ethyl acetate/methanol/conc. NH_4OH (v/v/v = 90/7/3−82/14/4) as eluent gave (*R*)-(−)-calycotomine **21** (10.0 mg, 0.045 mmol, 94%) as a solid: mp 139−141 °C; $[\alpha]_D^{20}$ = −33 (c = 0.83, water), lit[14a] $[\alpha]_D^{20}$ = −33.7 (c = 1.05, water) 96% ee; IR (film) ν 2600−3200 (broad), 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1 H), 6.59 (s, 1 H), 5.5 (broad, OH), 3.99 (dd, J = 9.2, 4.2 Hz, 1 H), 3.86 (s, 3 H), 3.86 (s, 3 H), 3.78 (dd, J = 10.8, 4.3 Hz, 1 H), 3.64 (dd, J = 10.8, 9.3 Hz, 1 H), 3.0−3.15 (m, 1 H), 2.65−2.75 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 147.4, 127.8, 127.5, 111.9, 109.1, 70.9, 64.0, 56.0, 55.8, 38.7, 37.2, 29.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{18}NO_3$, 224.1287, found, 224.1295.

***(R)*-(+)-Colchietine (22).** Conc. HCl (150 μL) was added to a solution of (*R*)-**14** (99% ee, 70.0 mg, 0.15 mmol) in a mixture of CH_2Cl_2 (3 mL) and ethanol (3 mL) at 0 °C. The reaction was stirred at this temperature for 75 min and quenched by addition of a semisaturated Na_2CO_3 solution (20 mL). Extraction with ethyl acetate and purification by flash chromatography [silica gel, ethyl acetate and ethyl acetate/methanol/conc. NH_4OH (v/v/v = 88/10/2) as eluent] gave (*R*)-(+)-*N*-demethyl-colchietine (43.0 mg, 0.136 mmol, 91%) as a solid: $[\alpha]_D^{20}$ = +37.5 (c = 0.85, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.62 (s, 1 H), 6.56 (s, 1 H), 4.0 (m, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.6−3.9 (broad, NH, OH); 3.25 (m, 1 H), 3.00 (m, 1 H), 2.6−2.85 (m, 4 H), 2.0−2.2 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 145.2, 144.0, 134.2, 130.2, 129.2, 127.7, 114.9, 113.8, 108.5, 56.0, 55.2, 55.1, 40.8, 38.4, 31.4, 29.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{24}NO_3$, 314.1756, found, 314.1771.

Reductive methylation: (*R*)-(+)-*N*-demethyl-colchietine (41.7 mg, 0.133 mmol), paraformaldehyde (24.0 mg, 0.8 mmol), zinc chloride (13 mg) and sodium cyanoborohydride (16.0 mg, 0.25 mmol) were stirred in methanol (7 mL) overnight. Silica gel was added, the solvent was removed and chromatography [silica gel, ethyl acetate and ethyl acetate/methanol/conc. NH_4OH (v/v/v = 92/6/2) as eluent] gave (*R*)-(+)-colchietine **22** (40.1 mg, 0.123 mmol, 92%) as a syrup: ee 98%, Chiralcel OD-H, *n*-heptane/isopropanol (v/v = 70/30) as eluent, flow 0.5 mL/min, 254 nm; t_R (minor) = 10.9 min, t_R (major) = 12.5 min; $[\alpha]_D^{20}$ = +8 (c = 0.80, $CHCl_3$), $[\alpha]_D^{20}$ = 0 (c = 0.80, methanol), lit[15] $[\alpha]_D^{20}$ = +8 (c = 1.0, methanol); IR (film) ν 2925, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 6.7 Hz, 2 H), 6.84 (d, J = 6.7 Hz, 2 H), 6.66 (s, 1 H), 6.52 (s, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.49 (m, 1 H), 3.21 (m, 1 H), 2.65−2.85 (m, 4 H), 2.55−2.65 (m, 1 H), 2.52 (s, 3 H), 1.95−2.2 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 145.1, 144.0, 134.6, 129.3, 128.6, 126.8, 114.3, 113.7, 109.4, 62.7, 56.0, 55.2, 47.6, 42.3, 37.1, 30.8, 24.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{26}NO_3$, 328.1913, found, 328.1927.

***(R)*-(+)-[1-(*p*-Methoxyphenyethyl)]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (23).** A mixture of **14** (68.0 mg, 0.146 mmol, >99% ee), iodomethane (40 μL, 0.64 mmol) and K_2CO_3 (120 mg, 0.86 mmol) in acetonitrile (3 mL) was stirred overnight in a stoppered flask at 80 °C. The product obtained after extractive workup (water/CH_2Cl_2) was dissolved in CH_2Cl_2 (2.5 mL) at 0 °C and an ice cold solution of HCl in ethanol (prepared from acetyl chloride (0.107 mL) and dry ethanol (2.5 mL) was added. The reaction was stirred at this temperature for 75 min and quenched by addition of a semisaturated Na_2CO_3 solution (20 mL). Extraction with ethyl acetate and purification by flash chromatography [silica gel, ethyl acetate and ethyl acetate/methanol/conc. NH_4OH (v/v/v = 90/8/2) as eluent] gave tetrahydroisoquinoline **23** (39.2 mg, 0.12 mmol, 82%) as a glass: $[\alpha]_D^{20}$ = +14 (c = 0.5, $CHCl_3$), lit[17] $[\alpha]_D^{20}$ = +20.5 (c = 1.0, $CHCl_3$); IR (film) ν 2932, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 6.60 (s, 1 H), 6.59 (s, 1 H),

dx.doi.org/10.1021/jo501099h | J. Org. Chem. 2014, 79, 7380−7390

3.96 (m, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.17 (m, 1 H), 3.01 (m, 1 H), 2.65−2.85 (m, 4 H), 1.95−2.15 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 147.2, 147.1, 134.3, 131.3, 129.2, 127.2, 113.8, 111.7, 109.1, 55.9, 55.7, 55.2, 55.0, 41.0, 38.4, 31.5, 29.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{26}NO_3$, 328.1913, found, 328.1929.

(*R*)-(+)-Almorexant Precursor 24. A mixture of **15** (filtrate of the crystallization, 95% ee, 68.0 mg, 0.146 mmol), iodomethane (30 μL, 0.48 mmol) and K_2CO_3 (100 mg, 0.72 mmol) in acetonitrile (2 mL) was stirred overnight in a stoppered flask at 80 °C. The product obtained after extractive workup (water/CH_2Cl_2) was dissolved in CH_2Cl_2 (1.5 mL) at 0 °C, and an ice cold solution of HCl in ethanol (prepared from 71.4 μL acetyl chloride and 1.5 mL dry ethanol) was added. The reaction was stirred at this temperature for 75 min and quenched by addition of a semisaturated Na_2CO_3 solution (20 mL). Extraction with ethyl acetate and purification by flash chromatography [silica gel, ethyl acetate and ethyl acetate/methanol/conc. NH_4OH (v/v/v = 93/5/2) as eluent] gave tetrahydroisoquinoline **24**^{20} (39.2 mg, 0.12 mmol, 82%) as a glass: $[\alpha]_D^{20}$ = +8 (c = 1.0, $CHCl_3$); IR (film) ν 2932, 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 2 H), 7.56 (d, J = 8.0 Hz, 2 H), 6.60 (s, 1 H), 6.58 (s, 1 H), 3.99 (m, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.25 (m, 1 H), 3.03 (m, 1 H), 2.70−2.95 (m, 4 H), 1.95−2.05 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$), CF_3 not observed, δ 147.4, 147.2, 146.6, 130.8, 128.7, 127.3, 125.3, 111.8, 109.0, 56.0, 55.8, 54.9, 40.9, 37.9, 32.2, 29.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{23}F_3NO_2$, 366.1681, found, 366.1699.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra and HPLC analyses for ee determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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dx.doi.org/10.1021/jo501099h | *J. Org. Chem.* 2014, 79, 7380−7390