Acid promoted CIDT for the deracemization of dihydrocinnamic aldehydes with Betti's base†

Goffredo Rosini,* Claudio Paolucci, Francesca Boschi, Emanuela Marotta, Paolo Righi and Francesco Tozzi

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Racemic α-epimerizable and unfunctionalized aldehydes have been converted into enantiomerically enriched mixtures through a sequence of (i) a conversion into the diastereoisomeric 3-substituted 1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines by reaction with the (*R*)- or (*S*)-1-(α-aminobenzyl)-2-naphthol (Betti's base), (ii) an acid promoted *crystallization-induced diastereoisomer transformation* (CIDT), and (iii) a clean cleavage of the dihydro-1,3-naphthoxazinic ring of the enriched diastereoisomer, easily collected by filtration, allowing the recovery of the enantiomerically enriched aldehydes and the chiral auxiliary.

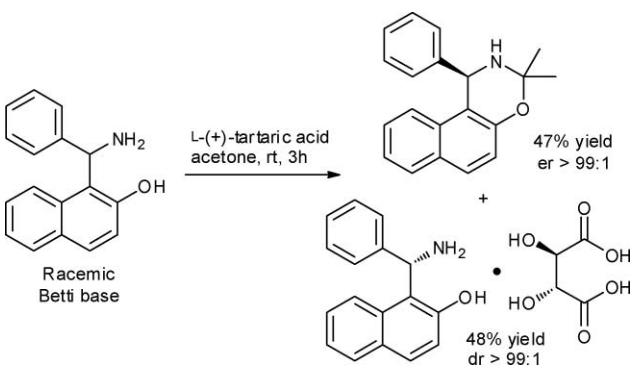
Introduction

The progress in the field of asymmetric synthesis during the last two decades is indubitable and impressive.[1] In spite of this progress due to the creativity and ingenuity of the many practitioners of the field, several hurdles hamper the use of enantioselective catalysis in industry.[2] The optical resolution of racemates[3] *via* formation of diastereoisomeric *p* and *n* derivatives with an enantiopure auxiliary and their separation by crystallization is still the preferred route in the preparation of a vast majority of enantiomeric pure or highly enriched compounds required for the manufacture of pharmaceuticals, agrochemicals and fragrances. More practical and efficient is the crystallization-induced diastereoisomer transformation (CIDT)[4] by which the racemic mixture of an epimerizable chiral compound can be, in principle, entirely converted into the desired highly enriched enantiomer by using an apt chiral non racemic auxiliary. In CIDT processes a 100% yield of a single diastereoisomer can be reached whenever the epimerization of the more soluble stereoisomer occurs with the precipitation of the less soluble diastereoisomer. Therefore, this kind of processes is very attractive for the pharmaceutical and fine chemical industries allowing the production of enantiomerically pure drugs and intermediates in higher yields (up to 100%) minimizing the problems associated with waste or recycling of the unwanted enantiomer, according to the principles of *green chemistry*.[5]

While a variety of very efficient examples[4,6] of this approach are reported in the literature, and applied at industrial scale too, little interest has been devoted to α-epimerizable, unfunctionalized aldehydes until Košmrlj and Weigel[7] demonstrated that (±)-2-ethylhexanal can be converted into (*R*)-2-ethylhexanal (94% yield, er = 99 : 1) by CIDT with methanol of the diastereoisomeric imines obtained with *trans*-(1*R*,2*R*)-6-nitro-1-aminoindan-2-ol, the only amine of the eight examined that provided crystalline imines.

As part of our program on the development of efficient and practical processes for the preparation of commercially important molecules,[8] we needed new methodologies to prepare enantiomerically enriched α-epimerizable α-alkyl aldehydes without the major limits of the classical resolution and those associated to the asymmetric synthesis. Therefore, our efforts were oriented towards the deracemization by CIDT methodology adopting the same *critical success factors* indicated by Košmrlj and Weigel to evaluate the "industrial feasibility" of their process: (a) >90% yield; (b) >90% ee; (c) protocol as simple as a resolution; (d) >95% recovery of the chiral auxiliary.

Attracted by the potentialities of the enantiomers of 1-(α-aminobenzyl)-2-naphthol (Betti's base),[9,10] easily made available by the very efficient and straightforward kinetic resolution recently developed by Hu[11] with (*R*,*R*)-tartaric acid (Scheme 1), we focused the attention on the deracemization of some "real world targets"[12] such as 3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanal[13] (Helional,® *d*,*l*-**2a**), 3-(4-*tert*-butylphenyl)-2-methylpropanal[14] (Lilial,® *d*,*l*-**2b**), 3-(4-isopropylphenyl)-2-methylpropanal[15] (Cyclamal, *d*,*l*-**2c**), and 3-(4-methoxyphenyl)-2-methylpropanal (Canthoxal®, *d*,*l*-**2d**), important perfumery ingredients,[16] readily available in racemic form.



Scheme 1 Hu's kinetic resolution of Betti's base.

Dipartimento di Chimica Organica "A. Mangini", Alma Mater Studiorum – Università di Bologna, Viale del Risorgimento 4, I-40136, Bologna, Italy. E-mail: goffredo.rosini@unibo.it; Fax: +39 051 2093654

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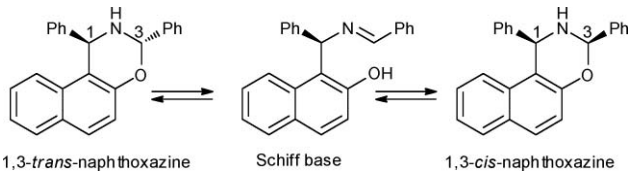
Racemic Betti's base, 1-(α-aminobenzyl)-2-naphthol (**1**), is easily available by a three-component condensation of β-naphthol with benzaldehyde and ammonia in a ratio 1 : 2 : 1 performed in alcoholic solution at room temperature for several hours, which is followed by acidic hydrolysis to furnish the base as hydrochloride together with one equivalent of benzaldehyde.[17] This reaction was discovered by M. Betti in Florence[18] at the beginning of the 20th century and in 1906 Betti himself successfully resolved[19] 1-(α-aminobenzyl)-2-naphthol with L-(+)-tartaric acid obtaining the corresponding enantiomers that successively he used to resolve some racemic aldehydes.[20] In 1970 Smith and Cooper have summarized the vicissitudes of the structure assignment to the condensation product, and reported the former spectroscopic evidences that showed this as a ring-chain tautomeric equilibrium of three forms: two isomeric naphthoxazines (ring) and a Schiff base (chain).[21] More recently, Fülöp and co-workers[22] through the NOESY spectra in $CDCl_3$ at 300 K on the 2,6-diaryl-perhydro-1,3-oxazines unequivocally showed that the *major* ring component in all tautomeric equilibria contains the 1,3-diaryl substituents in the *trans* position (Scheme 2). Therefore a naphthoxazinic system with two chiral centres could be represented by four stereoisomers but two of them, the *trans*-disposed ones, are decidedly predominant.



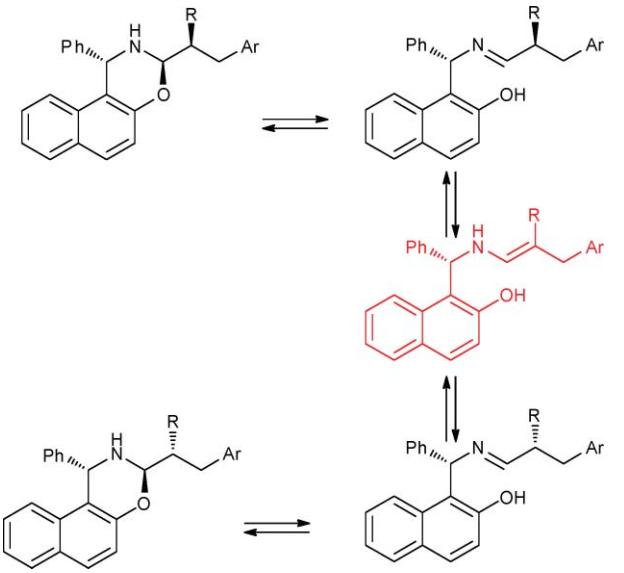
Scheme 2 Tautomeric equilibria of imines derived from Betti's base.

Results and discussion

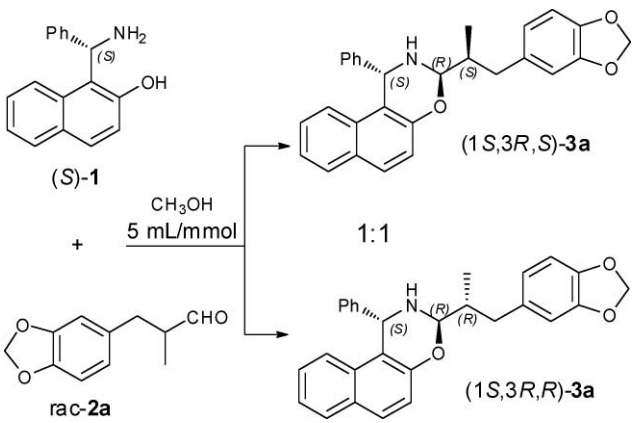
We were spurred by the peculiar role that the open chain component, the Schiff base, could play in favouring the major ring component, the *trans* 2,4-disubstituted 1,3-naphthoxazine in such equilibrium game.

The 1,3-naphthoxazine obtained from a racemic α-alkylaldehyde and (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**] has three stereogenic centres, one of which is defined, therefore should be represented by four stereoisomers. Only two of them are predominant due to the preferred *trans* disposition of the substituents and, more importantly, the possible equilibration through the Schiff base in a classical equilibrium. Of course, we figured on a concomitant imine-enamine equilibrium that can modify the configuration of the chiral centre of the starting aldehyde (Scheme 3). The reaction of (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**] with a slight excess of racemic aldehydes (**2a–e**) in methanol (5 mL $mmol^{-1}$) for 2 h at rt, gave the precipitation in almost quantitative yield of a 1 : 1 mixture of the two epimeric 1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines 1*S*,3*R*,*R*)- and (1*S*,3*R*,*S*)-**3a–e** (Scheme 4) as white solids.

They were clearly detected and quantified by HPLC analysis[23] while structure assignment was based on ^1H and ^{13}C NMR spectra. NOE experiments confirmed each epimer has the *trans* disposition of the two hydrogen atoms of the chiral centres of



Scheme 3 Imine/enamine equilibrium of naphthoxazines derived from Betti's base and racemic α-alkyldihydrocinnamic aldehydes.

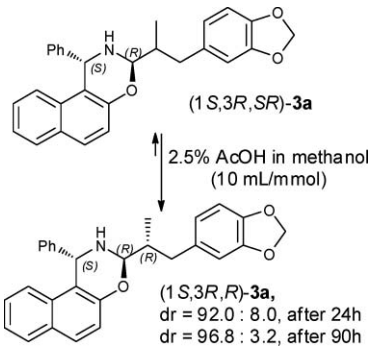


Scheme 4 Reaction of (*S*)-**1** with racemic Helional® in methanol.

the 1,3-oxazine ring, the preferred disposition already observed and reported by Fülöp and coworkers.[21,22] The independent preparation of (1*S*,3*R*,*S*)-**3a** and of (1*S*,3*R*,*R*)-**3a** by reaction of (*S*)-**1** with, respectively, (*S*)-**2a** (er = 95 : 5)[24] and (*R*)-**2a** (er = 93 : 7) allowed the assignment of the signals of the NMR spectra registered on the 1 : 1 mixture as well as the assignment of the corresponding absolute configurations. Moreover, the solubility in methanol of both diastereisomers was very low, but (1*S*,3*R*,*R*)-**3a** (76 mg/100 mL) was revealed to be three times less soluble when compared to (1*S*,3*R*,*S*)-**3a** (227 mg/100 ml).

The 1 : 1 mixture of (1*S*,3*R*,*R*)-**3a** and (1*S*,3*R*,*S*)-**3a** when suspended in refluxing methanol (10 mL $mmol^{-1}$ of substrate) and monitored by HPLC, remained unchanged in composition during many hours. However, a clean and progressive diastereoisomeric enrichment was observed when the same mixture was suspended in 2.5% acetic acid in methanol (10 mL $mmol^{-1}$ of substrate) and heated at 65 °C under stirring.[25] The progress of the CIDT reactions was efficiently monitored by TLC, ^1H NMR and HPLC analysis of aliquots of precipitate. The equilibrium was driven by the precipitation of the less soluble (1*S*,3*R*,*R*)-**3a** to reach a dr = 92 : 8 after 24 h and a dr = 96.8 : 3.2 after 90 h.

The isolation of the enriched isomer was performed in almost quantitative yield simply by filtration and washing of the solid (Scheme 5).



Scheme 5 The acid-promoted CIDT enrichment through naphthoxazinic derivatives.

The following example clearly shows the amazingly simplicity and efficiency of our CIDT protocol based on the utilization (*S*)-**1** or (*R*)-**1** as chiral auxiliaries. In fact, the more soluble oxazine (1*S*,3*R*,*S*)-**3a** (dr = 97.8 : 2.2), independently prepared from an enantiomerically enriched sample of the aldehyde (*S*)-**2** and Betti base (*S*)-**1**, underwent the acid promoted CIDT (2.5% acetic acid in methanol, 10 mL mmol^{-1}, 65 °C, 32 h) to give the less soluble (1*S*,3*R*,*R*)-**3a** that was isolated by a simple filtration in 95% yield and dr = 93 : 7 (Fig. 1).

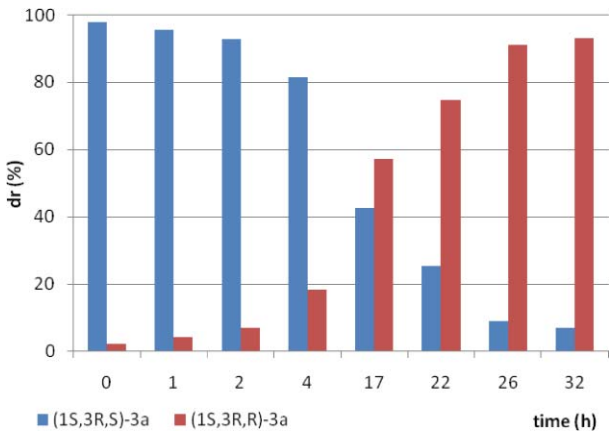


Fig. 1 The conversion of (1*S*,3*R*,*S*)-**3a** into (1*S*,3*R*,*R*)-**3a** by CIDT.

Higher dr, up to 99 : 1, can be obtained by prolonging reaction times. Therefore, an almost complete epimerization of (1*S*,3*R*,*S*)-**3a** was accomplished indicating that the conversion of the enriched aldehyde (*S*)-**2** into the other enatiomer (*R*)-**2** could be carried out with the Betti's base (*S*)-**1** and *vice versa* by using the Betti's base (*R*)-**1**. The same experiment performed in parallel on a sample of the less soluble (1*S*,3*R*,*R*)-**3a** with a dr = 98.3 : 1.7 gave a product with an increased diastereisomeric purity (dr > 99 : 1).

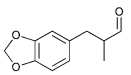
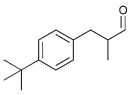
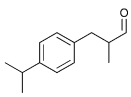
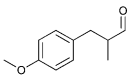
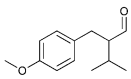
Then we faced the crucial step of the hydrolysis of dihydronaphthoxazinic derivatives to obtain the enantiomerically enriched aldehydes and the recovery the Betti's base. We successfully accomplished this task by suspending (1*S*,3*R*,*R*)-**3a** and Dowex 50W × 8-100 (2 g mmol^{-1}) in a THF : EtAc : 2% aq. TsOH mixture (1 : 1 : 0.05; 4 mL mmol^{-1}). During the reaction the aldehyde (+)-**2a** passed in solution as hydrolysis occurred while (*S*)-(+)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**] was catched by the Dowex resin. After 13 h at room temperature under magnetic stirring, the polymer-supported Betti's base was collected simply by filtration. The neutralized solution (Na_2CO_3) was added with water and the aldehyde was extracted with ether. The crude aldehyde was purified by bulb-to-bulb distillation (>90% yield). To determine the enantiomeric excess, a sample of this enriched (*R*)-(+)-Helional [(*R*)-(+)-**2a**] was reduced ($NaBH_4$ in methanol) to the corresponding alcohol (**4a**) and the enantiomeric purity determined by HPLC on a chiral stationary phase. The er of the aldehyde, when compared with the dr of the starting dihydro-naphthoxazine, showed a low erosion (1–5%) of the enantiomeric enrichment during the hydrolysis step. The (*S*)-1-(α-aminobenzyl)-2-naphthol free base [(*S*)-**1**] was released enantiomerically pure in quantitative yield, simply by treatment of the resin with aq. NH_4OH_{conc}/methanol/THF (2 : 1 : 8) under magnetic stirring at room temperature for 24 h.

Similar experiments performed on four additional racemic α-epimerizable, α-alkylhydrocinnamic aldehydes **2b–e** showed that the process is general for this kind of substrate (Table 1). Without optimization, dihydronaphthoxazines **3b–d** underwent significant diastereisomeric enrichment and their hydrolysis afforded enantiomerically enriched Lilial® (**2b**), Ciclamal (**2c**) and Canthoxal® (**2d**), important perfumery ingredients.[16]

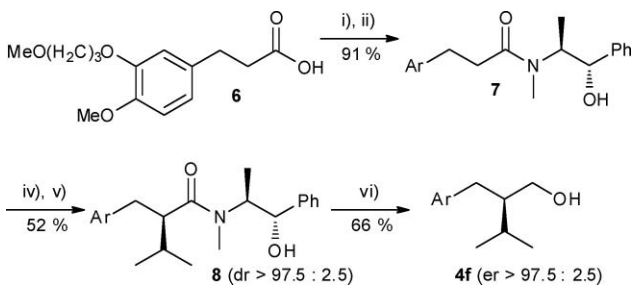
The aldehydes **2d** and **2e** differ only in the substituent adjacent to the carbonyl group, methyl group against isopropyl group, but the corresponding 1 : 1 mixtures of their naphthoxazines [respectively (1*S*,3*R*,*R*)-**3d**/(1*S*,3*R*,*S*)-**3d** and (1*S*,3*R*,*R*)-**3e**/(1*S*,3*R*,*S*)-**3e**] when treated according to the same protocol, gave a different diastereoisomeric enrichment. The 1 : 1 mixture of (1*S*,3*R*,*R*)-**3e**/(1*S*,3*R*,*S*)-**3e** underwent a more significant acid promoted enrichment giving the less soluble diastereoisomer in 85% yield (dr = 97 : 3). This encouraging result spurred us to undertake the preparation of a more ambitious "real world target". In facing this challenge we were well aware of the necessity that chiral intermediates involved as precursors in the multistep synthesis of pharmaceuticals must have, at least, an er > 99 : 1 and, more importantly, the performances of our approach will be compared with those of the existing methodologies already developed to prepare important chiral building blocks. One of such targets is alcohol **4f**, the chiral building block **A** of Aliskiren.

Aliskiren (CGP60536B, SPP-100, trade-names Tektura®, Rasilez®) is a highly efficient, nonpeptidic, orally administered drug that represents a novel class of renin inhibitors[26,27] with a huge potential for treatment of hypertension and related cardiovascular diseases. Currently, the development of more efficient and alternative methods for the synthesis of this compound is the focus of several pharmaceutical companies and academic groups.[28] Three main approaches have been followed for the preparation of the alcohol (*R*)-**4f**: (a) the amidation of the corresponding dihydrocynnamic acid (**6**) with (+)-pseudoephedrine followed by the diastereoselective alkylation with 2-iodopropane (Scheme 6)[28b] according to the Myers methodology that gave a single diastereoisomer (dr > 97.5 : 2.5), then reduced, without epimerization, to the desired alcohol **4f** (er > 97.5 : 2.5); (b) by diastereoselective alkylation of

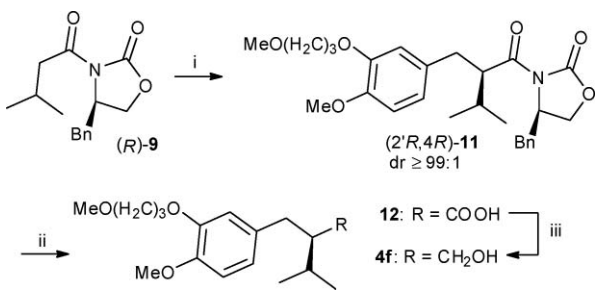
Table 1 The enantiomeric enrichment of the aldehydes by acid promoted CIDT of the corresponding naphthoxazines with (*S*)-Betti's base [(*S*)-**1**]

Racemic aldehyde **2**	Dihydronaphthoxazine[a] **3** yield,[b] dr[c]	CIDT of **3** T, time yield,[b] dr[c]	Hydrolysis[d] of **3** *enriched*-**2**[g] yield,[b] er
 **2a**	**3a** 95%, 1 : 1	2.5% AcOH in MeOH; 10 mL mmol^{-1} 65–68 °C, 24 h, 84%; *SR*/*SS* = 93:7	90%; er 90:10[e] (*R*)-(+)-**2a**
		2.5% AcOH in MeOH; 10 mL mmol^{-1} 65–68 °C, 90 h 83%; *SR*/*SS* = 96:4	90%; er 93:7[e]
 **2b**	**3b** 97%, 1 : 1	10% AcOH in MeOH; 3 mL mmol^{-1} 60 °C, 60 h, 96%; *SS*/*SR* = 90:10	(*S*)-(+)-**2b** 99%, er 85:15[f]
 **2c**	**3c** 96%, 1 : 1	10% AcOH in MeOH; 10 mL mmol^{-1} 60 °C, 60 h, 83%; major/minor = 75:25	(–)-**2c** 93%, er 75:25[f]
 **2d**	**3d** 96%, 1 : 1	5% AcOH in MeOH; 10 mL mmol^{-1} 60 °C, 48 h, 86%; dr = 73:27	(*R*)-(+)-**2d** 88%, er 71:29[e]
 **2e**	**3e** 91%, 1 : 1	2.5% AcOH in MeOH; 10 mL mmol^{-1} 60–62 °C, 48 h, 85%; dr = 97:3	(*R*)-(+)-**2e** 95%, er 96:4[e]

[a] All naphthoxazines **3** were prepared with (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**] in MeOH (5 mL mmol^{-1}). [b] Yields of isolated product. [c] Diastereoisomeric ratio determined by HPLC analysis (AD-H, 0.46 cm I. D. x 25 cm, 20 °C, *n*-hexane/isopropanol 9:1, 1 mL min^{-1}, 230 nm) and by ^{1}H NMR. [d] Dowex 50WX8-100 (2g/mmol), THF:EtOAc:2% aq. TsOH (1:1:0.05; 4 mL mmol^{-1}), r.t. 13 h. [e] Determined by HPLC analysis on the corresponding alcohol obtained by $NaBH_4$ reduction in methanol (CHIRALCEL® OD-H, 0.46 cm I. D. x 25 cm, 25 °C, *n*-hexane/isopropanol 95:5, 1 mL min^{-1}, 254 nm) [f] Determined by HPLC analysis on the *p*-methoxybenzoate of the corresponding alcohol. (CHIRALPAK® AD-H, 0.46 cm I. D. x 25 cm, 20 °C, *n*-hexane/isopropanol 95:5, 1 mL min^{-1}, 230 nm). [g] Absolute configuration assignment based on: Ref. 13b for **2a**; Ref. 14b for **2b**; Ref. 40 for **2d**; X-ray diffraction analysis on the tosylate of the corresponding alcohol for **2e** (see ESI†); absolute configuration of **2c** was not assigned.



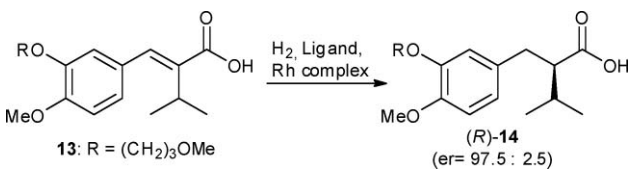
Scheme 6 i. H_2, Pd/C, EtOAc, rt; ii. $(COCl)_2$, DMF, rt; iii. (+)-pseudoephedrine, NaOH, PhMe–H_2O, rt; iv. LDA, LiCl, THF, 0 °C; v. 2-iodopropane, rt-reflux; vi. $BH_3.NH_3$, *n*-BuLi, THF.



Scheme 7 i. 1M LiHMBS, THF, **10**, –70 °C to r.t.; 86%. ii. LiOH, 30% H_2O_2 soln., THF–H_2O 3 : 1, 0 °C to r.t.; 95%. iii. $NaBH_4$, I_2, THF, 4d at r.t.; 90%.

the lithium enolate of (4*R*)-3-isovaleroyl-4-benzyl-oxazolidin-2-one [(*R*)-**9**] with 4-methoxy-3-(3-methoxypropoxy)benzyl bromide (**10**) following the method of Evans and co-workers (Scheme 7).[28d] Working at –75 °C in THF (at 460 g scale) a unique alkylation product (dr = 99 : 1) was obtained, successively hydrolyzed and then reduced to the *R* alcohol; (c) by synthesis and asymmetric catalytic hydrogenation of (*E*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzylidene)-3-methylbutanoic acid (**13**) to obtain (*R*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoic acid (**14**) that was reduced to the corresponding alcohol (Scheme 8). This enantioselective hydrogenation was carried out by using a variety of chiral ligands together with Rh- or Ru- precursors *in situ* to prepare the chiral non racemic Rh-complex.

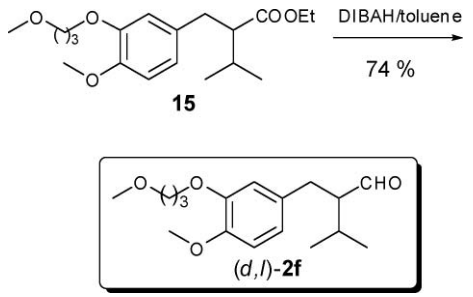
Even for a well developed methodology, such as catalytic asymmetric hydrogenation, its application to a moderately complex substrate rarely yields the necessary enantiomeric purity and further manipulations are necessary. The catalytic asymmetric hydrogenation of (*E*)-2-(4-methoxy-3-(3-methoxypropoxy)-



Scheme 8

benzylidene)-3-methylbutanoic acid (**13**) can be seen as an emblematic case: with the best catalysts very appreciable performances were reported: er > 97.5 : 2.5, S C^{-1} ratios greater than 5000, and turnover frequencies greater than 1000 mol mol^{-1}h^{-1}. These achievements resulted from the many studies devoted to the fine tuning of the chiral ligand as well as to the careful choice of reaction conditions.[29] However, a typical target value for the enantiomeric purity required for pharmaceutical applications is 99.5% and, therefore, the optical purity of the hydrogenation product, the acid (*R*)-**14** was recently enhanced to >99% ee by crystallization (from diethyl ether) of its salt with (*S*)-(–)-α-methyl benzylamine.[30]

To verify the effectiveness of our approach to the enantiomerically enriched aldehyde **2f** through the utilization of (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**], we prepared racemic ethyl 2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoate (**15**)[29g] which was reduced to the corresponding racemic aldehyde **2f** (Scheme 9).



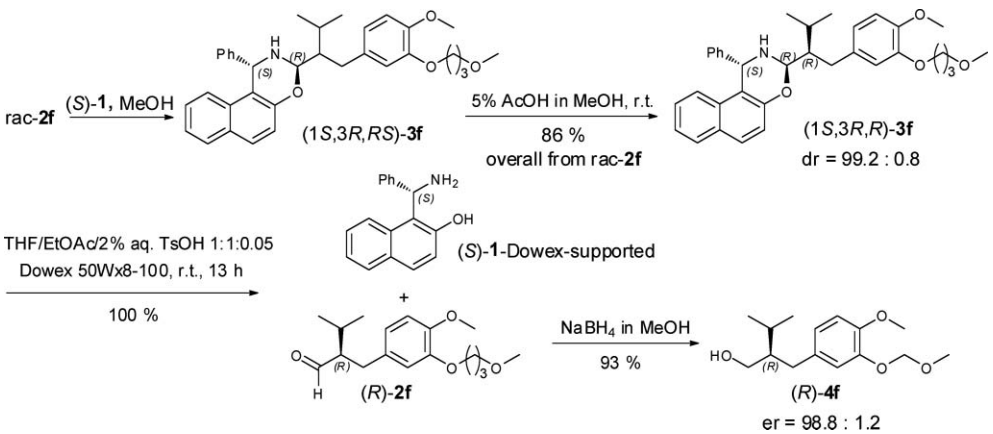
Scheme 9

The reaction of a slight excess of racemic aldehyde **2f** with (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**] in hot methanol for 30 min gives a 1 : 1 mixture of the two diastereoisomers **3f** (Scheme 10). Acetic acid is then added to the stirred mixture. After a few minutes a white solid starts to precipitate. After 24 h the solids are filtrated (73% yield; dr 96.4 : 3.6). Recrystallization from diisopropyl ether affords (1*S*,3*R*,*R*)-**3f** in a 64% overall yield and with dr 99.5 : 0.5. Moreover, the residue recovered by evaporation of the recrystallization mother liquors can be combined with the solvent obtained after the filtration at the end of the CIDT reaction. After stirring at r.t. for 64 h a second crop of (1*S*,3*R*,*R*)-**3f** (22% overall yield; dr 98.4 : 1.6) was obtained by filtration. The combined crops of naphthoxazine **3f** (dr = 99.2 : 0.8) were suspended in THF : EtOAc : 2% aq. TsOH = 1 : 1 : 0.05 (4 mL mmol^{-1}) and Dowex 50WX8-100 (2g mmol^{-1}) was added. The resulting mixture was stirred for 13–14 h during which time the organic solids progressively dissolved. The resin was then filtered and washed with Et_2O to recover the released aldehyde. Finally, a sample of the enriched aldehyde (*R*)-**2f** was reduced by sodium borohydride in methanol, giving the corresponding alcohol (*R*)-**4f** (er = 98.8 : 1.2) in 93% yield. These results clearly indicate that the CIDT methodology constitutes a viable and convenient alternative to the procedures described above for the preparation of building block **A** of aliskiren (see Schemes 6, 7 and 8).

Conclusions

The CIDT process we have developed for the enantiomeric enrichment of racemic α-alkylated, α-epimerizable aldehydes exploits the enantiomers of 1-(α-aminobenzyl)-2-naphthol (**1**). The method, when applied to a variety of "real world targets" having in common the α-alkyldihydrocinnamic structure, appears almost general and potentially scalable. Moreover, it fulfils the following requirements: (a) high availability of the enantiomers of Betti base used as chiral auxiliaries, easily prepared and resolved by using relatively inexpensive raw materials and reagents, (b) "fast-and-cheap-arrival" to stable 1 : 1 mixtures of epimeric naphthoxazines **3a–f**, (c) an efficient acid promoted crystallization-induced epimerization to the less soluble naphthoxazine conducted in an heterogeneous system with a minimum amount of methanol, (d) an effective and clean hydrolysis step to obtain the enantiomerically enriched aldehyde, avoiding significant racemisation during the chemical manipulations, (e) a straightforward recovery of (*S*)- and (*R*)-1-(α-aminobenzyl)-2-naphthol, and Dowex 50WX8-100, (f) the enantiomeric enrichment of the less soluble naphthoxazine obtained by the CIDT process can be further improved by crystallization and the diastereoisomers contained in the mother liquors can be treated again to undergo another CIDT enrichment without any loss of material.

The modest results obtained with racemic aldehydes **2b–c** may be improved by effecting the tuning of the chiral auxiliary, choosing the more appropriate Betti base. In fact, 1-(α-aminobenzyl)-2-naphthol is only the prototype (lead) of wide family of compounds. A large library of these compounds can be prepared by a domino, three-component reaction between β-naphthols, arylaldehydes and ammonia or primary amines that give rise the desired compounds in high yield and with high atom economy. Each racemic Betti base obtained by a parallel synthesis methodology, may be used directly with the racemic chiral aldehyde targeted to be enriched by the CIDT process we have described. The HPLC analyses of the diastereisomeric mixtures can drive the choice of the right Betti base for each chiral aldehyde we want to enrich and then try to effect its



Scheme 10

resolution only after having verified the best performances. Only two main signals, corresponding to four stereoisomers of the eight theoretically possible, are shown by HPLC analysis, each representative of a single racemic diastereoisomer, and the entity of their presence in the mixture can be monitored during an acid promoted CIDT process carried out as we have depicted. This approach allows the choice of the acid and the correct concentration of the acid in methanol, or other solvents, too.

Experimental

General experimental

(*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**] has been obtained enantiomerically pure by the efficient and practical kinetic resolution of racemic 1-(α-aminobenzyl)-2-naphtol (Betti base, *rac*-**1**)[31] with L-(+)-tartaric acid in acetone, developed by Hu and co-workers,[32] based on an enantioselective *N*,*O*-deketalization. Racemic 3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanal (Helional®, *rac*-**2a**), (4-*tert*-butylphenyl)-2-methylpropanal (Lilial,® *rac*-**2b**), 3-(4-isopropylphenyl)-2-methylpropanal (Cyclamal, *rac*-**2c**), 3-(4-methoxyphenyl)-2-methylpropanal (Cantoxal®, *rac*-**2d**) are commercial compounds and were used as obtained. Samples of (*S*)-(−)-Helional® (er = 97.8 : 2.2) and (*R*)-(+)-Helional® (er = 98.4 : 1.6) were kindly furnished by ENDURA S.p.A – Ravenna (Italy). Racemic 2-(4-methoxybenzyl)-3-methylbutanal (*rac*-**2e**) and 2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutanal (*rac*-**2f**) were prepared by reduction (DiBAH) of, respectively, ethyl 2-(4-methoxybenzyl)-3-methylbutanoate and ethyl 2-(4-methoxy-3-(3-methoxypropoxy)benzyl)-3-methylbutanoate prepared according to a well established procedure consisting into the synthesis of, respectively, ethyl (*E*)-ethyl 2-(4-methoxybenzylidene)-3-methylbutanoate and (*E*)-ethyl 2-[4-methoxy-3-(3-methoxypropoxy)benzylidene]-3-methylbutanoate[33] followed by palladium catalyzed hydrogenation (Electronic Supplementary Information, ESI†). Dowex 50WX8-100 has been purchased from Aldrich and used as received. During the crystallization-induced diastereoisomer transformations (CIDT), the diastereisomer ratios (dr) of naphthoxazines **3a–f** were monitored by HPLC analysis using a chiral Daicel CHIRALPAK® AD-H column and by ^{1}H NMR. The enantiomeric excess (ee) of the aldehydes **2a**, **2d–f** were indirectly determined, by analysis of the corresponding alcohols using a chiral Daicel CHIRALCEL® OD-H column (**4a**, **4e–f**) or a chiral Daicel CHIRALCEL® OJ-H column (**4d**). The enantiomeric excess of aldehydes **2b–c** has been indirectly determined by analysis of the corresponding *p*-methoxybenzoates **5b–c** using a chiral Daicel CHIRALCEL® OD-H column.

Synthesis of (1*S*,3*R*)-3-((*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*R*)-3a]. (*S*)-1-(α-Aminobenzyl)-2-naphthol [(*S*)-**1**], (2.5 g, 10 mmol) was suspended in methanol (5 mL mmol^{-1}) in a 100 mL round-bottomed flask with a stirring bar and (*R*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanal [(*R*)-**2a**, dr = 98.4 : 1.6] (2.5 g, 10 mmol) was added. The mixture was maintained for 2 h at ambient temperature under stirring. Chiral HPLC analysis (CHIRALPAK® AD-H, hexane/*i*-PrOH = 9 : 1, 1 mL min^{-1}, λ = 245 nm, 20 °C: t_R = 6.9) of a sample of the solid revealed the complete conversion of the aldehyde into the naphthoxazine (1*S*,3*R*,*R*)-**3a**. The white solid was collected by filtration in 97% yield: mp = 182–185 °C; $[\alpha]_D^{21}$ −134.3 (*c* 1.29, CH_2ClCH_2Cl). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76–7.69 (*m*, 2H), 7.36–7.30 (*m*, 1H), 7.30–7.21 (*m*, 7H), 7.08 (*d*, *J* = 9.0 Hz, 1H), 6.45 (*d*, *J* = 8.0 Hz, 1H), 6.40 (*d*, *J* = 1.6 Hz, 1H), 6.18 (*dd*, *J* = 7.8 and 1.7 Hz, 1H), 5.84–5.81 (*m*, 2H), 5.51 (*s*, 1H), 4.51 (*d*, *J* = 3.4 Hz, 1H), 2.64 (*dd*, *J* = 13.4 and 8.1 Hz, 1H), 2.42 (*bs*, 1H), 2.38 (*dd*, *J* = 13.4 and 6.8 Hz, 1H), 2.18–2.06 (*m*, 1H), 0.99 (*d*, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.0, 147.3, 145.4, 142.9, 134.0, 131.7, 129.4, 129.0, 128.6, 128.4, 128.1, 127.2, 126.4, 123.0, 122.9, 121.9, 119.2, 114.5, 109.3, 107.8, 100.5, 83.6, 53.8, 39.4, 38.4, 13.5. IR (KBr): 3357.9, 3070.1, 2893.0, 1616.6, 1590.8, 1487.6, 1435.9, 1391.7, 1240.5, 1185.2, 1041.5, 930.9, 816.6, 748.8, 719.6 cm^{-1}.

Synthesis of (1*S*,3*R*)-3-((*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*S*)-3a]. (*S*)-1-(α-Aminobenzyl)-2-naphthol [(*S*)-**1**], (2.5 g, 10 mmol) was suspended in methanol (5 mL mmol^{-1}) in a 100 mL round-bottomed flask with a stirring bar and (*S*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanal [(*S*)-**2a**, er = 97.8 : 2.2] (2.5 g, 10 mmol) was added. The mixture was maintained at ambient temperature under stirring for 2 h. Chiral HPLC analysis (CHIRALPAK® AD-H, hexane/*i*-PrOH = 90 : 10, 1 mL min^{-1}, λ = 245 nm, 20 °C: t_R = 8.2 min) of a sample of the solid revealed the complete conversion of the aldehyde into the naphthoxazine (1*S*,3*R*,*S*)-**3a**. The white solid was collected by filtration in 96% yield: mp = 147–150 °C; $[\alpha]_D^{22}$ +40.1 (*c* 1.12, CH_2ClCH_2Cl). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77–7.65 (*m*, 2H), 7.35–7.28 (*m*, 1H), 7.28–7.18 (*m*, 7H), 7.13 (*d*, *J* = 9.0 Hz, 1H), 6.61 (*d*, *J* = 7.9 Hz, 1H), 6.58 (*d*, *J* = 1.6 Hz, 1H), 6.48 (*dd*, *J* = 8.0 and 1.7 Hz, 1H), 5.85 (*s*, 2H), 5.48 (*s*, 1H), 4.49 (*d*, *J* = 5.1 Hz, 1H), 2.87 (*dd*, *J* = 13.4 and 4.4 Hz, 1H), 2.41 (*bs*, 1H), 2.38 (*dd*, *J* = 13.4 and 9.5 Hz, 1H), 2.03–1.92 (*m*, 1H), 0.93 (*d*, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.8, 147.3, 145.5, 142.9, 134.0, 131.9, 129.3, 129.0, 128.6, 128.4, 128.1, 127.1, 126.5, 123.1, 122.8, 122.1, 119.3, 114.5, 109.6, 107.9, 100.6, 84.5, 53.9, 39.6, 37.9, 13.4. IR (KBr): 3357.8, 3062.2, 2938.6, 2882.2, 1619.3, 1596.6, 1508.0, 1468.4, 1444.5, 1405.7, 1328.1, 1233.3, 1136.1, 1012.3, 945.0, 901.3, 808.7, 753.8, 736.7, 705.2 cm^{-1}.

Synthesis of (1*S*,3*R*,*SR*)-3-(1-arylalk-3-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3a–e]: General procedure. (*S*)-1-(α-Aminobenzyl)-2-naphthol [(*S*)-**1**], (2.5 g, 10 mmol) was suspended in methanol (5 mL mmol^{-1}) in a 100 mL round-bottom flask with a stirring bar and racemic aldehyde (*rac*-**2a–c**) was added in a slight excess. The mixture was maintained at ambient temperature under stirring for 2 h. Chiral HPLC analysis of a sample of the solid revealed the complete conversion of the aldehyde into a 1 : 1 mixture of two epimeric 1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines (1*S*,3*R*,*R*)-**3a–e** and (1*S*,3*R*,*S*)-**3a–e**. The solid was collected by filtration in a almost quantitative yield.

(1*S*,3*R*,*SR*)-3-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3a]. 95% yield of a white solid consisting into a 1 : 1 mixture

of (1*S*,3*R*,*S*) and (1*S*,3*R*,*R*) isomers (HPLC analysis with CHIRALPAK® AD-H, hexane/*i*-PrOH = 90 : 10, 1 mL min^{-1}, λ = 245 nm, 20 °C: t_R = 6.9 and 8.2 min), $[\alpha]_D^{21}$ −114.5 (*c* 1.05, CH_2ClCH_2Cl).

(1*S*,3*R*,*SR*)-3-(1-(4-*tert*-butylphenyl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3b]. 97% yield of a white solid consisting into 1 : 1 mixture of (1*S*,3*R*,*S*) and (1*S*,3*R*,*R*) (HPLC analysis with CHIRALPAK® AD-H, hexane/*i*-PrOH = 95 : 5, 1 mL min^{-1}, λ = 230 nm, 25 °C: t_R = 4.1 and 4.9 min); $[\alpha]_D^{20}$ −38.9 (*c* 1.08, CH_2ClCH_2Cl).

(1*S*,3*R*,*SR*)-3-(1-(4-isoproylphenyl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3c]. 96% yield of a white solid consisting into 1 : 1 mixture of (1*S*,3*R*,*S*) and (1*S*,3*R*,*R*) isomers (HPLC analysis with CHIRALPAK® AD-H, hexane/*i*-PrOH = 90 : 10, 1 mL min^{-1}, λ = 245 nm, 20 °C: t_R = 4.0 and 4.6 min) $[\alpha]_D^{21}$ −46.3 (*c* 1.00, CH_2ClCH_2Cl).

(1*S*,3*R*,*SR*)-3-(1-(4-methoxyphenyl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3d]. 96% yield of a white solid consisting into 1 : 1 mixture of (1*S*,3*R*,*S*) and (1*S*,3*R*,*R*) isomers (HPLC analysis with CHIRALPAK® AD-H, hexane/*i*-PrOH = 95 : 5, 1 mL min^{-1}, λ = 230 nm, 20 °C: t_R = 7.6 and 8.5 min); $[\alpha]_D^{20}$ −42.5 (*c* 0.99, CH_2ClCH_2Cl).

(1*S*,3*R*,*SR*)-3-(1-(4-methoxyphenyl)-3-methylbutan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3e]. 91% yield of a white solid consisting of 1 : 1 mixture of (1*S*,3*R*,*S*) and (1*S*,3*R*,*R*) isomers determined by ^{1}H NMR analysis: (400 MHz, C_6D_6) diagnostic signals; (1*S*,3*R*,*R*)-**3e** δ: 5.16(*s*, 1H), 4.80(*bs*, 1H) 3.36 (*s*, 3H), 2.86 (*dd*, *J* = 13.8 and 4.7 Hz, 1H), 2.45 (*dd*, *J* = 13.8 and 7.5 Hz, 1H), 0.85 (*d*, *J* = 6.8 Hz, 3H) 0.80 (*d*, *J* = 6.8 Hz, 3H); (1*S*,3*R*,3*S*)-**3e**[34] δ: 5.13 (*s*, 1H), 4.73 (*bs*, 1H), 3.31 (*s*, 3H), 2.79 (*dd*, *J* = 13.8 and 8.7 Hz, 1H), 2.56 (*dd*, *J* = 13.8 and 5.0 Hz, 1H), 0.96 (*d*, *J* = 6.9 Hz 3H), 0.90 (*d*, *J* = 6.9 Hz, 3H; $[\alpha]_D^{20}$ +19.9 (*c* 1.12, CH_2ClCH_2Cl); $[\alpha]_D^{20}$ +19.9 (*c* 1.12, CH_2ClCH_2Cl).

CIDT of (1*S*,3*R*,*SR*)-3-(1-arylalk-3-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazines (1*S*,3*R*,*SR*)-3a–e: General procedure. The 1 : 1 diastereoisomeric mixture of (1*S*,3*R*,*S*)- and (1*S*,3*R*,*R*)-oxazine **3a–e** was suspended in methanol and acetic acid was added as specified in each case. The solid was collected by filtration after stirring at 60–68 °C for the time indicated. Diastereoisomeric ratios (dr) were determined by HPLC analysis as already described for the 1 : 1 mixtures of isomers.

CIDT of (1*S*,3*R*,*SR*)-3-(1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3a]. CIDT conditions: 2.5% AcOH, MeOH, 10 mL mmol^{-1}, 65–68 °C. After 24 h the suspension was filtered to afford (1*S*,3*R*,*R*)-**3a** as a solid (84% yield, dr = 93 : 7), $[\alpha]_D^{22}$ −128.3 (*c* 1.205, CH_2ClCH_2Cl). After 90 h: 83% yield, dr = 96 : 4.

Epimerization of naphthoxazine (1*S*,3*R*,*S*)-3a by CIDT into (1*S*,3*R*,*R*)-3a. CIDT conditions: 2.5% AcOH, MeOH, 10 mL mmol^{-1}, 65 °C. The epimerization reaction was performed by using naphthoxazine (1*S*,3*R*,*S*)-**3a** (dr = 97.8 : 2.2). After 32 h the suspension was filtered to afford naphthoxazine (1*S*,3*R*,*R*)-**3a** (dr = 93 : 7) as a solid (95% yield).

Further enrichment of (1*S*,3*R*,*R*)-3a by CIDT procedure. CIDT conditions: 2.5% AcOH, MeOH, 10 mL mmol^{-1}, 65 °C. The reaction was performed by using naphthoxazine (1*S*,3*R*,*R*)-**3a** (dr = 98.3 : 1.7). After 22 h the suspension was filtered to afford (1*S*,3*R*,*R*)-**3a** in 95% yield with dr = 99 : 1.

CIDT of (1*S*,3*R*,*SR*)-3-(1-(4-*tert*-butylphenyl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3b]. CIDT conditions: 10% AcOH, MeOH, 3 mL mmol^{-1}, 60 °C. After 60 h the suspension was filtered to afford (1*S*,3*R*,*S*)-**3b** as a solid (96% yield, dr = 90 : 10). $[\alpha]_D^{20}$ +20.5 (*c* 1.09, $CH_2ClCH_2Cl_2$); (1*S*,3*R*,*S*)-**3b** (HPLC t_R = 4.9 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78–7.70 (*m*, 2H), 7.37–7.31 (*m*, 1H), 7.31–6.98 (*m*, 12H), 5.54 (*s*, 1H), 4.52 (*d*, *J* = 5.0 Hz, 1H), 2.93 (*dd*, *J* = 13.3 and 4.6 Hz, 1H), 2.49 (*bs*, 1H), 2.47 (*dd*, *J* = 13.3 and 9.3 Hz, 1H), 2.05 (m, 1H), 1.28(s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.9, 148.5, 142.9, 137.0, 131.7, 129.3, 129.0, 128.9, 128.6, 128.4, 128.2, 127.1, 126.5, 124.9, 123.0, 122.8, 119.3, 114.5, 84.6, 53.9, 39.3, 37.6, 34.3, 31.4, 13.6. Minor isomer (1*S*,3*R*,*S*)-**3b** diagnostic signals; (HPLC t_R = 4.1 min) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.74(*d*, *J* = 8.2 Hz, 2H), 2.68(*dd*, *J* = 13.4 and 8.2 Hz, 1H), 2.18(m, 1H), 1.24(s, 9H), 1.01(d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.1, 148.2, 142.9, 137.0, 131.6, 129.5, 129.0, 128.9, 128.6, 128.3, 128.1, 127.0, 126.4, 124.9, 123.0, 122.9, 119.2, 114.4, 83.6, 53.8, 39.2, 38.2, 34.2, 31.3, 13.6.

CIDT of (1*S*,3*R*,*SR*)-3-(1-(4-isoproylphenyl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3c]. CIDT conditions: 10% AcOH, MeOH, 10 mL mmol^{-1}, 60 °C. After 60 h the suspension was filtered to afford (−)-**3c** as a solid (83% yield, dr = 75 : 25). $[\alpha]_D^{20}$ −105.0 (*c* 1.00, CH_2ClCH_2Cl). Major isomer (HPLC t_R = 4.0 min) ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.75–7.65 (*m*, 2H), 7.36–7.17(*m*, 8H), 7.12–7.04 (*m*, 1H), 6.90 (*d*, *J* = 7.8 Hz, 2H), 6.74 (*d*, *J* = 7.8 Hz, 2H), 5.51 (*s*, 1H), 4.51 (*d*, *J* = 3.5 Hz, 1H), 2.87–2.68 (*m*, 1H), 2.69 (*dd*, *J* = 13.3 and 8.1 Hz, 1H), 2.43 (*dd*, *J* = 13.3 and 6.7 Hz, 1H), 2.38 (*bs*, 1H), 2.16 (*m*, 1H), 1.17 (*d*, *J* = 6.9 Hz, 6H), 1.00 (*d*, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.1, 146.0, 142.9, 137.4, 131.7, 129.5, 129.0, 128.9, 128.6, 128.4, 128.1, 127.1, 126.4, 126.1, 123.0, 122.9, 119.3, 114.5, 83.7, 53.8, 39.2, 38.3, 33.6, 24.1, 23.9, 13.5; Minor isomer (+)-**3c** diagnostic signals; (HPLC t_R = 4.6 min) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.48(*s*, 1H), 2.92 (*dd*, *J* = 13.4 and 4.4 Hz, 1H), 2.03 (*m*, 1H), 1.20 (*d*, *J* = 6.9 Hz, 6H), 0.94 (*d*, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.9, 146.2, 142.9, 137.4, 131.7, 129.3, 129.2, 129.0, 128.6, 128.4, 128.2, 127.1, 126.5, 126.1, 123.0, 122.9, 119.2, 114.4, 84.6, 53.9, 39.4, 37.7, 33.6, 24.04, 23.96, 13.6

CIDT of (1*S*,3*R*,*SR*)-3-(1-(4-methoxyphenyl)propan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*,3*R*,*SR*)-3d]. CIDT conditions: 5% AcOH, MeOH, 10 mL mmol^{-1}, 60 °C. After 48 h the suspension was filtered to afford (1*S*,3*R*,*R*)-**3c** as a solid (86% yield, dr = 73 : 23). $[\alpha]_D^{21}$ −81.5 (*c* 0.71, CH_2ClCH_2Cl). Major isomer (1*S*,3*R*,*R*)-**3d** (HPLC t_R = 7.6 min), ^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.76–7.66 (*m*, 2H), 7.36–7.30 (*m*, 1H), 7.30–7.21 (*m*, 7H), 7.07 (*d*, *J* = 8.9 Hz, 1H), 6.72 (*m*, 2H), 6.58 (*m*, 2H), 5.53 (*s*, 1H), 4.51 (*d*, *J* = 3.8 Hz, 1H),

3.70 (*s*, 3H), 2.65 (*dd*, *J* = 13.5 and 8.3 Hz, 1H), 2.45 (*bs*, 1H), 2.41 (*dd*, *J* = 13.5 and 6.6 Hz, 1H), 2.13 (*m*, 1H), 1.00 (*d*, *J* = 87.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 153.1, 143.0, 132.4, 131.7, 129.9, 129.5, 129.0, 128.6, 128.4, 128.2, 127.1, 126.4, 123.0, 122.9, 119.2, 114.4, 113.5, 83.6, 55.1, 53.8, 39.4, 37.8, 13.5. Minor isomer 1*S*,3*R*,*S*-**3d** diagnostic signals (HPLC t_R = 8.5 min), ^{1}H NMR (400 MHz,$CDCl_3$) δ: 3.72(*s*, 3H), 2.88(*dd*. *J* = 13.5 and 4.4 Hz, 1H), 1.99(*m*, 1H), 0.92(*d*, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 152.8, 142.9, 132.1, 131.7, 130.2, 129.3, 128.9, 128.5, 128.4, 128.2, 127.6, 126.4, 123.0, 122.8, 119.3, 114.4, 113.5, 84.6, 55.2, 53.9, 39.5, 37.2, 13.5.

CIDT of (1*S*,3*R*,*SR*)-3-(1-(4-methoxyphenyl)-3-methylbutan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1*S*, 3*R*,*SR*)-3e]. CIDT conditions: 5% AcOH, MeOH, 10 mL mmol^{-1}, 60 °C. After 48 h the suspension was filtered to afford (1*S*,3*R*,*R*)-3e as a solid (85% yield, dr = 97 : 3). $[\alpha]_D^{19}$ +130.2 (*c* 0.84, $CH_2ClCH_2Cl_2$), mp = 154–156 °C. (1*S*,3*R*,*R*)-isomer: ^{1}H NMR (400 MHz,C_6D_6) δ: 7.78–7.68 (*m*, 2H), 7.36–7.31 (*m*, 1H), 7.30–7.08 (*m*, 10H), 6.79 (*d*, *J* = 8.7 Hz, 2H), 5.52 (*s*, 1H), 4.70 (*d*, *J* = 4.0 Hz, 1H), 3.78 (*s*, 3H), 2.79 (*dd*, *J* = 13.8 and 5.4 Hz, 1H), 2.56 (*dd*, *J* = 13.8 and 6.9 Hz, 1H), 2.40 (*bs*, 1H), 2.03–1.86 (*m*, 2H), 0.84 (*d*, *J* = 6.7 Hz, 3H), 0.81 (*d*, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ: 159.1, 154.2, 144.0, 134.8, 133.2, 131.1, 130.5, 130.0, 129.9, 129.6, 129.0, 128.0, 127.5, 124.04, 124.02, 120.5, 115.8, 114.8, 84.3, 55.5, 54.8, 51.0, 32.3, 28.4, 21.0, 20.3; IR (KBr): 3328.7, 3055.5, 3023.6, 2958.0, 2932.0, 1621.7, 1597.0, 1513.5, 1462.8, 1244.0, 1233.8, 1029.4, 896.5, 822.3, 803.3, 749.7, 736.9, 699.8 cm^{-1}.

Synthesis of (1*S*,3*R*,*R*)-3-(1-(4-methoxy-3-(3-methoxypropoxy)phenyl)-3-methylbutan-2-yl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazine [(1*S*,3*R*,*R*)-3f] through a one-pot condensation-CIDT process. Racemic aldehyde **2f** (1.72 g, 5.83 mmol) was added dropwise to a stirred suspension of (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**], (1.4 g, 5.77 mmol) in methanol (28.8 mL) and the mixture was warmed to 55–60 °C. After 15 min HPLC and NMR analysis of an aliquot of the solution showed two diastereoisomeric compounds in 1 : 1 ratio (CHIRALPAK® AD-H, hexane/*i*-PrOH = 90 : 10, 1 mL min^{-1}, λ = 230 nm, 20 °C: t_R = 8.4 and 10.0 min). After 30 min a solution of acetic acid in methanol (9 : 1 ratio, 28.8 mL) was added and the reaction was left to cool at ambient temperature under an efficient stirring. Within few minutes a solid product began to form and the resulting suspension was stirred for an additional 24 h. The naphthoxazine (1*S*,3*R*,*R*)-**3f** (white solid,[35] 2.208 g, 72.8% yield, dr = 96.4 : 3.6) was collected by filtration. The diastereoisomeric purity of (1*S*,3*R*,*R*)-**3f** was further increased to dr = 99.5 : 0.5 (1.94 g, 64% overall yield) by crystallization from diisopropyl ether (66 mL): mp = 108–110 °C; (HPLC t_R = 10.0 min), $[\alpha]_D^{20}$ +83.3 (*c* 1.03, $PhCH_3$); ^{1}H NMR (400 MHz, C_6D_6) δ: 7.76–7.70 (*m*, 1H), 7.57 (*d*, *J* = 9.0 Hz, 1H), 7.41–7.35 (*m*, 1H), 7.32–7.24 (*m*, 3H), 7.15–6.93 (*m*, 6H), 6.82 (*dd*, *J* = 8.2 and 2.0 Hz, 1H), 6.65 (*d*, *J* = 8.2 Hz, 1H), 5.18 (*s*, 1H), 4.88–4.78 (*m*, 1H), 4.06–3.93 (*m*, 2H), 3.47 (*s*, 3H), 3.42–3.35 (*m*, 2H), 3.06 (*s*, 3H), 2.90 (*dd*, *J* = 13.8 and 5.0 Hz, 1H), 2.51 (*dd*, *J* = 13.8 and 7.6 Hz, 1H), 2.11–1.93 (*m*, 5H), 0.87 (*d*, *J* = 6.7 Hz, 3H), 0.85 (*d*, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ: 154.1, 150.1, 149.3, 143.9, 135.4, 133.1, 130.4, 129.9, 129.7, 129.5, 128.9, 127.9, 127.4, 123.95, 123.92, 122.2, 120.4, 115.9, 115.7, 113.3, 84.2, 70.0, 66.7, 58.9, 56.3, 54.7, 50.8, 32.7, 30.9, 28.4, 20.9, 20.2; IR (KBr): 3366.4, 3049.2, 2054.9, 2894.9, 2889.2, 2834.9, 2792.0, 1622.1, 1597.8, 1519.6, 1469.9, 1445.9, 1264.3, 1247.2, 1234.3, 1139.5, 1117.4, 886.6, 812.7 cm^{-1}. Minor isomer (1*S*,3*R*,*S*)-**3f** diagnostic signals (HPLC t_R = 8.4 min), NMR (400 MHz,$CDCl_3$) δ: 5.13(s, 1H), 3.42(*s*, 3H), 3.05(*s*, 3H), 2.61(*dd*. *J* = 13.8 and 5.3 Hz, 1H), 0.94(*d*, *J* = 6.8 Hz, 3H), 0.90(*d*, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 150.1, 149.2, 144.0, 135.3, 133.1, 130.5, 129.9, 129.7, 129.4, 129.1, 127.8, 127.3, 124.0, 123.9, 122.4, 120.3, 115.7, 115.6, 113.2, 84.9, 70.0, 66.7, 58.9, 56.2, 54.6, 51.4, 33.4, 30.9, 29.2, 21.4, 20.8.

The naphthoxazines **3f**, recovered from the mother liquor of crystallization, were added to the original methanol–AcOH filtrate of the CIDT reaction. After stirring for 64 h at ambient temperature a second crop of (1*S*,3*R*,*R*)-**3f** (0.655 g, 21.9%, dr = 98.4 : 1.6) was obtained simply by filtration.

Hydrolysis of diastereoisomerical enriched naphtoxazines 3a–f to non racemic aldehydes 2a–f: General procedure. To a suspension[36] of diastereoisomerical enriched naphthooxazines **3a–f** in THF : EtOAc 1 : 1 (4 mL mmol^{-1}) a 2% aqueous solution of TsOH (0.2 mL mmol^{-1}) and Dowex 50WX8-100 (2g mmol^{-1}) were added. The resulting mixture was stirred for 13–14 h during which time the organic solids progressively dissolved. The resin was filtered and washed with Et_2O (three times with 4 mL g^{-1} of resin). The organic solution was transferred into a separator funnel and the red aqueous phase was removed. The organic solution was then cooled with a water-ice bath and neutralized by addition of saturated aqueous solution of Na_2CO_3. The organic layer was then washed with water, brine and dried over Na_2SO_4. After solvent distillation the non racemic aldehydes **2a–f** were purified by bulb to bulb distillation:

(*R*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanal [(*R*)-2a]. Colorless oil (90% yield), $[\alpha]_D^{20}$ +4.1 (*c* 1.30, $CHCl_3$), ^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[13b]

(*S*)-3-(4-*tert*-butylphenyl)-2-methylpropanal [(*S*)-2b]. Colorless oil (99% yield), $[\alpha]_D^{26}$ +3.4 (*c* 1.03, $CHCl_3$); for (*R*)-**2b**, lit[14b] $[\alpha]_D^{25}$ −5.1 (*c* 1.00, $CHCl_3$), ^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[9]

(−)-3-(4-isopropylphenyl)-2-methylpropanal [(−)-2c]. Colorless oil (93% yield), $[\alpha]_D^{23}$ −3.1 (*c* 1.88, $CHCl_3$); ^{1}H NMR spectrum is in agreement with that previously reported.[37] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.9, 147.3, 136.5, 129.3, 126.9, 48.4, 36.7, 34.1, 24.4, 13.6.

(*R*)-3-(4-methoxyphenyl)-2-methylpropanal [(*R*)-2d]. Colorless oil (88% yield), $[\alpha]_D^{24}$ −1.6 (*c* 1.50, $CHCl_3$); ^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[38]

(−)-2-(4-methoxybenzyl)-3-methylbutanal [(−)-2e]. Colorless oil (95% yield), $[\alpha]_D^{21}$ −36.4 (*c* 1.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (*d*, *J* = 2.7 Hz, 1H), 7.07 (*m*, 2H), 6.81 (*m*, 2H), 6.79 (*m*, 1H), 3.77 (*s*, 3H), 2.93 (*dd*, *J* = 14.3 and 9.2 Hz, 1H), 2.71 (*dd*, *J* = 14.3 and 5.1 Hz, 1), 2.46 (*m*, 1H), 2.05 (*m*, 1H), 0.96 (*d*, *J* = 6.9 Hz, 3H), 0.95 (*d*, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.2, 158.0, 131.5, 129.8, 113.9, 59.9,

55.2, 31.2, 28.2, 19.9, 19.8; IR (film): 2960.8, 2873.6, 2835.7, 2717.6, 1724.0, 1612.1, 1513.2, 1465.2, 1247.9, 1178.4, 1036.2, 911.0, 733.2 cm^{-1}.

(*R*)-2-(4-methoxy-3-(3methoxypropoxy)benzyl)-3-methylbutanal [(*R*)-2f]. Colorless oil (95% yield), $[\alpha]_D^{18}$ −28.2 (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.68 (*d*, *J* = 2.8 Hz, 1H), 6.77 (*d*, *J* = 8.1 Hz, 1H), 6.71 (*d*, *J* = 2.0 Hz, 1H), 6.69 (*dd*, *J* = 8.1 and 2.0 Hz, 1H), 4.09 (*t*, *J* = 6.5 Hz, 2H), 3.82 (*s*, 3H), 3.57 (*t*, *J* = 6.2 Hz, 2H), 3.36 (*s*, 3H), 2.92 (*dd*, *J* = 14.2 and 9.2 Hz, 1H), 2.70 (*dd*, *J* = 14.2 and 5.0 Hz, 1H), 2.50–2.44 (*m*, 1H), 2.14–1.99 (*m*, 3H), 1.04 (d, *J* = 8.0 Hz, 3H), 1.03 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.2, 148.4, 147.9, 132.1, 121.0, 114.1, 111.9, 69.3, 66.0, 59.7, 58.6, 56.0, 31.7, 29.6, 28.3, 19.9, 19.8; IR(film): 2959.3, 2931.9, 2874.3, 2834.0, 2723.3, 1722.3, 1607.0, 1590.0, 1515.9, 1464.9, 1442.9, 1261.2, 1236.8, 1140.1, 1120.5, 1027.5 cm^{-1}.

Reduction of non racemic aldehydes 2a–f to non racemic alcohols 4a–f: General procedure. $NaBH_4$ (2 eq.) was added to a water-ice cooled solution of enriched aldehyde **2a–f** in MeOH (2 mL $mmol^{-1}$). The resulting solution was stirred for 1 h at 0 °C and 1 h at ambient temperature. After solvent evaporation the residue was partitioned between 2*N* HCl (2 mL $mmol^{-1}$ of aldehyde) and CH_2Cl_2. The organic layer was washed with water, brine and dried over $MgSO_4$. After solvent evaporation, the residue was directly purified by flash-chromatography on silica gel (Pet. Ether/Et_2O = 3 : 2).

(*R*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropan-1-ol, [(*R*)-4a]. R_f 0.33, colorless oil obtained in 88% yield with 86% ee, determined by HPLC using a CHIRALCEL® OD-H column, hexane/*i*-PrOH = 95 : 5, 1 mL min^{-1}, λ = 254 nm, 25 °C: (*R*)-**4a** t_R = 11.4 and (*S*)-**4a** t_R = 12.5 min. $[\alpha]_D^{20}$ +9.9 (*c* 1.34, $CHCl_3$); lit:[13b] ee = 90% $[\alpha]_D^{22}$ +11.1 (*c* 0.98, $CHCl_3$); ^1H and ^{13}C NMR spectra coincided with those previously reported.[13b]

***S*)-3-(4-*tert*-butylphenyl)-2-methylpropan-1-ol, [(*S*)-4b].** R_f 0.39, colorless oil obtained in 84% yield. $[\alpha]_D^{26}$ −2.4 (*c* 1.25, $CHCl_3$), lit:[39] ee = 99%, $[\alpha]_D$ −4.9 (*c* 2.5, $CHCl_3$). ^1H and ^{13}C NMR spectra coincided with those previously reported.[39]

(+)-3-(4-isopropylphenyl)-2-methylpropan-1-ol, [(+)-4c]. R_f 0.38, colorless oil obtained in 90% yield after distillation, bp = 128 °C at 1 mmHg. $[\alpha]_D^{24}$ +5.0 (*c* 1.87, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.16–7.12 (*m*, 2H), 7.11–7.07 (*m*, 2H), 3.53 (*dd*, *J* = 10.6 and 5.8 Hz, 1H), 3.46 (*dd*, *J* = 10.6 and 6.0 Hz, 1H), 2.88 (*hept*, *J* = 6.9 Hz, 1H), 2.70 (*dd*, *J* = 13.5 and 6.4 Hz, 1H), 2.40 (*dd*, *J* = 13.5 and 8.6 Hz, 1H), 1.93 (*m*, 1H), 1.43 (*bs*, 1H), 1.24 (*d*, *J* = 6.9 Hz, 6H), 0.92 (*d*, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.4, 137.8, 129.0, 126.3, 67.7, 39.3, 37.8, 33.6, 24.0, 16.5; IR (film) 3340.0, 2958.8, 2925.5, 2871.1, 1512.2, 1461.1, 1419.9, 1382.1, 1034.8, 986.2, 846.8, 799.8 cm^{-1}.

(*R*)-3-(4-methoxyphenyl)-2-methylpropan-1-ol, [(*R*)-4d]. R_f 0.28, colorless oil obtained in 92% yield with 42% ee, determined by HPLC analysis using a CHIRALCEL® OJ-H column, hexane/*i*-PrOH = 90 : 10, 1 mL min^{-1}, λ = 230 nm, 25 °C: (*R*)-**4d** t_R = 9.4 and (*S*)-**4d** t_R = 10.5 min. $[\alpha]_D^{25}$ +4.7 (*c* 1.43, $CHCl_3$); lit[40] 99% ee, $[\alpha]_D^{25}$ +12.9 (*c* 0.96, $CHCl_3$). ^1H NMR spectrum is in agreement with that previously reported.[40] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 132.6, 130.0, 113.7, 67.6, 55.2, 38.8, 37.9, 16.4.

(+)-3-(4-methoxyphenyl)-3-methylbutan-1-ol, [(+)-4e]. R_f 0.37, colorless oil obtained in 93% yield with 92% ee, determined by HPLC analysis using a CHIRALCEL® OD-H column, hexane/*i*-PrOH = 95 : 5, 1 mL min^{-1}, λ = 230 nm, 25 °C: (*S*)-**4c** t_R = 8.9 and (*R*)-**4c** t_R = 12.1 min. $[\alpha]_D^{21}$ +11.5 (*c* 1.74, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.10 (*m*, 2H), 6.83 (*m*, 2H), 3.78 (*s*, 3H), 3.54 (*d*, *J* = 5.6 Hz, 2H), 2.65 (*dd*, *J* = 13.8 and 5.5 Hz, 1H), 2.46 (*dd*, *J* = 13.8 and 9.1 Hz, 1H), 1.90–1.78 (*m*, 1H), 1.66–1.57 (*m*, 1H), 1.22 (*bs*, 1H), 0.97 (*d*, *J* = 6.9 Hz, 3H), 0.95 (*d*, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 133.3, 129.8, 113.7, 62.9, 55.2, 48.8, 33.4, 27.7, 19.6, 19.4. IR (film): 3368.0, 2955.8, 2834.5, 1611.4, 1512.0, 1465.5, 1246.8, 1177.3, 1037,3, 818.2 cm^{-1}.

(*R*)-2-(4-methoxy-3-(3-methoxypropoxy)benzyl)-3-methylbutan-1-ol, [(*R*)-4f]. Purified by bulb to bulb distillation and obtained as colorless oil in 98% yield with 97.5% ee, determined by HPLC using a CHIRALCEL® OD-H column, hexane/*i*-PrOH = 97 : 3, 1 mL min^{-1}, λ = 230 nm, 20 °C: (*S*)-**4c** t_R = 22.2 and (*R*)-**4c** t_R = 24.7 min. $[\alpha]_D^{18}$ +8.5 (*c* 1.49, $CHCl_3$). ^1H and IR spectra coincided with those previously reported.[28d] ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.2, 147.5, 134.0, 121.1, 114.2, 111.7, 69.3, 65.9, 62.7, 58.5, 55.9, 48.6, 33.9, 29.5, 27.6, 19.5, 19.4.

Synthesis of 4-methoxybenzotes 5b–c from non racemic alcohols 4b–c: General procedure. To a solution of alcohol **4b–c** in $CHCl_3$ (filtered on neutral alumina), 1 mL $mmol^{-1}$, and Et_3N (2 eq) at 0 °C was added 4-methoxybenzoyl chloride (1.5 eq). After 2 h the cold bath was removed and the reaction was stirred at ambient temperature for 13 h. Et_2O (10 mL $mmol^{-1}$ of substrate) was added and washed, in succession, with HCl 1 N, water (three times) and brine. The organic solution was dried on $MgSO_4$ and after solvent evaporation ester **5b–c** were isolated by flash chromatography on silica gel (Pet. Ether/Et_2O = 4 : 1)

(*S*)-3-(4-*tert*-butylphenyl)-2-methylpropyl 4-methoxybenzoate [(*S*)-5b]. Colorless oil obtained in 98% yield with 70% ee, determined by HPLC analysis using a CHIRALCEL® OD-H column, hexane/*i*-PrOH = 95 : 5, 1 mL min^{-1}, λ = 254 nm, 25 °C: (*S*)-**5b** t_R = 5.4 and (*R*)-**5b** t_R = 9.1 min. $[\alpha]_D^{26}$ +18.0 (*c* 1.39, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.02–7.98 (*m*, 2H), 7.32–7.28 (*m*, 2H), 7.13–7.09 (*m*, 2H), 6.94–6.90 (*m*, 2H), 4.18 (*dd*, *J* = 10.8 and 5.8 Hz, 1H), 4.12 (*dd*, *J* = 10.8 and 6.2 Hz, 1H), 3.85 (*s*, 3H), 2.78 (*dd*, *J* = 13.7 and 6.5 Hz, 1H), 2.53 (*dd*, *J* = 13.7 and 7.7 Hz, 1H), 2.24 (*m*, 1H), 1.30 (*s*, 9H) 1.02 (*d*, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 163.3, 148.8, 136.5, 131.5, 128.8, 125.2, 122.9, 113.6, 66.8, 55.4, 39.4, 34.7, 34.3, 31.4, 17.0; IR (film): 2960.4, 1713.5, 1606.7, 1511.0, 1274.6, 1256.9, 1167.2, 1101.6 cm^{-1}.

(−)-3-(4-isopropylphenyl)-2-methylpropyl 4-methoxybenzoate [(−)-5c]. Colorless oil obtained in 95% yield with 50% ee, determined by HPLC analysis using a CHIRALCEL® OD-H column, hexane/*i*-PrOH = 95 : 5, 1 mL min^{-1}, λ = 254 nm, 25 °C: minor isomer-**5b** t_R = 7.6 and major-**5b** t_R = 10.5 min. $[\alpha]_D^{24}$ −13.5 (*c* 2.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.02–7.97 (*m*, 2H), 7.16–7.08 (*m*, 4H), 6.94–6.89 (*m*, 2H), 4.18 (*dd*, *J* = 10.8 and 5.9 Hz, 1H), 4.12 (*dd*, *J* = 10.8 and 6.2 Hz, 1H), 3.84 (*s*, 3H), 2.87 (*m*, 1H), 2.78 (*dd*, *J* = 13.6 and 6.6 Hz, 1H), 2.52 (*dd*, *J* = 13.6 and 7.7 Hz, 1H), 2.23 (*m*, 1H), 1.23 (*d*, *J* = 7.0 Hz, 6H) 1.02 (*d*,

J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2, 163.1, 146.3, 137.1, 131.4, 128.9, 126.2, 122.8, 113.5, 68.8, 55.3, 39.6, 34.8, 33.8, 24.13, 24.06, 17.0; IR (film) 3008.2, 2959.9, 2932.8, 2840.8, 1713.6, 1606.5, 1511.8, 1462.6, 1316.1, 1257.4, 1167.1, 1101.9, 1031.3, 847.0, 770.5, 696.3 cm^{-1}.

(*R*)-2-(4-methoxybenzyl)-3-methylbutyl 4-methylbenzenesulfonate, [(*R*)-5e]. To a solution of (*R*)-**4e** (208 mg, 1 mmol) in $CHCl_3$ (2 mL, filtered on neutral alumina) and Et_3N (202 mg, 2 mmol) at 0 °C *p*-toluenesulfonyl chloride (286 mg, 1.5 mmol) was added. After 30 min the cold bath was removed. The reaction was allowed to stand at ambient temperature for 9 h, then Et_2O (10 mL) was added and the organic phase was washed, in succession, with HCl 1*N*, water (three times) and brine. The organic solution was dried ($MgSO_4$), the solvent distilled and the crude product was purified by flash chromatography (Pet. ether/Et_2O = 4 : 1, R_f 0.27) to obtain 334 mg (92% yield) of (*R*)-**5e**: crystallized from *n*-hexane, mp = 71–73 °C; 99.9% ee, determined by HPLC analysis using a CHIRALPAK® AD-H column, hexane/*i*-PrOH = 95 : 5, 1 mL min^{-1}, λ = 254 nm, 20 °C: (*R*)-**5e** t_R = 11.8 min [(*S*)-**5e** t_R = 10.9 undetected]. $[\alpha]_D^{22}$ +28.4 (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (*m*, 2H), 7.31 (*m*, 2H), 6.92 (*m*, 2H), 6.74 (*m*, 2H), 3.92 (*dd*, *J* = 9.7 and 4.8 Hz, 1H), 3.87 (*dd*, *J* = 9.7 and 5.3 Hz, 1H), 3.77 (*s*, 3H), 2.62 (*dd*, *J* = 13.9 and 5.5 Hz, 1H), 2.42 (*s*, 3H), 2.39 (*dd*, *J* = 13.9 and 9.4 Hz, 1H), 1.79 (*m*, 1H), 1.66 (*m*, 1H), 0.89 (*d*, *J* = 6.8 Hz, 3H), 0.88 (*d*, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.9, 144.6, 133.0, 131.8, 129.8, 129.7, 127.9, 113.7, 70.1, 55.2, 46.0, 32.9, 27.6, 21.6, 19.6, 19.3; IR (KBr): 2973.7, 2933.6, 2872.2, 1610.8, 1597.6, 1511.7, 1354.6, 1244.8, 1190.0, 1175.3, 1038.6, 939.1, 912.1, 836.3, 819.5 cm^{-1}.

(*R*)-2-(4-methoxy-3-(3-methoxypropoxy)benzyl)-3-methylbutanoic acid, [(*R*)-5f]. To a solution of (*R*)-**4f** (195 mg, 0.5 mmol) in acetone (6.5 mL) at 0 °C, Jones reagent was added dropwise until the orange colour persists (0.6 mL). After 60 min the reaction was quenched by isopropyl alcohol (0.5 mL) addition and stirred for further 30 min. The solid salt was eliminated by filtration on celite and washing with Et_2O. The organic layer was neutralized with aqueous $NaHCO_3$ and the organic solvents evaporated. The residue was taken up with CH_2Cl_2 and washed with water, brine and dried on $MgSO_4$. After solvent evaporation the residue was purified by flash chromatography (pet. ether/EtOAc 1 : 4) to give 123 mg (66% yield) of (*R*)-**5f** as light yellow oil; $[\alpha]_D^{21}$ +36.8 (*c* 1.00, CH_2Cl_2), lit[28d] $[\alpha]_D^{21}$ +42.1 (*c* 1.00, CH_2Cl_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.0, 148.1, 147.9, 132.2, 120.9, 114.1, 111.8, 69.4, 65.9, 58.6, 55.9, 54.4, 35.0, 30.3, 29.4, 20.4, 19.9; ^{1}H and IR spectra are in agreement with those previously reported.[28d]

Recovery of (*S*)-Betti, [(*S*)-1]. The polymer-supported Betti base, as recovered by filtration from hydrolysis of diastereoisomerical enriched naphtoxazines 3a-f, was treated for three times and under slow stirring with a solution of THF/NH_4OHconc/MeOH in 8 : 2 : 1 ratio (3 mL g^{-1} polymer-supported). After solvent evaporation under reduced pressure the Betti base (*S*)-**1** was recovery with 99% yield and er > 99.75 : 0.25.

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13 (*a*) Racemic Helional® (IFF), also named Tropional®, is a fragrance produced industrially *via* a cross-aldol condensation of piperonal and propanal followed by catalytic hydrogenation (K. Bauer, D. Garbe, H. Surburg, *Common Fragrance and Flavor Materials*, Wiley-VCH, 1997) with an annual production of about 300–350 tons; (*b*) Enders and Backes have published the first EPC synthesis of both enantiomers (ee = 90%) through the SAMP/RAMP hydrazone-alkylation strategy (D. Enders and M. Backes, *Tetrahedron: Asymmetry*, 2004, **15**, 1813–1817) and described the olfactory evaluations and odour threshold values of each enantiomer.

14 (*a*) Racemic Lilial® (Givaudan) is a lily-of-the-valley odorant and a precursor of the fungicide Fenpropimorph (W. Himmele, F.-Kohlmann, W. Herberle, German Patent, DE 2822326). Similarly to Helional® it is produced industrially *via* a cross-aldol condensation of 4-*tert*-butyl-benzaldehyde and propanal followed by hydrogenation (M. S. Carpenter, W. M. Jr Easter, U.S. Patent, 2,875,131, 1959, Givaudan); (*b*) The EPC synthesis of both enantiomers of Lilial has been performed exploiting the SAMP/RAMP methodology for enantioselective alkylation reactions (D. Enders and H. Dyker, *Liebigs Ann. Chem.*, 1990, **11**, 1107); (*c*) Through the enantioselective hydrogenation of the corresponding unsaturated alcohol catalyzed by an iridium complex followed by oxidation (A. Lightfoot, P. Schinder and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1998, **37**, 2897); (*d*) The hydrogenation of the corresponding unsaturated acid with a ruthenium complex incorporating (*R*)-BINAP followed by reduction (T. Yamamoto, in *Current Topics in Flavours and Fragrances*K. A. D. Swift, ed., Kluver Academic, Dordrech, The Nederlands1999, pp 33–38).

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