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Approach to a better understanding and modeling of (*S*)-dihydrofuran-2-yl, (*S*)-tetrahydrofuran-2-yl-, and furan-2-yl-β-dialkylaminoethanol ligands for enantioselective alkylation

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Abstract—This paper outlines our efforts to study the influence of an oxygen atom adjacent to the stereogenic center of β-aminoalcohol derivatives used as ligands for catalysts in the asymmetric alkylation of aldehydes. Thirty-four enantiomerically pure (*S*)-dihydrofuran-2-yl, (*S*)-tetrahydrofuran-2-yl-, and furan-2-yl-β-dialkylamino alcohols have been prepared from 1,4:3,6-dianhydromannitol, 1,4:3,6-dianhydrosorbitol, and aminoacids, and then have been evaluated as ligands for the enantioselective addition of diethylzinc to benzaldehyde. Attention has been focused on the structural features governing the extent of chiral induction, the reaction rate, and the chemical yield of 1-phenyl-1-propanol which has been promoted by this wide collection of β-dialkylamino alcohols.

1. Introduction

Chirality has a longstanding influence on the thinking of chemists and the preparation of enantiomerically pure compounds is a paramount task in synthesis. In 1984, Oguni and Omi[1] reported that the reaction of diethylzinc with benzaldehyde, catalyzed by a small amount of chiral 2-amino-1-alcohols in toluene at room temperature, gave optically active 1-phenyl-1-propanol (Fig. 1, **A**) almost quantitatively in near 50% ee. Since then, the interest in the enantioselective addition of dialkylzinc reagents catalyzed by chiral ligands has grown considerably.[2–4] Moreover, it has been found that stereocontrol is most easily achieved by selective promotion or catalysis of comparably unreactive systems, where racemic background reaction is slow.

Carbon–carbon bond forming reactions lie at the heart of organic synthesis and the dialkylzinc reaction with aldehydes allows access to chiral alcohols that are ubiquitous in the structures of natural products and drug compounds. Among the various types of chiral ligands explored in these reactions, several β-dialkylamino alcohols have proven to be especially efficient ligands and the enantioselective addition of organozinc reagents to aldehydes using chiral amino

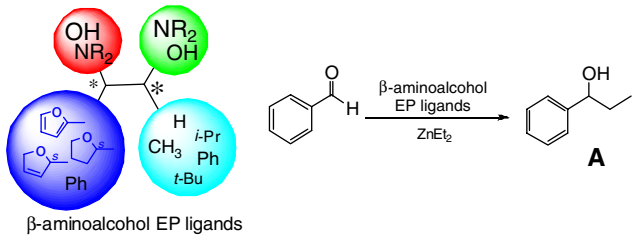

Figure 1.

alcohol derivatives has received a wide attention as a model system for exploring asymmetric C–C bond formation. Extensive mechanistic studies by Noyori et al. utilizing 3-*exo*-dimethylaminoisoborneol (DAIB) as the amino alcohol ligand have led to a good understanding of this complex reaction.[5] These pioneering studies revealed that 'slight structural changes sometimes have remarkable chemical consequences. Organozinc complexes formed from β-dialkylamino alcohols and dialkylzinc present a typical example.[6] This sentence clearly indicates how much any difference, although slight, may be relevant and how little we know about the parameters that influence the effectiveness of a chiral non-racemic ligand in stereoinducing chirality catalyzing the reaction of dialkylzinc reagents with aldehydes. Until now, several aspects have not been well defined; how would an additional oxygen atom, adjacent to the stereogenic center of β-amino alcohol derivatives, influence the effectiveness as ligands in asymmetric

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alkylation reactions? What happens when the oxygen atom belonging to a five-membered ring is bonded to the β-amino alcohol residue through a proximal stereogenic carbon atom? These, and other similar, interesting questions convinced us to systematically explore the argument devising well-focused experiments driven to collect data and pursue answers for a better understand of the mechanistic principles underlying catalysis in enantioselective alkylation reactions.

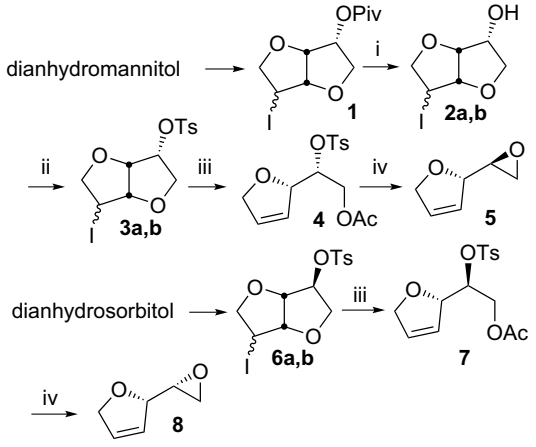
Herein, we will outline our efforts to design a class of enantiomerically pure dialkylaminoethanol ligands having some structural and/or electronic modules, including five-membered rings containing oxygen, that have been varied in a systematic fashion to study the influence (reaction time, yield, and enantiomeric excess) of each module in performing the reaction of diethylzinc with benzaldehyde to obtain enantiomerically enriched 1-phenyl-1-propanol. We assumed the structure of 2-*N*,*N*-dialkylaminoethanol to be a molecular scaffold and (*S*)-dihydrofuran-2-yl, (*S*)-tetrahydrofuran-2-yl-, and furan-2-yl substituents on one of the two carbon atoms of the base structure (Fig. 1). Therefore, we have prepared and characterized several enantiomerically pure (*S*)-dihydrofuran-2-yl, (*S*)-tetrahydrofuran-2-yl, and furan-2-yl-β-dialkylaminoethanols starting from (3*R*,3a*R*,6*R*,6a*R*)-hexahydrofuro[3,2-*b*]furan-3,6-diol (dianhydromannitol), (3*R*,3a*R*,6*S*,6a*R*)-hexahydrofuro[3,2-*b*]furan-3,6-diol (dianhydrosorbitol),[7] and aminoacids.

The catalytic ability of each chiral ligand has been studied in the asymmetric addition of diethylzinc addition to benzaldehyde.

2. Results and discussion

2.1. Ligand synthesis. Preparation of EP (*S*)-dihydrofuran-2-yl and (*S*)-tetrahydrofuran-2-yl-β-dialkylaminoethanols

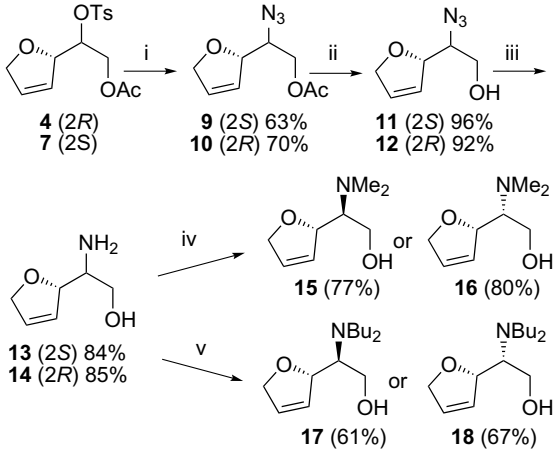
The preparation of building blocks **4** and **5** from dianhydromannitol, and **7** and **8** from dianhydrosorbitol was performed according to two modified procedures[8,9] already published and are summarized in Scheme 1.



Scheme 1. Reagents and conditions: (i) aq 15% NaOH, MeOH, rt to 40 °C, 90 min, 96%; (ii) TsCl, Py, 5 °C, 40 h, 97%; (iii) (a) BuLi, THF, −75 °C; (b) AcCl, −75 °C to rt, 95% for **4**, 90% for **7**; (iv) NaOMe, CH_2Cl_2/MeOH 15:1, 89% for **5**, 93% for **8**.

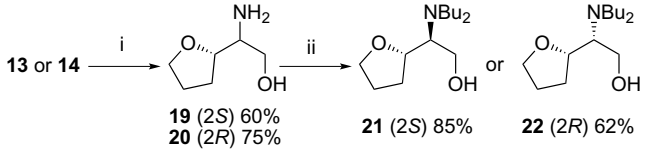
The key step of both processes is the alkyllithium-promoted eliminative ring cleavage of halides derived from 1,4:3,6-dianhydrohexitols.[10]

The stereoselectivity of each step was very high and the yields ranged from good to excellent. All these structures have in common the absolute configuration of the stereogenic center of the dihydrofuran ring. The epimeric (2*R*)- and (2*S*)-[(*S*)-2,5-dihydrofuran-2-yl]-2-(tosyloxy)ethyl acetates, respectively, **4** and **7**, were converted into (*S*)-2-amino-2-[(*S*)-2,5-dihydrofuran-2-yl]ethanol **13** and into its (2*R*)-epimer **14** following the procedure illustrated in Scheme 2, based on sodium azide substitution with inversion of configuration followed by alkaline hydrolysis and reductive cleavage of the azido group. Therefore, compounds **13** and **14** were used as versatile intermediates for the preparation of the N,N-dialkylated derivatives **15**–**18** (Scheme 2) according to already known procedures.



Scheme 2. Reagents and conditions: (i) NaN_3, DMF, 100 °C, 24 h; (ii) 15% NaOH aq, MeOH, 5 h; (iii) $LiAlH_4$, THF; (iv) CH_2O, HCO_2H, 80 °C, 4 h; (v) *n*-BuI, K_2CO_3, MeCN, reflux, 30 h.

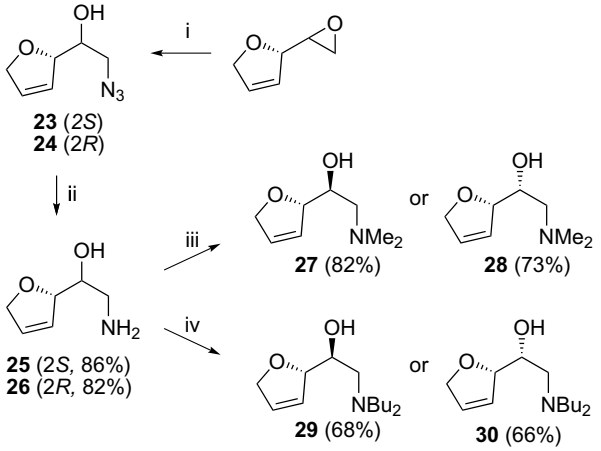
Moreover, dihydrofuranyl derivatives **13** and **14** were converted into the corresponding tetrahydrofurans **19** and **20** and then into the epimeric *N*,*N*-di(*n*-butyl) derivatives (2*S*)-**21** and (2*R*)-**22** (Scheme 3).



Scheme 3. Reagents and conditions: (i) 10% Pd(C), H_2, MeOH/HCl concn 20:1; (ii) *n*-BuI, K_2CO_3, MeCN, reflux, 30 h.

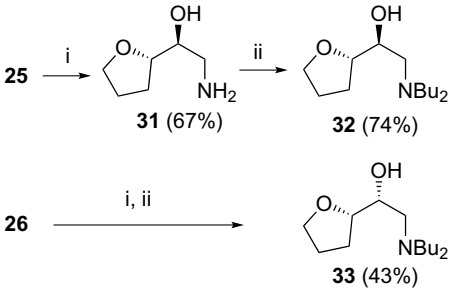
The oxiranes, (*S*)-2-[(*S*)-oxiran-2-yl]-2,5-dihydrofurane **5** and (*S*)-2-[(*R*)-oxiran-2-yl]-2,5-dihydrofurane **8**, Scheme 1, were used as building blocks to prepare, respectively, (*S*)-2-amino-1-[(*S*)-2,5-dihydrofuran-2-yl]ethanol **25** and its epimer **26**, which in turn were converted into the epimeric N,N-dialkylated couples **27**, **28** and **29**, **30**

(Scheme 4). Clean reactions and satisfying yields of the enantiomerically pure compounds made this approach very effective.



Scheme 4. Reagents and conditions: (i) NaN_3, MeOH–H_2O, see lit.[22]; (ii) $LiAlH_4$, THF; (iii) CH_2O, HCO_2H, 80 °C, 4 h; (iv) *n*-BuI, K_2CO_3, MeCN, reflux, 30 h.

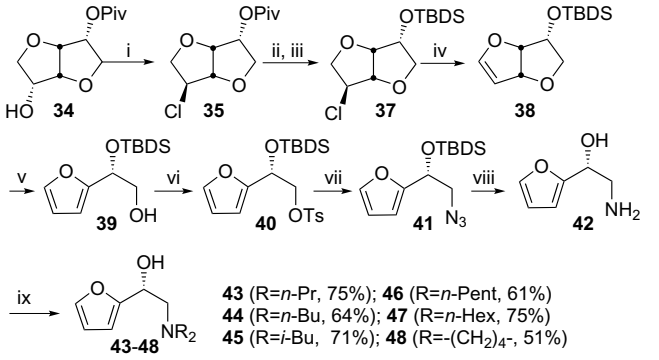
The same 2-dihydrofuranyl derivatives **25** and **26** were converted into the corresponding (2*S*)- and (2*R*)-epimers of 2-amino-1-[(*S*)-tetrahydrofuran-2-yl]ethanol by Pd-catalyzed hydrogenation and then transformed into their *N*,*N*-di-*n*-Bu derivatives **32** and **33** (Scheme 5).



Scheme 5. Reagents and conditions: (i) 10% Pd(C), H_2, MeOH/HCl concn 20:1; (ii) *n*-BuI, K_2CO_3, MeCN, reflux, 30 h.

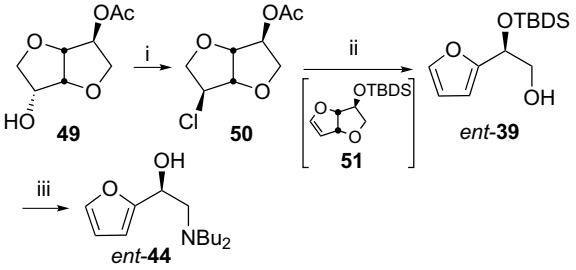
2.2. Preparation of EP furan-2-yl-β-dialkylaminoethanols

1,4:3,6-Dianhydrohexitols, dianhydromannitol, and dianhydrosorbitol, have been used as chiral sources for the preparation of enantiomerically pure furanyl-2-yl-β-aminoethanols as well. The entire process to obtain (*R*)-2-amino-(1-furan-2-yl)ethanol **42** from 1,4:3,6-dianhydromannitol monopivalate **34**[8] is shown in Scheme 6. After a straightforward conversion into the chlorine derivative **35** and the replacement of the protecting group, an efficient and clean base-induced 1,2-elimination of hydrogen chloride gave the bicyclic dehydrohalogenated compound **38.** This key intermediate underwent cleavage of the condensed tetrahydrofuran ring by an acid promoted 1,2-elimination that gave the mono protected 2-furanyl ethandiol **39**. This step involved the loss of the stereogenic center that characterizes the 2-dihydro- and 2-tetrahydrofuranyl β-amino ethanols already obtained. The efficiency of the process can be ascribed to the driving force associated with the aromatization to a furan ring.



Scheme 6. Reagents and conditions: (i) Ph_3P, CCl_4, 50 °C, 20 h, 89%; (ii) 15% aq NaOH, MeOH, 50 °C, 2 h, 90% for **36**; (iii) *t*-$BuMe_2SiCl$, Im., DMF, 0 °C to rt, 3 h, 93%; (iv) *t*-BuOK, THF, rt to 50 °C, 3 h, 92%; (v) PTSA (2.5 mol %), THF, rt to 45–50 °C, 35 min., 90%; (vi) TsCl, Et_3N, CH_2Cl_2, 4–5 °C, 24 h, 93%; (vii) NaN_3, DMF, 95 °C, 16 h, 91%; (viii) $LiAlH_4$, THF, 83%; (ix) RI (2.1 equiv), K_2CO_3 (2.1 equiv), MeCN (1 mL/mmol), 82 °C, 24–36 h.

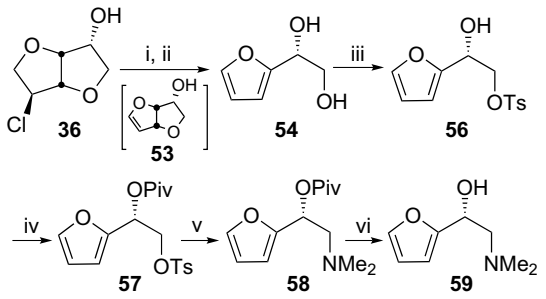
A straightforward synthetic sequence allowed the conversion of compound **39** into the hydroxyl-protected azide **41** and then into (*R*)-2-amino-1-(furan-2-yl)ethanol **42**,[11] which is the precursor of a collection of *N*,*N*-dialkylamino derivatives **43**–**48**. A similar approach was followed for the preparation of *ent*-**44** starting from the monoacetylated isosorbite[12] **49** (Scheme 7). The eliminative ring opening was performed on the protected intermediate **51** and gave *ent*-**39**, which was efficiently converted into the desired *ent*-**44** according to the procedure already used to prepare the enantiomer **44**.



Scheme 7. Reagents and conditions: (i) $SOCl_2$, Py, rt to 50 °C, 3 h, 97%; (ii) (a) *t*-BuOK, THF, rt to 50 °C, 0.5 h; (b) TBDMSCl, rt, 0.5 h; (c) PTSA (2.5 mol %), PhMe, rt to 50–55 °C, 72% overall; (iii) (a) TsCl, Et_3N, CH_2Cl_2, 4–5 °C, 24 h, 92% for *ent*-**40**; (b) NaN_3, DMF, 95 °C, 16 h, 85% for *ent*-**41**; (c) $LiAlH_4$, THF, 82% for *ent*-**42**; (d) *n*-BuI (2.1 equiv), K_2CO_3 (2.1 equiv), MeCN, 82 °C, 24 h, 63% *ent*-**44**.

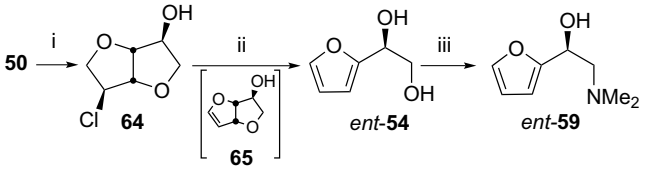
Unfortunately, the conversion of amino alcohol **42** into (*R*)-2-(dimethylamino)-1-(furan-2-yl)ethanol **59** failed under the classical conditions of an Escheweiler–Clarke reaction.[13] The dimethylamino derivative **59** was finally obtained through conversion of compound **36** into (*R*)-2-furanylethan-1,2-diol **54**[14] and therefore into the primary

O-Ts derivative **56**. The pivaloyl ester **57** of the latter compound underwent a clean substitution reaction with dimethylamine in a sealed tube, to give the *N*,*N*-dimethylamino derivative **59** after alkaline hydrolysis (Scheme 8).



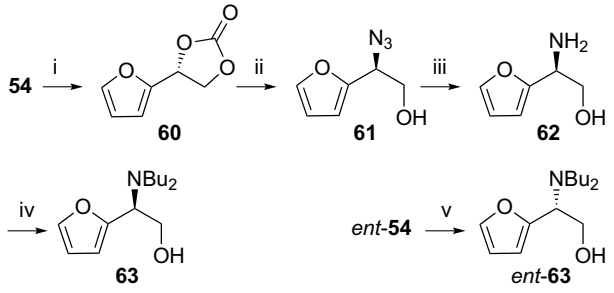
Scheme 8. Reagents and conditions: (i) *t*-BuOK, THF, rt to 50 °C, 2 h; (ii) PTSA (2.5 mol %), THF, rt to 45 °C, 35 min, 94% for **54**; (iii) (a) Bu_2SnO, $PhCH_3$, azeotr. distil.; (b) TsCl, $CHCl_3$, 90% for **56**; (iv) PivCl, Et_3N, CH_2Cl_2, 0 °C to rt, 14 h, 94%; (v) Me_2NH (5.6 M in EtOH), 50 °C, sealed tube, 24 h, 68%; (vi) 15% NaOH aq MeOH, rt 18 h, 92%.

The same procedure was used to prepare *ent*-**59** starting from compound **50**, derived from monoacetylated isosorbite[12] (Scheme 9).



Scheme 9. Reagents and conditions: (i) 15% aq NaOH, MeOH, rt to 50 °C, 94%; (ii) (a) *t*-BuOK, THF, rt to 50 °C, 4 h; (b) PTSA (2.5 mol %), THF, rt to 50–55 °C, 80%; (iii) (a) Bu_2SnO, $PhCH_3$, azeotr. distil.; (b) TsCl, $CHCl_3$, 93% for *ent*-**56**; (c) PivCl, Et_3N, CH_2Cl_2, 0 °C to rt, 14 h, 93% for *ent*-**57**; (d) Me_2NH (5.6 M in EtOH), 50 °C, sealed tube, 24 h, 65% for *ent*-**58**; (e) 15% NaOH aq. MeOH, rt 18 h, 93% for *ent*-**59**.

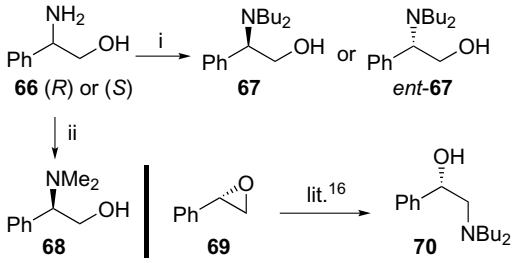
2-(Dibutylamino)-2-(furan-2-yl)ethanol enantiomers **63** and *ent*-**63** were prepared from diols **54** and *ent*-**54** according to a well-established procedure[15] and summarized in Scheme 10.



Scheme 10. Reagents and conditions: (i) lit.[15] (a) $(MeO)_2CO$, KOH 60–90 °C, 86%; (ii) NaN_3, DMF, H_2O, 120 °C, 10 h, 83%; (iii) H_2/Lindlar catalyst, MeOH, 87%; (iv) *n*-BuI, K_2CO_3, MeCN, 83 °C, 24 h, 74%; (v) (a) lit.[15] $(MeO)_2CO$, KOH 60–90 °C, 75% for *ent*-**60**; (b) NaN_3, DMF, H_2O, 120 °C, 10 h, 85% for *ent*-**61**; (c) H_2/Lindlar catalyst, MeOH, 93% *ent*-**62**; (d) *n*-BuI, K_2CO_3, MeCN, 83 °C, 24 h, 61% for *ent*-**63**.

2.3. Preparation of EP phenyl-β-dialkylamino alcohols and other structures related to the structure of norephedrine

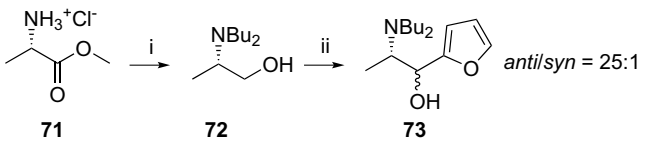
Over the course of our studies on the ability of tetrahydrofuran-2-yl, dihydrofuran-2-yl, and furan-2-yl-β-dialkylaminoethanol ligands to induce chirality through diethyl zinc reaction with aldehydes, we required phenyl-β-dialkylamino alcohol derivatives to carry out comparative studies to establish the influence of the furan ring in this type of asymmetric catalysis. Our main goal was to reveal the participation of the furan ring with its asymmetric conformations and the chelating attitude of its oxygen atom in determining the preferential structures of transition states with benzaldehyde and diethylzinc. Therefore, (*R*)-alaninol **66** and (*S*)-alaninol *ent*-**66** were converted into the corresponding *N*,*N*-dibutyl derivatives **67** and *ent*-**67** by reaction with *n*-butyl iodide, while the preparation of the *N*,*N*-dimethyl derivatives **68** from (*R*)-**66** was performed according to the Escheweiler–Clarke reaction[13] (Scheme 11). The*N*,*N*-dibutyl derivative **70** was obtained as previously reported.[16]



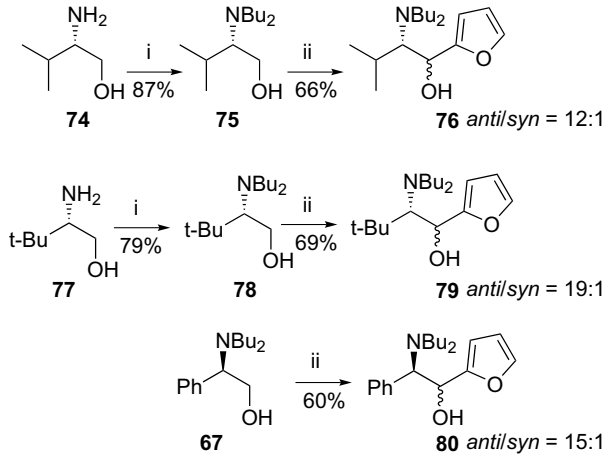
Scheme 11. Reagents and conditions: (i) *n*-BuI, K_2CO_3, MeCN, 83 °C, 24 h, 58%; (ii) From (*R*)-**66**: CH_2O, HCO_2H, 80 °C, 8 h, 85%.

We also examined some derivatives of norephedrine and with the interesting results already obtained with these compounds by Soai et al.,[17] therefore we considered what could be the behavior of a ligand having the same structure with two well-defined stereogenic centers but with a furanyl group instead of a phenyl one.

We decided to prepare (1*S*,2*S*)-2-(dibutylamino)-1-(furan-2-yl)propan-1-ol **73** and its *syn*-diastereoisomer according to the procedure[18] depicted in Scheme 12, and a small collection of analogues with *i*-propyl **76**, *t*-butyl **79**, and phenyl **80** groups instead of the methyl group typical for ephedrine (Scheme 13).



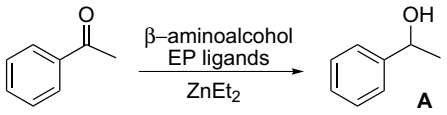
Scheme 12. Reagents and conditions: (i) (a) *n*-BuI, K_2CO_3, THF/DMSO 4:1, reflux, 36 h, (b) $LiAlH_4$, THF, 42% overall; (ii) (a) Swern oxidation; (b) 2-lithiumfuran, 77%.



Scheme 13. Reagents and conditions: (i) *n*-BuI, K_2CO_3, MeCN, 83 °C, 24 h; (ii) (a) Swern oxidation; (b) 2-lithiumfuran.

2.4. Asymmetric addition of Et_2Zn to benzaldehyde. Reactions with (*S*)-dihydrofuran-2-yl- and (*S*)-tetrahydrofuran-2-yl-aminoethanol derivatives as ligands

To verify the effectiveness of the ligands prepared as depicted, we chose the reaction of diethylzinc with benzaldehyde as a standard reaction (Scheme 14).



Scheme 14.

The reactions were performed according to the reaction conditions already established by Soai et al. for *N*,*N*-dialkylnorephedrines as ligands:[17] treatment of the aldehyde with diethylzinc (1 M solution in *n*-hexane) at 0 °C. The progress of each reaction was monitored by chiral gas chromatography.[19] The reactions were quenched with 10% HCl and extracted with diethyl ether when the conversion of the benzaldehyde was judged complete. The organic phase was dried, the solvent evaporated, and the product purified by a short silica gel column by flash chromatography.

The results of these reactions performed with (*S*)-dihydrofuran-2-yl- and (*S*)-tetrahydrofuran-2-yl-aminoethanol derivatives as ligands are summarized in Table 1.

Under the reaction conditions used, all ligands in Table 1 proved to be rather efficient as catalysts in the alkylation reactions. Yields of 1-phenyl-1-propanol **A** are referred to the isolated product and ranged from 38% to 93% from reactions protracted until benzaldehyde was entirely converted. In all the cases studied, besides the desired chiral compound **A**, a small amount of benzyl alcohol was detected as a by-product for the more sluggish reactions.[5c,j] The comparative results of entry 7 (Table 1) show that the yield of **A** was significantly increased by using more ligand, allowing the conversion of benzaldehyde by alkylation to occur faster, minimizing the formation of benzyl alcohol by reduction. From the results reported in Table 1 it is clear that besides the two adjacent stereogenic centers, these (*S*)-dihydrofuran-2-yl, and (*S*)-tetrahydrofuran-2-yl-β-dialkylamino alcohols show a modest enantioselectivity. 2-(2,5-Dihydrofuran-2-yl)-2-aminoethanol derivatives **15**–**18** catalyzed the formation of 1-phenyl-1-propanol and the absolute configuration of the major enantiomer was the same as the carbon atom of the ligand bearing the dialkylated nitrogen. The isomeric 1-(2,5-dihydrofuran-2-yl)-2-aminoethanol derivatives **27**–**30** with the same (*S*)-dihydrofuran-2-yl group showed a different enantioselectivity giving a scalemic mixture of 1-phenyl-1-propanol where the major enantiomer was that with the absolute configuration *opposite* to that of the carbon atom of the ligands bearing the secondary hydroxyl group. A reinforcing effect, albeit small, was observed for those epimers of ligands with two *opposite* absolute configurations (**28** > **27**, **30** > **29**). The same trend was observed with (*S*)-2-(dibutylamino)-2-[(*S*)-tetrahydrofuran-2-yl]ethanol **21** and its (*R*)-dibutylamino epimer **22**, while the epimeric 2-amino-1-[(*S*)-tetrahydrofuran-2-yl]ethanol derivatives **32** and **33** showed more significant difference both in yield and in asymmetric induction: matching for ligand **33** gave (*S*)-1-phenylpropan-1-ol with 52% ee and mismatching for ligand **32** generated the (*R*)-enantiomer with only 8% ee. In every case, small changes were observed in ee with the nature of the alkyl groups.

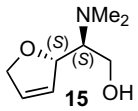
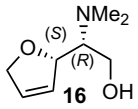
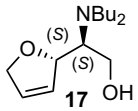
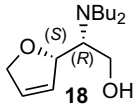
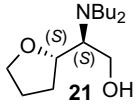
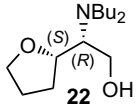
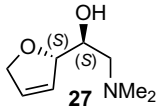
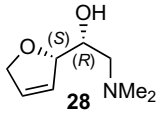
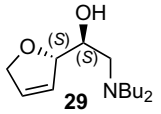
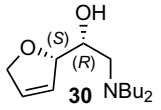
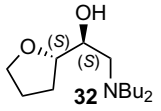
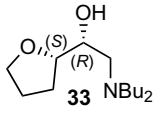
2.5. Reactions with furan-2-yl-aminoethanol derivatives as ligands

The reactions of diethylzinc with benzaldehyde carried out in the presence of furan-2-yl-aminoethanol derivatives are summarized in Table 2 and clearly indicate these ligands work better than those depicted in Table 1.

As can be seen from Table 2, the addition of diethylzinc to benzaldehyde in *n*-hexane at 0 °C in the presence of 6% of ligands **59** and *ent*-**59** was completed in only 2 h and led to 1-phenylpropan-1-ol in near 88% yield of isolated product with 70–77% ee. It was shown that the enantioselectivity of the reaction was very sensitive to the position of the hydroxyl group: better results were always observed with ligands bearing the hydroxy group on the stereogenic center. For example, when ligands **63** and *ent*-**63** were employed, (*S*)-1-phenylpropanol and (*R*)-1-phenylpropanol were, respectively, obtained in high yield but with low ee values (21% and 15% ee, Table 2, entries 9 and 10), while the corresponding isomers **44** and *ent*-**44** with the secondary hydroxyl group on stereogenic center, not only showed higher catalytic activity, but also gave the product with better ee values (73% and 72% ee, Table 2, entries 2 and 3).

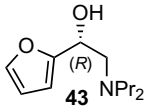
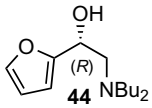
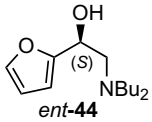
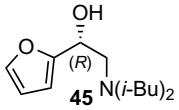
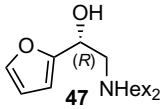
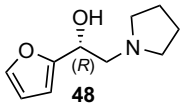
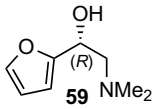
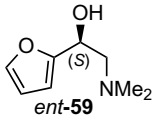
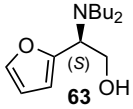
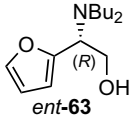
Similar results were also obtained with ligand **48** too (72% ee, Table 2, entry 6). Whereas the (*R*)-2-amino-1-(furan-2-yl)-ethanol derivatives (Table 2, entries 1, 2, and 5–7) catalyzed the reaction to give (*S*)-1-phenylpropanol as the main enantiomer, (*R*)-2-di-*n*-butylamino-2-(furan-2-yl)ethanol (Table 2, entry 10) gave mainly (*R*)-1-phenylpropanol showing the same selectivity already observed for the (*S*)-dihydrofuran-2-yl and (*S*)-tetrahydrofuran-2-yl analogues (Table 1).

Table 1. Asymmetric addition of diethylzinc to benzaldehyde to obtain 1-phenyl-1-propanol **A** using (*S*)-dihydrofuran-2-yl and (*S*)-tetrahydrofuran-2-yl-β-dialkylaminoethanol as ligands

Entry[a]	Ligands	Mol (%)	Time (h)	Y[b] (%)	ee[c] (%)	**A**[d]
1	 **15**	8.0	22	77	37	(*S*)
2	 **16**	10.0	22	63	46	(*R*)
3	 **17**	8.0	5.5	93	50	(*S*)
4	 **18**	8.0	5.5	75	37	(*R*)
5	 **21**	6.0	5	86	30	(*S*)
6	 **22**	6.0	6	76	35	(*R*)
7	 **27**	6.5 11.0	28 7	52 88	17 18	(*R*) (*R*)
8	 **28**	18.0	16	73	55	(*S*)
9	 **29**	6.5	24	46	30	(*R*)
10	 **30**	6.5	18	93	50	(*S*)
11	 **32**	6.0	23	38	8	(*R*)
12	 **33**	6.0	23	70	52	(*S*)

[a] The molar ratio Et_2Zn/benzaldehyde was 2.1:1. All the reactions were performed in *n*-hexane at 0 °C following the procedure developed by Soai et al.[17]
[b] Isolated yields.
[c] Determined by the observed rotations and confirmed by GC.[19]
[d] Absolute configuration of product **A**.

Table 2. Asymmetric addition of diethylzinc to benzaldehyde to obtain 1-phenyl-1-propanol (**A**) using furan-2-yl β-amino alcohols as ligands

Entry[a]	Ligands	Mol (%)	Time (h)	Y[b] (%)	ee[c] (%)	**A**[d]
1	 **43**	6.0	5	66	70	(*S*)
2	 **44**	6.0	4	83	73	(*S*)
3	 *ent*-**44**	6.0	5	94	72	(*R*)
4	 **45**	6.0	24	62	5	(*R*)
5	 **47**	6.0	24	67	64	(*S*)
6	 **48**	6.0	5	88	72	(*S*)
7	 **59**	6.0 10.0	2 2	85 92	76 77	(*S*) (*S*)
8	 *ent*-**59**	6.0	2	73	75	(*R*)
9	 **63**	6.0	4	83	21	(*S*)
10	 *ent*-**63**	6.0	4	85	15	(*R*)

[a] The molar ratio of Et_2Zn/benzaldehyde was 2.1:1. All the reactions were performed in *n*-hexane at 0 °C following the procedure developed by Soai et al.[17]
[b] Isolated yields.
[c] Determined by the observed rotations and confirmed by GC.[19]
[d] Absolute configuration of product **A**.

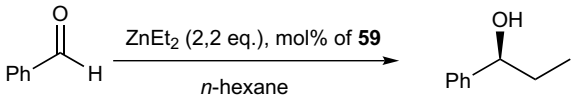
A maximum value of 76% ee was observed with dimethyl derivative **59**. When ligand **59**, diethylzinc, and benzaldehyde were in a 1:1:1 ratio, no reaction was observed, while the alkylation of benzaldehyde occurred in 40 min at 0 °C giving (*S*)-1-phenylpropanol (79.3% ee) in high yield (94%) with a 1:2.1:1 ratio of the reagents. Increasing the

length of the *n*-alkyl groups of the ligands diminished the rate of the reaction with only a slight effect on the enantioselectivity, while a loss of efficiency both in rate and in enantioselectivity was observed working with the di-*i*-butyl derivative **45**.

Furthermore, the effects of the amount of the catalyst and temperature on the asymmetric induction in the presence of ligand **59** were examined. When increasing the amount of chiral ligand **59** from 6 to 10 or 20 mol %, no significant variation in product ee was observed (Table 3, entries 2–4); reducing the amount to 2% was detrimental: the reaction required 17 h to be complete and the enantioselectivity dropped to 41% ee (Table 3, entry 1).

Lowering the reaction temperature from 0 °C to −20 °C led no an increase in selectivity while an increase to 30 °C resulted in a small decrease in the ee value (Table 3, entries 5 and 6).

Table 3. The influence of the amount of catalyst **59** and temperature on the reaction rate and selectivity



Entry	Ligand **59** (mol %)	*T* (°C)	Time (h)	ee (%)
1	2	0	17	41
2	6	0	2	76
3	10	0	<2	77
4	20	0	1	78
5	10	−20	2	77
6	10	30	1	70

All the results reported in Tables 1–3 were achieved using *n*-hexane as a solvent. Next, the influence of the solvent on the selectivity of ligand **59** was examined and Table 4 summarizes the results collected.

It is worth noting that *iso*-propyl ether (Table 4, entry 3) is the only co-solvent that did not decrease the reaction rate maintaining the same selectivity already observed for ligand **59** in *n*-hexane. Tetrahydrofuran, furan, and toluene had detrimental effects both on rate and selectivity (Table 4, entries 1, 2, 4, and 5), while *t*-BuOMe slowed down the reaction without reduction of the selectivity (Table 4, entries 6 and 7).

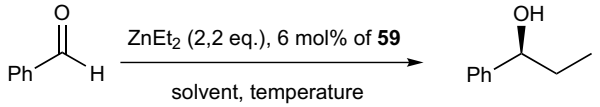
The selectivity induced by ligand **59** was constant during the reaction, as shown by the results collected in Table 5 by monitoring the ee values of the product at different reaction times.

2.6. Reactions with phenyl-aminoethanol derivatives as ligands

The results shown in Tables 1 and 2 indicated that 1-substituted-2-amino-1-ethanol derivatives were more effective and enantioselective than the isomeric 2-substituted 2-amino-1-ethanol derivatives. Moreover, 2-dialkylamino-1-(furan-2-yl)ethanol compounds were found to exhibit higher enantioselectivities (up to 77% ee for ligand **59**, Table 2) than 2-dialkyamino-1-(2,5-dihydrofuran-2-yl)ethanol derivatives (up to 55% ee for ligand **28** with *anti*-configuration, Table 1) and the 2-dialkylamino-1-(2,5-tetrahydrofuran-2-yl)ethanol derivatives (up to 52% ee for the ligand **33** with *anti*-configuration, Table 1). The additional stereogenic center of the 2-dihydrofuranyl and 2-tetrahydrofuranyl ring, directly adjacent to the carbon bearing the hydroxyl group, resulted in a detrimental effect on the enantioselectivity of the ligands with *syn*-configuration. These results appeared in contrast with the nucleophilicity of the oxygen atoms of hydrogenated furan with respect to the less available oxygen of furan due to its aromaticity. In light of these results our attention was focused on the role that the furan ring plays and we attempted to give an answer to the questions: is the C-2 bonded furanyl group involved in effective catalyst that controls the entire process? Does it work better than the rotationally symmetric phenyl group? To give an answer to these questions, ligands **67**, **68**, and **70** were prepared and tested (Table 6).

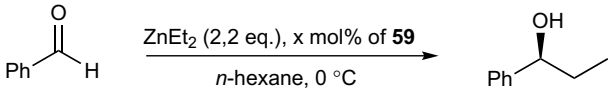
It is worth noting the influence of the phenyl group, when compared to the furanyl group, both on the reaction rate and the effectiveness of the asymmetric induction. The different relationship between the absolute configuration of these ligands and that induced in 1-phenylpropanol **A** is due to the different group priority in the structure of ligands. 2-(Dialkylamino)-2-phenylethanol **67**, *ent*-**67**, and **68** as well as (*S*)-2-(dibutylamino)-1-phenylethanol **70**

Table 4. The effect of the solvent on the effectiveness of ligand **59**



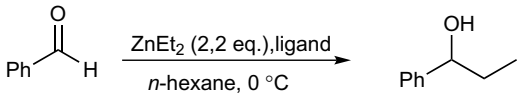
Entry	Solvent	*T* (°C)	Time (h)	ee (%)
1	THF/*n*-hexane 1:4	18	22	43
2	THF/*n*-hexane 2:3	18	24	47
3	*i*-Pr_2O/*n*-hexane 1:1	0	3	78
4	Furan/*n*-hexane 1:1	0	27	58
5	Toluene/*n*-hexane 1:1	0	20	67
6	*t*-BuOMe/*n*-hexane 1:1	0	20	76
7	*t*-BuOMe/*n*-hexane 1:8	0	22	75

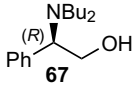
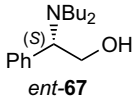
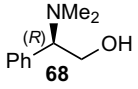
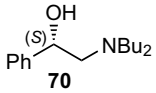
Table 5. The constancy of enantioselectivity of ligand **59** induced alkylation reactions



Entry	Ligand **59** (mol %)	Conversion %	ee (%)
1	6	30	74
2	6	50	75
3	6	100	74
4	4	13	73
5	4	20	77
6	4	33	77
7	4	100	76

Table 6. The alkylation reaction performed with phenyl-aminoethanol derivatives as ligands



Entry[a]	Ligands	Mol (%)	Time (h)	Y[b] (%)	ee[c] (%)	A[d]
1	 **67**	6.0	21	82	16	(*S*)
2	 *ent*-**67**	6.0	26	75	15	(*R*)
3	 **68**	6.0	24	71	22	(*S*)
4	 **70**	6.0	24	70	60	(*S*)

[a] The molar ratio of Et_2Zn/benzaldehyde was 2.1:1. All the reactions were performed in *n*-hexane at 0 °C following the procedure developed by Soai et al.[17]
[b] Yields of isolated product.
[c] Determined by the observed rotations and confirmed by GC.[19]
[d] Absolute configuration of product **A**.

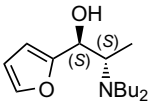
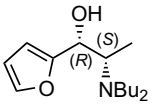
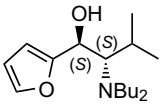
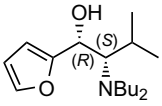
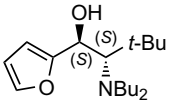
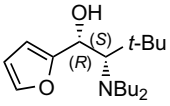
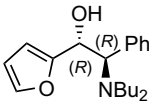
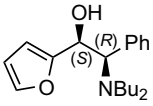
required over 20 h to complete the reaction against the 4 h required for the corresponding furanyl substituted ligands (Table 2, entries 3, 9, and 10). It is interesting to note that the lower ee value observed with ligand **70** (60% ee in 24 h, Table 6, entry 4) compared with the result of ligand **44** (73% ee in 4 h, Table 2, entry 2) under the same reaction conditions.

2.7. Reactions with 2-substituted 2-(dialkylamino)-1-(furan-2-yl)ethanol ligands

The investigations of Soai et al. established the effectiveness of *N*,*N*-dialkylnorephedrines as ligands in the catalyzed addition of dialkylzincs to aliphatic and aromatic aldehydes.[17] Among them *N*,*N*-di-*n*-butylnorephedrine was found to be the most effective catalyst. Inspired by these outstanding achievements we prepared some derivatives having the base structure of norephedrine but with a furanyl group instead of the phenyl group and a variety of sidechains. Finally, we focused our attention on (1*R*,2*S*)-2-(dibutylamino)-1-(furan-2-yl)-2-phenylethanol **80**, a 2-aminoethanol in which both the phenyl group and the furanyl group are present in well-established absolute configurations. The results obtained with these ligands with two adjacent stereogenic centers are shown in Table 7.

In their pioneering paper, Soai et al.[17] reported that (1*S*,2*R*)-(−)-*N*,*N*-di-*n*-butylnorephedrine (DBNE), a *syn*-diastereoisomer, catalyzed the addition of diethylzinc to benzaldehyde and gave (*S*)-1-phenyl-1-propanol in quantitative yield with 90% ee. (1*R*,2*S*)-2-(Dibutylamino)-1-(furan-2-yl)propan-1-ol *syn*-**73** showed lower effectiveness both in yield (71%) and in induction power (58% ee). Better results were obtained with ligand *anti*-**73** (75% and 70% ee). It is worth noting the great difference in reaction rate of ligands *anti*-**73** and *syn*-**73** when compared with the other ligands shown in Table 7 (10 h against 24 h). For these latter ligands, the lower reactivity was accompanied by a major inducing power (60–83% ee). In particular, their *syn*-isomer

Table 7. Alkylation reactions promoted by norephedrine like ligands

Entry[a]	Ligands	Time (h)	Y[b] (%)	ee[c] (%)	A[d]
1	 *anti*-**73**	10	75	70	(*R*)
2	 *syn*-**73**	10	71	58	(*S*)
3	 *anti*-**76**	24	85	78	(*R*)
4	 *syn*-**76**	24	75	83	(*S*)
5	 *anti*-**79**	24	67	60	(*R*)
6	 *syn*-**79**	24	75	75	(*S*)
7	 *anti*-**80**	24	86	76	(*S*)
8	 *syn*-**80**	24	**100**	**83**	(*R*)

[a] The molar ratio of Et_2Zn/benzaldehyde was 2.1:1. All the reactions were performed in *n*-hexane at 0 °C following the procedure developed by Soai et al.[17]
[b] Yields of isolated product.
[c] Determined by the observed rotations and confirmed by GC.[19]
[d] Absolute configuration of product **A**.

was more effective than the corresponding *anti* one; the reverse observed for *syn*-**73** and *anti*-**73** ligands. The ligand *syn*-**80** showed the best performances in yield and ee.

3. Conclusions

In conclusion, we have developed a family of chiral ligands including 34 enantiomerically pure (*S*)-dihydrofuran-2-yl, (*S*)-tetrahydrofuran-2-yl, and furan-2-yl-β-dialkylaminoethanol derivatives, prepared from 1,4:3,6-dianhydromannitol, 1,4:3,6-dianhydrosorbitol, and amino acids through efficient and stereoselective synthetic schemes. The molecular architecture of these ligands, built from varying modules grafted in a controlled manner on a common chiral skeleton, allowed some variation of steric and/or electronic characteristics, and has been used as a tool to determine the influence of each module on the catalytic properties. In this systematic study, we have employed a well-established enantioselective process, the amino alcohol-promoted addition of diethylzinc to benzaldehyde. Some important conclusions can be drawn from this study: (a) all the dialkylamino alcohol ligands we have prepared and tested accelerated the alkylation of benzaldehyde by diethylzinc and revealed catalytic properties; (b) besides the two adjacent stereogenic centers, all (*S*)-dihydrofuran-2-yl and (*S*)-tetrahydrofuran-2-yl-β-dialkylamino alcohol ligands revealed a modest enantioselectivity; (c) while the 2-(2,5-dihydrofuran-2-yl)-2-aminoethanol and 2-(tetrahydrofuran-2-yl)-2-aminoethanol derivatives induced preferentially the formation of 1-phenylpropan-1-ol enantiomer having the same absolute configuration of the carbon atom bearing the secondary dialkylated nitrogen, 1-(2,5-dihydrofuran-2-yl)-2-aminoethanol and 1-(2,5-tetrahydrofuran-2-yl)-2-aminoethanol derivatives induced the formation of 1-phenylpropan-1-ol with the major enantiomer having the opposite configuration with respect to that of the carbon atom of the ligand bearing the secondary hydroxyl group; (d) with 1-(2,5-dihydrofuran-2-yl)-2-aminoethanol derivatives, a significant reinforcing effect has been observed when the two chiral centers of the ligands have opposite absolute configurations; (e) the nature of alkyl groups on the nitrogen atom of ligands did not influence significantly the induction power; (f) better results have been recorded with 2-dialkylamino-1-(furan-2-yl)-1-ethanol ligands while the induction power of the isomeric 2-dialkylamino-2-(furan-2-yl)-1-ethanol derivatives was very low; (g) for the best ligand in this series, compound **59**, we have investigated the effect of the catalyst amount on the reaction rate and enantioselectivity, the influence of temperature and of the solvent on the effectiveness; the selectivity and the constancy of enantioselectivity during the alkylation reaction promoted by ligand **59**; (h) enantiomerically pure 2-dibutylamino-1-(furan-2-yl)-1-ethanol was more effective as a ligand than 2-dibutylamino-1-phenyl-1-ethanol, both in terms of reaction rate and in enantioselectivity; (i) this beneficial effect of the furan-2-yl group instead of the phenyl group was not observed with ligand *anti*-**73** when compared with the corresponding *N*,*N*-di-*n*-butylnorephedrine developed by Soai et al.; (j) while *anti*-**73** was more effective than *syn*-**73**, the ligands *anti*-**76**, *anti*-**79**, and *anti*-**80** were less effective than the corresponding *syn*-isomers. These latters showed the best induction power with 83%, 75%, and 83% ee, respectively.

Extensive mechanistic studies by Noyori et al. utilizing (2*S*)-3-exo-(dimethylamino)isoborneol (DAIB) as the amino alcohol ligand for the alkylation of aldehydes with dialkylzinc reagents have led to a good understanding of this complex reaction. From the experimental results of the most important and effective dialkylamino alcohol ligands, a consistent empirical correlation between the absolute configuration of ligand and product has been established and the mechanism of the process has been studied by several groups. More recently, several semiempirical TS models[20,4e] have been developed for the enantioselective chiral β-amino alcohol catalyzed additions of organozinc reagents to benzaldehyde and general trends for varying chiral β-amino alcohol ligands have been reproduced by these models. It is likely that our findings will be useful material for a detailed theoretical investigation of the selectivity determining interactions for structures *inside* the class of β-amino alcohol ligands we have prepared and tested.

4. Experimental

Melting points were obtained with a Büchi apparatus and are uncorrected. Yields are for isolated compounds. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively. Chemical shifts are in ppm downfield of TMS. For optical rotation a Perkin Elmer 341 polarimeter was used. Bulb to bulb distillations were done on a Büchi GRK-50 Kugelrohr; boiling points refer to air-bath temperatures and are uncorrected. All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. Anhydrous solvents and reagents were obtained as follows: benzene distilled over CaH_2; DMSO distilled at 3 mm of pressure over CaH_2; THF was distilled over sodium benzophenone.

4.1. (3*R*,3a*R*,6*S*,6a*S*) and (3*R*,3a*R*,6*R*,6a*S*)-6-iodohexahydrofuro[3,2-*b*]furan-3-ols 2a and 2b

To a solution of isomeric esters **1**[8] (17 g, 0.05 mol) dissolved in MeOH (50 mL), a 15% water solution of NaOH (8 mL, 0.03 mol) was added. The reaction mixture was warmed at 40 °C and stirred for 90 min. After solvent evaporation, under reduced pressure, the residue was dissolved in CH_2Cl_2 (300 mL) and washed with H_2O (15 mL, twice). The water layer was extracted with CH_2Cl_2 (15 mL, twice), and then the combined organic phases dried over $MgSO_4$. The residue, after solvent evaporation, was filtered through a silica plug with petroleum ether/Et_2O 1:3 to give 12.29 g (96%) of **2a** and **2b**. A small sample was flash chromatographed (petroleum ether/EtOAc 1:1) to isolate both the isomers as pure compounds.

4.1.1. (3*R*,3a*R*,6*S*,6a*S*)-6-Iodohexahydrofuro[3,2-*b*]furan-3-ol 2a. The first eluted was the major isomer **2a** as a white solid ($R_f = 0.42$, petroleum ether/EtOAc 2:3): mp 107–108 °C (crystallized from *n*-hexane); $[\alpha]_D^{22} = +60.2$ (*c* 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.85–4.78 (m, 2H), 4.38–

4.29 (m, 2H), 4.29–4.19 (m, 2H), 4.01 (dd, 1H, $J = 9.3$, 6.3 Hz), 3.58 (dd, 1H, $J = 9.3$, 6.3 Hz), 2.65 [d, 1H, $J = 7.7$ Hz (OH)]; ^{13}C NMR ($CDCl_3$): δ 90.3, 81.6, 77.8, 74.4, 72.3, 26.3. IR (KBr) 3440 cm^{-1}; Anal. Calcd for $C_6H_9IO_3$: C, 28.15; H, 3.54; I, 49.56. Found: C, 28.23; H, 3.51; I, 49.26.

4.1.2. (3*R*,3a*R*,6*R*,6a*S*)-6-Iodohexahydrofuro[3,2-*b*]furan-3-ol 2b. The minor isomer **2b** as a white solid ($R_f = 0.3$, petroleum ether/EtOAc 2:3); mp 50–51 °C (crystallized from *i*-propyl ether); $[\alpha]_D^{22} = +76.9$ (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.55 (dd, 1H, $J = 5.4$, 4.3 Hz), 4.48–4.41 (m, 1H), 4.43–4.35 (m, 1H), 4.28–4.21 (m, 1H), 4.11 (ddd, 1H, $J = 11.0$, 7.3, 4.3 Hz), 3.96 (dd, 1H, $J = 9.6$, 6.0 Hz), 3.81 (dd, 1H, $J = 11.0$, 8.2 Hz), 3.64 (dd, 1H, $J = 9.6$, 6.0 Hz), 2.70 [br s, 1H (OH)]; ^{13}C NMR ($CDCl_3$): δ 82.4, 80.8, 75.8, 74.1, 72.9, 21.8; IR (KBr) 3492 cm^{-1}; Anal. Calcd for $C_6H_9IO_3$: C, 28.15; H, 3.54; I, 49.56. Found: C, 28.26; H, 3.55; I, 49.68.

4.2. (3*R*,3a*S*,6*S*,6a*S*)- and (3*R*,3a*S*,6*R*,6a*S*)-6-iodohexahydrofuro[3,2-*b*]furan-3-yl 4-methylbenzenesulfonates 3a and 3b

To a solution of **2a** and **2b** (12 g, 0.0468 mol) in pyridine (47 mL), TsCl (13.4 g, 0.070 mol) was added at 5 °C and the reaction flask stored in the refrigerator. After 40 h, the reaction mixture was slowly added to a well stirred water-ice solution. The solid product was isolated by filtration on a Büchner funnel, washed with water, and dried under vacuum. Crystallization from MeOH gave 18.62 g (97%) of **3a** and **3b** as a white solid. A small sample was flash chromatographed to isolate both the isomers as pure compounds.

4.2.1. (3*R*,3a*S*,6*S*,6a*S*)-6-Iodohexahydrofuro[3,2-*b*]furan-3-yl 4-methylbenzenesulfonate 3a. Isolated as a white solid ($R_f = 0.48$, petroleum ether/EtOAc 7:3); mp 109–111 °C (crystallized from MeOH); $[\alpha]_D^{22} = +69.2$ (*c* 1.51, $CHCl_3$), [lit.[21] mp 109–110 °C, $[\alpha]_D^{20} = 71$; ^{1}H NMR ($CDCl_3$): δ 7.82 (d, 2H, $J = 8.4$ Hz), 7.36 (d, 2H, $J = 8.4$ Hz), 4.93–4.84 (m, 1H), 4.82–4.77 (m, 2H), 4.28 (dd, 1H, $J = 3.5$, 1.6 Hz), 4.20 (dd, 1H, $J = 11.0$, 3.5 Hz), 4.15 (dd, 1H, $J = 11.0$, 1.6 Hz), 3.98 (dd, 1H, $J = 9.6$, 6.3 Hz), 3.74 (dd, 1H, $J = 9.6$, 6.9 Hz), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 145.3, 133.0, 129.9, 128.0, 90.5, 80.1, 78.3, 78.1, 70.7, 25.5, 21.7; IR (KBr) 2979, 2941, 2874, 1355, 1190, and 1177 cm^{-1}.

4.2.2. (3*R*,3a*S*,6*R*,6a*S*)-6-Iodohexahydrofuro[3,2-*b*]furan-3-yl 4-methylbenzenesulfonate 3b. Isolated as a white solid: ($R_f = 0.28$, petroleum ether/EtOAc 7:3); mp 138–140 °C (crystallized from MeOH); $[\alpha]_D^{22} = +99.9$ (*c* 1.07, $CHCl_3$), {lit.[21] mp 137–137.5 °C, $[\alpha]_D^{20} = +107$}; ^{1}H NMR ($CDCl_3$): δ 7.82 (d, 2H, $J = 8.3$ Hz), 7.35 (d, 2H, $J = 8.3$ Hz), 4.96 (dd, 1H, $J = 11.6$, 6.1 Hz), 4.61–4.56 (m, 1H), 4.42–4.38 (m, 1H), 4.18–4.11 (m, 1H), 4.03 (ddd, 1H, $J = 10.8$, 7.3, 4.5 Hz), 3.90 (dd, 1H, $J = 10.0$, 6.1 Hz), 3.81–3.71 (m, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 145.4, 133.2, 130.1, 128.0, 82.5, 79.5, 79.3, 76.1, 70.7, 21.8, 21.6; IR (KBr) 2979, 2940, 2882, 1359, 1193, and 1178 cm^{-1}.

4.3. (*R*)-2-[(*S*)-2,5-Dihydrofuran-2-yl]-2-(tosyloxy)ethyl acetate 4

A mixture of **3a** and **3b** (9 g, 0.0219 mol) dissolved in THF (190 mL) was reacted at −75 °C with BuLi (14.8 mL 1.6 M in hexane, 0.0236 mol). After 30 min at −75 °C, the reaction was quenched by the slow addition of AcCl (1.96 g, 0.025 mol) dissolved in THF (10 mL). After 30 min at −75 °C, the reaction was left to warm spontaneously at room temperature before being quenched with H_2O (2 mL). After solvent evaporation the residue was dissolved in CH_2Cl_2 (100 mL) and, in succession, washed twice with water (7 mL), dried over $MgSO_4$, and the solvent distilled under reduced pressure supporting the residue on silica gel (12 g). From flash chromatography ($R_f = 0.3$, petroleum ether/EtOAc 7:3) acetate **4** (6.97 g, 95%) was obtained as a white solid: mp 60–61 °C (crystallized from MeOH); $[\alpha]_D^{20} = -34.1$ (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.80 (d, 2H, $J = 8.3$ Hz), 7.34 (d, 2H, $J = 8.3$ Hz), 6.02–5.97 (m, 1H), 5.78–5.73 (m, 1H), 4.98–4.90 (m, 1H), 4.73 (ddd, 1H, $J = 6.9$, 4.7, 3.0 Hz), 4.59–4.43 (m, 2H), 4.30 (dd, 1H, $J = 12.4$, 3.0 Hz), 4.14 (dd, 1H, $J = 12.4$, 6.9 Hz), 2.44 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.4, 144.7, 134.1, 129.6, 129.5, 127.8, 124.7, 84.6, 80.8, 75.9, 62.2, 21.5, 20.5; IR (KBr) 1743 cm^{-1}; Anal. Calcd for $C_{15}H_{18}O_6S$: C, 55.20; H, 5.56; S, 9.82. Found: C, 55.03; H, 5.58; S, 9.81.

4.4. (*S*)-2-[(*S*)-Oxiran-2-yl]-2,5-dihydrofuran 5

To a mechanically stirred solution of **4** (5.26 g, 16.11 mmol) in CH_2Cl_2/MeOH 15:1 (30 mL), a 4 M solution of NaOMe in MeOH (4.5 mL, 18 mmol) was slowly added over 30 min and stirred at room temperature for an additional 30 min. After filtration and solvent evaporation, the residue was distilled at 85 °C, 20 mm, to give epoxide **5** (1.62 g, 89%) as colorless oil: $[\alpha]_D^{25} = -148.9$ (*c* 1.3, $CHCl_3$), {lit.[8] bp 77 °C 16 mm, $[\alpha]_D^{29} = -152.6$ (*c* 2.56, $CHCl_3$), ^{1}H and ^{13}C NMR spectra were identical to those previously reported}.

4.5. (*S*)-2-[(*S*)-2,5-Dihydrofuran-2-yl]-2-(tosyloxy)ethyl acetate 7

A mixture of **6a** and **6b**[9] (26.5 g, 0.0646 mol) dissolved in THF (600 mL) was reacted at −75 °C with BuLi (28.5 mL 2.5 M in hexane, 0.071 mol). After 30 min at −75 °C, the reaction was quenched by slow addition of AcCl (5.04 mL, 0.071 mol) dissolved in THF (10 mL). After 30 min at −75 °C, the reaction temperature was left to rise to 0 °C spontaneously and quenched with water (5 mL). The mixture was concentrated under reduced pressure and the residue was taken up with a mixture of Et_2O/EtOAc 3:1 (300 mL). The organic solution was, in succession, washed with water (20 mL), 5% aqueous $Na_2S_2O_5$ (10 mL), water (10 mL, twice), and brine. After being dried over $MgSO_4$, the solvents were distilled under reduced pressure. The solid residue was crystallized two times: first with 100 mL and then 50 mL of *i*-Pr_2O to give 16.2 g of acetate **7**. From the crystallization solvents, by flash chromatography, were recovered 2.8 g of **7** (19 g overall, 90%): mp 64–65 °C (crystallized from *i*-Pr_2O);

$[\alpha]_D^{24} = -113.8$ (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.79 (d, 2H, $J = 8.3$ Hz), 7.34 (d, 2H, $J = 8.3$ Hz), 6.03–5.97 (m, 1H), 5.71–5.66 (m, 1H), 4.99–4.93 (m, 1H), 4.79–4.73 (m, 1H), 4.60–4.55 (m, 2H), 4.22 (dd, 1H, $J = 12.3$, 3.7, Hz), 4.14 (dd, 1H, $J = 12.3$, 7.7 Hz), 2.44 (s, 3H), 1.86 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.3, 144.7, 133.9, 129.8, 129.6, 127.9, 124.3, 84.4, 79.8, 75.9, 62.4, 21.5, 20.4; IR (KBr) 1740 cm^{-1}; Anal. Calcd for $C_{15}H_{18}O_6S$: C, 55.20; H, 5.56; S, 9.82. Found: C, 55.31; H, 5.57; S, 9.80.

4.6. (*S*)-2-[(*R*)-Oxiran-2-yl]-2,5-dihydrofuran 8

Tosylate **7** (6.35 g, 19.46 mmol) was treated with NaOMe in MeOH under the same conditions of the corresponding isomer **4**, distilled at 89 °C, 35 mm, to give epoxide **8** (2.03 g, 93%) as a colorless oil: $[\alpha]_D^{20} = -174.5$ (*c* 2.0, $CHCl_3$), {lit.[9] bp 84 °C 40 mm, $[\alpha]_D^{29} = -176.7$ (*c* 2.67, $CHCl_3$)}, H^1 and ^{13}C NMR spectra were identical to those previously reported.[9]

4.7. (*S*)-2-Azido-2-[(*S*)-2,5-dihydrofuran-2-yl]ethyl acetate 9

A mixture of **4** (6.5 g, 0.020 mol) and NaN_3 (2.6 g, 0.040 mol) in DMF (20 mL) was warmed at 100 °C under N_2. After 24 h, the reaction mixture was cooled to room temperature, diluted with water (200 mL), and extracted with Et_2O (3×100 mL). The organic phase was first washed with water (twice, 15 mL) then with brine (30 mL) and finally dried over $MgSO_4$. After solvent evaporation, under reduced pressure and purification by flash chromatography ($R_f = 0.32$, petroleum ether/Et_2O 3:2), azido acetate **9** (2.48 g, 63%) was obtained as colorless oil: $[\alpha]_D^{22} = -119$ (*c* 1.53, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.12–6.07 (m, 1H), 5.80–5.75 (m, 1H), 5.02–4.95 (m, 1H), 4.78–4.62 (m, 2H), 4.29 (dd, 1H, $J = 11.6$, 4.9 Hz), 4.23 (dd, 1H, $J = 11.6$, 7.8 Hz), 3.62–3.55 (m, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.5, 129.6, 125.3, 85.5, 75.8, 63.5, 62.8, 20.6; IR (film) 2110, 1746 cm^{-1}; Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.62; H, 5.64; N, 21.28.

4.8. (*R*)-2-Azido-2-[(*S*)-2,5-dihydrofuran-2-yl]ethyl acetate 10

Tosylate **7** (5.86 g, 0.018 mol) was left to react with NaN_3 (2.34 g, 0.036 mol) in DMF (36 mL) as described above for the corresponding epimer **4**. From flash chromatography ($R_f = 0.40$, petroleum ether/Et_2O 7:3) was recovered azido **10** (2.48 g, 70%) as a colorless oil: $[\alpha]_D^{23} = -68.0$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.12–6.07 (m, 1H), 5.87–5.81 (m, 1H), 4.95–4.87 (m, 1H), 4.77–4.60 (m, 2H), 4.31 (dd, 1H, $J = 11.6$, 3.8 Hz), 4.08 (dd, 1H, $J = 11.6$, 7.7 Hz), 3.76 (ddd, 1H, $J = 7.7$, 4.8, 3.8 Hz), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.2, 129.4, 125.0, 85.4, 75.5, 63.6, 63.1, 20.3; IR (film) 2112 and 1747 cm^{-1}. Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.78; H, 5.63; N, 21.27.

4.9. (*S*)-2-Azido-2-[(*S*)-2,5-dihydrofuran-2-yl]ethanol 11

To a solution of **9** (2.2 g, 11.1 mmol) in MeOH (11 mL), a 15% water solution of NaOH (3 mL, 11.2 mmol) was added and stirred at room temperature for 5 h. After concentration, under reduced pressure, the residue was taken up with CH_2Cl_2 (100 mL) and the water layer separated. The organic phase was dried over $MgSO_4$ and the crude, after solvent distillation, purified by flash chromatography ($R_f = 0.23$, petroleum ether/EtOAc 3:1) to give azido alcohol **11** (1.65 g, 96%) as a colorless oil: $[\alpha]_D^{23} = -103.5$ (*c* 1.29, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.10–6.05 (m, 1H), 5.83–5.78 (m, 1H), 5.09–5.02 (m, 1H), 4.79–4.63 (m, 2H), 3.85 (dd, 1H, $J = 11.5$, 5.5 Hz), 3.81 (dd, 1H, $J = 11.5$, 6.0 Hz), 3.43–3.37 (m, 1H), 3.18 [br s, 1H (OH)]; ^{13}C NMR ($CDCl_3$): δ 128.9, 125.8, 86.3, 75.7, 65.4, 62.5; IR (film) 3401, 2106 cm^{-1}; Anal. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.52; H, 5.87; N, 27.16.

4.10. (*R*)-2-Azido-2-[(*S*)-2,5-dihydrofuran-2-yl]ethanol 12

Acetate **10** (2.30 g, 0.0116 mol) was submitted to a saponification reaction under the same conditions as described for the corresponding epimer **9**. From flash chromatography ($R_f = 0.25$, petroleum ether/EtOAc 3:1) azido **12** (1.66 g, 92%) was obtained as a colorless oil: $[\alpha]_D^{23} = -81.5$ (*c* 1.92, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.10–6.03 (m, 1H), 5.90–5.85 (m, 1H), 4.98–4.91 (m, 1H), 4.78–4.62 (m, 2H), 3.86–3.76 (m, 1H), 3.73–3.62 (m, 2H), 2.38 [br s, 1H (OH)]; ^{13}C NMR ($CDCl_3$): δ 129.1, 125.9, 86.4, 75.6, 67.0, 62.3; IR (film) 3405 and 2112 cm^{-1}; Anal. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.55; H, 5.84; N, 27.18.

4.11. (*S*)-2-Amino-2-[(*S*)-2,5-dihydrofuran-2-yl]ethanol 13

A solution of **11** (1.5 g, 9.66 mmol) in dry THF (96 mL) was added dropwise under N_2 to an $LiAlH_4$ suspension (0.368 g, 9.7 mmol) in dry THF (58 mL). The reaction mixture was first stirred at room temperature for 1 h then heated at solvent reflux. After 2 h, the reaction was cooled at −10 °C and the excess hydride quenched with saturated aqueous solution of NH_4Cl (2.5 mL). After being warmed to room temperature the reaction mixture was stirred until a gray solid material was separated from the organic phase. After filtration by Büchner the solid material was washed many times with CH_2Cl_2. The organic phase was dried on $MgSO_4$, and after solvent evaporation the residue was bulb to bulb distilled to give **13** (1.05 g, 84%) as a hygroscopic white solid: $[\alpha]_D^{21} = -120.1$ (*c* 1.14, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.05–5.99 (m, 1H), 5.81–5.76 (m, 1H), 4.87–4.80 (m, 1H), 4.72–4.58 (m, 2H), 3.64 (dd, 1H, $J = 10.9$, 4.9 Hz), 3.55 (dd, 1H, $J = 10.9$, 6.9 Hz), 2.84 (ddd, 1H, $J = 6.6$, 4.9, 3.9 Hz), 2.55 [br s, 3H (OH and NH_2)]; ^{13}C NMR ($CDCl_3$): δ 127.9, 126.8, 87.1, 75.4, 63.6, 55.9; IR (film) 3352, 3282, 2849 cm^{-1}; Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.67; H, 8.56; N, 10.87.

4.12. (*R*)-2-Amino-2-[(*S*)-2,5-dihydrofuran-2-yl]ethanol 14

Azido **12** was reduced under the same conditions as described above for the corresponding epimer **11**. Bulb to bulb distillation gave **14** (0.60 g, 85%) as a hygroscopic white solid: mp 56–59 °C; $[\alpha]_D^{23} = -143.7$ (*c* 1.32, $CHCl_3$);

^{1}H NMR ($CDCl_3$): δ 6.05–6.00 (m, 1H), 5.87–5.82 (m, 1H), 4.85–4.78 (m, 1H), 4.72–4.58 (m, 2H), 3.68 (dd, 1H, $J = 10.9$, 4.4 Hz), 3.48 (dd, 1H, $J = 10.9$, 6.7 Hz), 3.00–2.93 (m, 1H), 2.14 [br s, 3H (OH and NH_2)]; ^{13}C NMR ($CDCl_3$): δ 128.3, 126.2, 88.0, 75.2, 63.1, 56.3; IR (KBr) 3473, 1851 cm^{-1}; Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 54.94; H, 8.55; N, 10.80.

4.13. (*S*)-2-[(*S*)-2,5-Dihydrofuran-2-yl]-2-(dimethylamino)-ethanol 15

A mixture of **13** (0.514 g, 3.98 mmol) 99% formic acid (0.6 mL, 16 mmol) and 40% aqueous formaldehyde (0.6 mL, 8 mmol) was heated at 80 °C for 4 h. After being cooled to room temperature, the reaction mixture was basified with 30% aqueous NH_4OH (1 mL) and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3×5 mL) and the organic phase dried over K_2CO_3. The crude, after solvent evaporation, was bulb to bulb distilled to give **15** (0.484 g, 77%) as a colorless oil: $[\alpha]_D^{21} = -114.8$ (*c* 1.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.98–5.93 (m, 1H), 5.79–5.74 (m, 1H), 4.99–4.91 (m, 1H), 4.71–4.55 (m, 2H), 3.45 (dd, 1H, $J = 10.4$, 5.5 Hz), 3.39 [br s, 1H (OH)], 3.38 (dd, 1H, $J = 10.4$, 9.3 Hz), 2.66 (ddd, 1H, $J = 9.3$, 6.8, 5.5 Hz), 2.47 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 127.8, 127.4, 84.6, 74.5, 68.5, 58.0, 41.4; IR (film) 3476 cm^{-1}; Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.24; H, 9.65; N, 8.92.

4.14. (*R*)-2-[(*S*)-2,5-Dihydrofuran-2-yl]-2-(dimethylamino)-ethanol 16

Amine **14** (0.450 g, 3.48 mmol) was dimethylated under the same conditions as described above for the corresponding epimer **13**. Bulb to bulb distillation gave **16** (0.438 g, 80%) as a colorless oil: $[\alpha]_D^{21} = -92.7$ (*c* 1.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.96–5.91 (m, 1H), 5.83–5.77 (m, 1H), 5.14–5.06 (m, 1H), 4.68–4.54 (m, 2H), 3.64 (dd, 1H, $J = 11.0$, 8.5 Hz), 3.55 (dd, 1H, $J = 11.0$, 5.1 Hz), 3.44 [br s, 1H (OH)], 2.63 (ddd, 1H, $J = 8.5$, 5.1, 3.7 Hz), 2.42 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 128.2, 127.0, 83.1, 75.6, 68.3, 57.4, 41.3; IR (film) 3409 cm^{-1}; Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.23; H, 9.64; N, 8.93.

4.15. (*S*)-2-(Dibutylamino)-2-[(*S*)-2,5-dihydrofuran-2-yl]-ethanol 17

To a solution of **13** (0.517 g, 4 mmol) in acetonitrile (4 mL) were added, in succession, K_2CO_3 dry (1.13 g, 8.2 mmol) and *n*-BuI (1.5 g, 8.2 mmol). The reaction mixture was refluxed for 30 h then cooled at room temperature and filtered. The filtrate was concentrated under reduced pressure, then the residue purified by flash chromatography ($R_f = 0.45$, petroleum ether/EtOAc 2:3) to give, after bulb to bulb distillation, **17** (0.589 g, 61%) as a colorless oil: $[\alpha]_D^{19} = -135.0$ (*c* 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.96–5.91 (m, 1H), 5.76–5.71 (m, 1H), 4.98–4.89 (m, 1H), 4.68–4.54 (m, 2H), 3.41 [br s, 1H (OH)], 3.39 (dd, 1H, $J = 10.1$, 5.5 Hz), 3.33–3.25 (m, 1H), 2.85 (ddd, 1H, $J = 10.5$, 7.1, 5.5 Hz), 2.70–2.63 (m, 4H), 1.57–1.19 (m, 8H), 0.91 (t, 6H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 127.6, 127.4, 85.0, 74.4, 65.3, 57.8, 50.4, 31.6, 20.4, 14.0; IR (film) 3436, 2956, 2991, 2860 cm^{-1}; Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.27; N, 5.80. Found: C, 69.45; H, 11.24; N, 5.79.

4.16. (*R*)-2-(Dibutylamino)-2-[(*S*)-2,5-dihydrofuran-2-yl]-ethanol 18

Amine **14** (0.208 g, 1.61 mmol) was alkylated with *n*-BuI under the same conditions as described above for the corresponding epimer **13**. Flash chromatography ($R_f = 0.53$, petroleum ether/EtOAc 3:2) and bulb to bulb distillation gave **18** (0.258 g, 67%) as a colorless oil: $[\alpha]_D^{24} = -35.5$ (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.93–5.88 (m, 1H), 5.85–5.80 (m, 1H), 5.07–4.99 (m, 1H), 4.68–4.54 (m, 2H), 3.58–3.52 (m, 2H), 3.13 [br s, 1H (OH)], 2.81–2.63 (m, 3H), 2.53–2.43 (m, 2H), 1.52–1.18 (m, 8H), 0.91 (t, 6H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 128.6, 126.7, 84.6, 75.6, 65.2, 58.0, 50.4, 31.5, 20.3, 14.0; IR (film) 3422 cm^{-1}; Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.27; N, 5.80. Found: C, 69.50; H, 11.28; N, 5.78.

4.17. (*S*)-2-Amino-2-[(*S*)-tetrahydrofuran-2-yl]ethanol 19

Compound **13** (0.300 g, 2.76 mmol) dissolved in MeOH/HCl concn 20:1 (10 mL) was added to a pre-hydrogenated suspension of 10% Pd(0) on C (0.05 g) in MeOH (5 mL) and hydrogenated (H_2, 2 atm) for 8 h, then filtered on Celite. The filtrate was basified by 15% aqueous NaOH and concentrated under reduced pressure. After bulb to bulb distillation, the saturated amine **19** (0.217 g, 60%) was obtained as a hygroscopic white solid: mp 57–60 °C; $[\alpha]_D^{20} = +2.6$ (*c* 2.14, MeOH); ^{1}H NMR ($CDCl_3$): δ 3.88–3.69 (m, 3H), 3.61 (dd, 1H, $J = 10.9$, 4.0 Hz), 3.45 (dd, 1H, $J = 10.9$, 6.8 Hz), 2.80–2.72 (m, 1H), 2.71 [br s, 3H (OH and NH_2)], 2.02–1.82 (m, 3H), 1.70–1.58 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 80.4, 67.9, 64.1, 56.4, 28.2, 25.9; IR (film) 3349, 2830 cm^{-1}; Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.07; H, 10.02; N, 10.70.

4.18. (*R*)-2-Amino-2-[(*S*)-tetrahydrofuran-2-yl]ethanol 20

Dihydrofuran **14** (0.236 g, 1.83 mmol) was hydrogenated under the same conditions as described above for the corresponding epimer **13**. From flash chromatography and bulb to bulb distillation, **20** (0.180 g, 75%) was obtained as a colorless oil: $[\alpha]_D^{21} = -9.2$ (*c* 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.89–3.80 (m, 1H), 3.79–3.64 (m, 3H), 3.49 (dd, 1H, $J = 11.0$, 6.6 Hz), 2.94–2.87 (m, 1H), 2.84 [br s, 3H (OH and NH_2)], 2.03–1.84 (m, 3H), 1.77–1.65 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 80.7, 68.0, 63.9, 55.7, 27.6, 25.6; IR (film) 3355, 2968 cm^{-1}; Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.04; H, 10.02; N, 10.71.

4.19. (*S*)-2-(Dibutylamino)-2-[(*S*)-tetrahydrofuran-2-yl]-ethanol 21

Amine **19** (0.2 g, 1.5 mmol) alkylation, with *n*-BuI and K_2CO_3, was performed as the corresponding dihydrofuran **13**. After flash chromatography ($R_f = 0.34$ light petroleum/

EtOAc 2:3) and bulb to bulb distillation the alkylated amine **21** (0.311 g, 85%) was obtained as colorless oil: $[\alpha]_D^{20} = -51.4$ (*c* 2.54, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.90–3.78 (m, 2H), 3.77–3.68 (m, 1H), 3.70 [br s, 1H (OH)], 3.35 (dd, 1H, $J = 10.0$, 5.3 Hz), 3.18–3.09 (m, 1H), 2.82–256 (m, 5H), 1.98–1.76 (m, 3H), 1.57–1.20 (m, 9H), 0.91 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 78.2, 67.5, 65.4, 58.1, 50.6, 31.8, 29.8, 25.6, 20.5, 14.1; IR (film) 3435, 2956, 2861 cm^{-1}; Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01; N, 5.75. Found: C, 68.96; H, 12.04; N, 5.73.

4.20. (*R*)-2-(Dibutylamino)-2-[(*S*)-tetrahydrofuran-2-yl]-ethanol 22

Amine **20** (0.128 g, 0.976 mmol) was alkylated with *n*-BuI under the same conditions as described above for the corresponding isomer **13**. From flash chromatography ($R_f = 0.32$ petroleum ether/EtOAc 3:2) and bulb to bulb distillation, **22** (0.148 g, 62%) was obtained as a colorless oil: $[\alpha]_D^{19} = +17.4$ (*c* 1.93, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.01–3.93 (m, 1H), 3.85–3.68 (m, 2H), 3.67 (dd, 1H, $J = 10.7$, 6.3 Hz), 3.57 (dd, 1H, $J = 10.7$, 7.8 Hz), 3.21 [br s, 1H (OH)], 2.73–2.55 (m, 3H), 2.50–2.39 (m, 2H), 2.10–1.99 (m, 1H), 1.92–1.77 (m, 2H), 1.75–1.60 (m, 1H), 1.50–1.20 (m, 8H), 0.91 (t, 6H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 78.7, 68.2, 64.7, 59.2, 50.5, 31.6, 30.9, 25.5, 20.4, 14.0; IR (film) 3460, 2956, 2931, 2871 cm^{-1}; Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01; N, 5.75. Found: C, 69.29; H, 12.02; N, 5.77.

4.21. (*S*)-2-Amino-1-[(*S*)-2,5-dihydrofuran-2-yl]ethanol 25

Azide **23**[22] (2.79 g, 0.0180 mol) was reduced, with $LiAlH_4$, as described above for the corresponding regioisomer **9**. Bulb to bulb distillation gave amino alcohol **25** (2 g, 86%) as a hygroscopic waxy material: $[\alpha]_D^{20} = -129.5$ (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.02–5.97 (m, 1H), 5.83–5.78 (m, 1H), 4.82–4.75 (m, 1H), 4.72–4.58 (m, 2H), 3.59–3.52 (m, 1H), 2.81 (dd, 1H, $J = 12.8$, 4.1 Hz), 2.74 (dd, 1H, $J = 12.8$, 7.7 Hz), 2.64 [br s, 3H (OH and NH_2)]; ^{13}C NMR ($CDCl_3$): δ 128.0, 126.4, 88.0, 75.3, 73.8, 44.0; IR (film) 3360, 2857 cm^{-1}; Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.93; H, 8.57; N, 10.83.

4.22. (*R*)-2-Amino-1-[(*S*)-2,5-dihydrofuran-2-yl]ethanol 26

Azido **24**[22] (3.20 g, 0.0296 mol) was reduced under the same conditions as described above for its isomer **9**. Bulb to bulb distillation gave **26** (2.18 g, 82%) as a waxy solid: $[\alpha]_D^{21} = -133.6$ (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.02–5.97 (m, 1H), 5.93–5.87 (m, 1H), 4.78–4.71 (m, 1H), 4.71–4.57 (m, 2H), 3.54 (ddd, 1H, $J = 7.90$, 5.20, 3.5 Hz), 2.89 (dd, 1H, $J = 12.8$, 3.56 Hz), 2.72 (dd, 1H, $J = 12.8$, 7.9 Hz), 2.46 [br s, 3H (OH and NH_2)]; ^{13}C NMR ($CDCl_3$): δ 127.9, 126.8, 87.9, 75.6, 74.3, 43.7; IR (KBr) 3462, 2875 cm^{-1}; Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.97; H, 8.55; N, 10.81.

4.23. (*S*)-1-[(*S*)-2,5-Dihydrofuran-2-yl]-2-(dimethylamino)-ethanol 27

Amine **25** (0.467 g, 3.62 mmol) was methylated as described for the corresponding regioisomer **13**. Bulb to bulb distillation gave dimethylamine **27** (0.466 g, 82%) as a colorless oil: $[\alpha]_D^{20} = -146.9$ (*c* 1.46, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.05–5.99 (m, 1H), 5.85–5.80 (m, 1H), 4.81–4.74 (m, 1H), 4.74–4.59 (m, 2H), 3.71 (dt, 1H, $J = 10.1$, 3.7 Hz), 3.43 [br s, 1H (OH)], 2.53 (dd, 1H, $J = 12.2$, 10.1 Hz), 2.28 (s, 6H), 2.21 (dd, 1H, $J = 12.2$, 3.5 Hz); ^{13}C NMR ($CDCl_3$): δ 128.2, 126.3, 87.5, 75.5, 69.3, 61.3, 45.5; IR (film) 3428, 2945, 2775, 1461 cm^{-1}; Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.19; H, 9.64; N, 9.94.

4.24. (*R*)-1-[(*S*)-2,5-Dihydrofuran-2-yl]-2-(dimethylamino)-ethanol 28

Alcohol **26** (0.299 g, 2.31 mmol) was dimethylated under the same condition as described above for the corresponding isomer **13**. From bulb to bulb distillation **28** (0.264 g, 73%) was obtained as a colorless oil: $[\alpha]_D^{23} = -83.0$ (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.01–5.97 (m, 1H), 5.94–5.90 (m, 1H), 4.77–4.70 (m, 1H), 4.71–4.59 (m, 2H), 3.64 (ddd, 1H, $J = 9.7$, 5.2, 3.6 Hz), 3.48 [br s, H, (OH)], 2.44 (dd, 1H, $J = 12.3$, 9.7 Hz), 2.35 (dd, 1H, $J = 12.3$, 3.6 Hz), 2.28 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 127.8, 126.8, 88.1, 75.7, 69.9, 61.5, 45.5; IR (film) 3418, 2947, 2855, 2778, 1462 cm^{-1}; Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.19; H, 9.65; N, 8.89.

4.25. (*S*)-2-(Dibutylamino)-1-[(*S*)-2,5-dihydrofuran-2-yl]-ethanol 29

Amino **25** (0.226 g, 1.75 mmol) was alkylated with *n*-BuI as described for the corresponding isomer **13**. Bulb to bulb distillation gave dibutylamine **29** (0.287 g, 68%) as a colorless oil ($R_f = 0.2$ petroleum ether/EtOAc 1:1): $[\alpha]_D^{24} = -148.8$ (*c* 1.68, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.04–5.99 (m, 1H), 5.86–5.80 (m, 1H), 4.82–4.75 (m, 1H), 4.74–4.58 (m, 2H), 3.64 (dt, 1H, $J = 10.2$, 4.0 Hz), 3.56 [br s, 1H (OH)], 2.60–2.47 (m, 3H), 2.46–2.35 (m, 3H), 1.50–1.20 (m, 8H), 0.91 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 128.1, 126.4, 87.5, 75.5, 68.9, 56.3, 53.9, 29.2, 20.5, 14.0; IR (film) 3447, 2957, 2932, 2861, 1467 cm^{-1}; Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.27; N, 5.80. Found: C, 69.46; H, 11.30; N, 5.82.

4.26. (*R*)-2-(Dibutylamino)-1-[(*S*)-2,5-dihydrofuran-2-yl]-ethanol 30

Amine **26** (0.254 g, 1.97 mmol) was alkylated with *n*-BuI under the same conditions as described above for the corresponding isomer **13**. From flash chromatography ($R_f = 0.24$, petroleum ether/EtOAc 1:1) and bulb to bulb distillation, **30** (0.315 g, 66%) was obtained as a colorless oil: $[\alpha]_D^{22} = -16.1$ (*c* 1.72, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.01–5.93 (m, 2H), 4.73–4.58 (m, 3H), 3.78 [br s, 1H (OH)], 3.58–3.49 (m, 1H), 2.63–2.35 (m, 6H), 1.50–1.20 (m, 8H), 0.91 (t, 6H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 127.5, 127.4, 88.3, 75.7, 69.6, 57.1, 54.0, 29.3, 20.5, 13.9;

IR (film) 3436, 2957, 2932, 2861, 1407 cm^{-1}; Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.27; N, 5.80. Found: C, 69.53; H, 11.24; N, 5.78.

4.27. (*S*)-2-Amino-1-[(*S*)-tetrahydrofuran-2-yl]ethanol 31

Dihydrofuran **25** (0.187 g, 1.44 mmol) was hydrogenated under the same conditions described for the corresponding regioisomer **13**. After bulb to bulb distillation, the saturated amine **31** (0.127 g, 67%) was isolated as a colorless oil: $[\alpha]_D^{24} = -1.7$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.90–3.73 (m, 3H), 3.50–3.43 (m, 1H), 3.04 [br s, 3H (OH and NH_2)], 2.85–2.68 (m, 2H), 2.00–1.82 (m, 3H), 1.78–1.64 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 80.6, 74.1, 68.2, 44.6, 27.7, 26.0; IR (film) 3468 cm^{-1}; Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.80; H, 10.02; N, 10.71.

4.28. (*S*)-2-(Dibutylamino)-1-[(*S*)-tetrahydrofuran-2-yl]-ethanol 32

Amine **31** (0.148 g, 1.37 mmol) alkylation, with *n*-BuI and K_2CO_3, was performed as for the corresponding isomer **13**. After flash chromatography ($R_f = 0.13$ petroleum ether/EtOAc 1:1) and bulb to bulb distillation the alkylated amine **32** (0.248 g, 74%) was obtained as a colorless oil. $[\alpha]_D^{24} = -55.4$ (*c* 1.36, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.94–3.86 (m, 1H), 3.81–3.68 (m, 2H), 3.55 (ddd, 1H, $J = 10.2$, 4.8, 3.6 Hz), 3.57 [br s, 1H (OH)], 2.59–2.48 (m, 3H), 2.46–2.34 (m, 3H), 2.00–1.67 (m, 4H), 1.49–1.20 (m, 8H), 0.91 (t, 6H, $J = 7.3$ Hz).^{13}C NMR ($CDCl_3$): δ 80.5, 69.4, 68.3, 57.2, 53.8, 29.2, 27.4, 25.8, 20.5, 14.0. IR (film) 3452, 2957, 2872, 1466 cm^{-1}. Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01; N, 5.75. Found: C, 68.89; H, 11.98; N, 5.74.

4.29. (*R*)-2-(Dibutylamino)-1-[(*S*)-tetrahydrofuran-2-yl]-ethanol 33

Dihydrofuran **26** (0.285 g, 2.20 mmol) was hydrogenated under the same conditions as described for the corresponding isomer **13** and the resulting tetrahydrofuranylamine was submitted to alkylation with *n*-BuI (0.830 g, 4.51 mmol) in refluxing acetonitrile (2.5 mL) in the presence of K_2CO_3 (0.623 g, 4.51 mmol) for 30 h. After the usual work-up from flash chromatography ($R_f = 0.2$ petroleum ether/EtOAc 1:1) and bulb to bulb distillation **33** (0.231 g, 43%) was obtained as a colorless oil: $[\alpha]_D^{23} = +68.0$ (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.90–3.82 (m, 1H), 3.78–3.66 (m, 2H), 3.53 (ddd, 1H, $J = 10.1$, 6.2, 3.7 Hz), 3.42 [br s, 1H (OH)], 2.62–2.47 (m, 3H), 2.45–2.34 (m, 3H), 2.04–1.82 (m, 4H), 1.48–1.22 (m, 8H), 0.91 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 81.5, 69.0, 68.4, 57.9, 54.0, 29.3, 27.8, 25.7, 20.5, 14.0; IR (film) 3436 cm^{-1}; Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01; N, 5.75. Found: C, 69.01; H, 11.97; N, 5.73.

4.30. (3*R*,3a*R*,6*S*,6a*S*)-6-Chlorohexahydrofuro[3,2-*b*]furan-3-yl pivalate 35

A flask equipped with a reflux condenser was charged with **34**[8] (10.06 g, 0.0437 mol) in CCl_4 (44 mL) and Ph_3P (22.87 g, 0.0872 mmol) was added in one portion at room temperature under N_2. The reaction mixture, after 2 h at room temperature was warmed at 50 °C and stirred for 20 h. After the addition of petroleum ether (80 mL), the solid material was removed by filtration on Büchner funnel and the filtrate concentrated under reduced pressure. The residue was taken up with petroleum ether (40 mL) and filtrated again to eliminate the last solid material. After solvent evaporation the crude material was distilled at 135 °C/1 mm to give chloride **35** (9.646 g, 84%) as a colorless oil ($R_f = 0.4$, petroleum ether/Et_2O 6:1): $[\alpha]_D^{27} = +96.6$ (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.17–5.10 (m, 1H), 4.97–4.93 (m, 1H), 4.58 (dd, 1H, $J = 4.5$, 0.6 Hz), 4.36–4.33 (m, 1H), 4.11–4.04 (m, 2H), 3.94 (dd, 1H, $J = 10.0$, 6.0 Hz), 3.82 (dd, 1H, $J = 10.0$, 4.9 Hz), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 177.7, 88.8, 80.4, 75.2, 73.4, 71.0, 60.5, 38.6, 27.0; IR (film) 2972, 2873, 1734 cm^{-1}. Anal. Calcd for $C_{11}H_{17}ClO_4$: C, 53.12; H, 6.89; Cl, 14.26. Found: C, 53.00; H, 6.90; Cl, 14.31.

4.31. (3*R*,3a*R*,6*S*,6a*S*)-6-Chlorohexahydrofuro[3,2-*b*]furan-3-ol 36

To a solution of **35** (9.20 g, 0.037 mol) in MeOH (35 mL), 15% aqueous NaOH (5 mL, 0.0187 mol) was added and the resulting solution warmed at 50 °C. After 2 h, the reaction mixture was cooled at room temperature and the solvent distilled under reduced pressure. The residue was transferred into separator funnel with CH_2Cl_2 (100 mL) and the aqueous layer separated. The organic phase was, in succession, dried over $MgSO_4$, concentrated under reduced pressure, and the residue supported on silica gel. From flash chromatography ($R_f = 0.26$, petroleum ether/EtOAc 1:1) and distillation at 97 °C/1 mm, alcohol **36** (5.50 g, 90%) was obtained as a colorless oil. $[\alpha]_D^{27} = +56.6$ (*c* 1.6, $CHCl_3$), [lit.[23]: $[\alpha]_D^{20} = +52$ (*c* 1.0, $CHCl_3$)]; ^1H NMR spectrum was identical to that previously reported;[23] ^{13}C NMR ($CDCl_3$): δ 88.5, 81.8, 75.9, 73.7, 72.2, 61.0.

4.32. *tert*-Butyl((3*R*,3a*S*,6*S*,6a*S*)-6-chlorohexahydrofuro[3,2-*b*]furan-3-yloxy)dimethylsilane 37

To a solution of **36** (5.2 g, 0.0316 mol) and *t*-$BuMe_2SiCl$ (5.48 g, 0.0363 mol) in DMF (19 mL), imidazole (5.38 g, 0.079 mol) was added at 0 °C and under nitrogen. The reaction was left at this temperature for 1 h, then 3 h at room temperature before quenching by water addition (80 mL). After extraction with Et_2O (2 × 100 mL), the organic phase was washed with water (15 mL), brine (10 mL) and dried over $MgSO_4$. The crude, after solvent evaporation and flash chromatography ($R_f = 0.35$, petroleum ether/Et_2O 19:1), gave **37** (8.19 g, 93%) as a colorless oil: $[\alpha]_D^{21} = +83.1$ (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.63–4.56 (m, 2H), 4.36–4.28 (m, 2H), 4.16 (dd, 1H, $J = 10.6$, 3.6 Hz), 4.08 (d, 1H, $J = 10.6$ Hz), 3.81 (dd, 1H, $J = 8.6$, 6.1 Hz), 3.56 (dd, 1H, $J = 8.6$, 7.1 Hz), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 88.7, 81.8, 76.0, 73.8 72.8, 61.2, 25.8, 18.4, −4.8, −5.1; IR (film): 2.954, 2930, 2858, 1472, 1461, and 1255 cm^{-1}; Anal. Calcd for $C_{12}H_{23}ClO_3Si$: C, 51.69; H, 8.31; Cl, 12.71, Si, 10.07. Found: C, 51.75; H, 8.29; Cl 12.74.

4.33. *tert*-Butyldimethyl{(3*R*,3a*S*,6a*R*)-2,3,3a,6a-tetrahydrofuro[3,2-*b*]furan-3-yloxy}silane 38

To *t*-BuOK (36 mL 1 M in THF, 0.036 mol), a solution of chloride **37** (5.56 g, 0.020 mol) in dry THF (7 mL) was added at room temperature. The reaction was warmed at 50 °C for 3 h, then cooled to room temperature, and quenched with water (0.5 mL). The reaction mixture was diluted by petroleum ether (100 mL) and the solid material removed by filtration on a Büchner funnel. The crude, after solvent evaporation, was purified by flash chromatography on Florisil ($\varnothing = 5$, $h = 6$ cm, petroleum ether/Et_2O 1:1) to give unsaturated ether **38** (4.36 g, 92%) as a colorless oil: $[\alpha]_D^{21} = +66.3$ (*c* 1.30, C_6H_6); ^1H NMR (C_6D_6): δ 6.57–6.55 (m, 1H), 5.36 (dd, 1H, $J = 6.4$, 2.6 Hz), 5.05 (dt, 1H, $J = 2.5$, 0.4 Hz), 4.48–4.42 (m, 1H), 4.31–4.22 (m, 1H), 4.01 (dd, 1H, $J = 8.2$, 6.4 Hz), 3.59 (dd, 1H, $J = 9.6$, 8.2 Hz), 1.18 (s, 9H), 0.30 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (C_6D_6): δ 152.1, 101.1, 85.3, 82.8, 75.0, 67.5, 26.6, 19.1, −4.0, −4.2; IR (film): 2955, 2930, 2859, and 1610 cm^{-1}; Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15; Si, 11.59. Found: C, 59.53; H, 9.13.

4.34. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-(furan-2-yl)-ethanol 39

To a solution of **38** (5.348 g, 0.022 mol) in dry THF (60 mL) and under nitrogen, pyridinium *p*-toluensulfonate (0.138 g, 2.5 mol %) was added, and the resulting solution warmed at 45–50 °C. After 35 min, when PTSA was completely dissolved, the reaction was completed. $NaHCO_3$ (0.146 g, 2 mmol) was added, and then after solvent evaporation and flash chromatography ($R_f = 0.16$, petroleum ether/Et_2O 85:15) purification, **39** (4.86 g, 90%) was isolated as a colorless oil: $[\alpha]_D^{22} = +64.6$ (*c* 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.36 (dd, 1H, $J = 1.8$, 0.9 Hz), 6.33 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.27–6.25 (m, 1H), 4.79 (dd, 1H, $J = 7.0$, 4.5 Hz), 3.85–3.65 (m, 2H), 2.17 [br s, 1H (OH)], 0.89 (s, 9H), 0.09 s, (3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 154.1, 141.9, 110.2, 107.2, 69.3, 65.9, 25.8, 18.2, −5.0, −5.2; IR (film): 3428, 2955, 2930, 2884, 2858 cm^{-1}; Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15; Si, 11.59. Found: C, 59.32; H, 9.17.

4.35. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-(furan-2-yl)ethyl 4-methylbenzenesulfonate 40

To a solution of **39** (2.59 g, 0.0107 mol) and Et_3N (1.62 g, 0.016 mol) in CH_2Cl_2 (10.5 mL), TsCl (2.44 g, 0.0128 mol) was added in one portion and at 0 °C. After 24 h at 4–5 °C, the reaction was diluted by Et_2O (100 mL) addition, and in succession, washed with 2 M HCl (10 mL), water (3 × 10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, and after solvent evaporation the residue was flash chromatographed ($R_f = 0.12$, petroleum ether/Et_2O 40:1) to give **40** (3.94 g, 93%) as a colorless oil: $[\alpha]_D^{21} = +46.5$ (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.77–7.72 (m, 2H), 7.32–7.30 (m, 2H), 7.30 (dd, 1H, $J = 1.8$, 0.9 Hz), 6.29 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.23–6.21 (m, 1H), 4.92 (dd, 1H, $J = 7.5$, 4.7 Hz), 4.18 (dd, 1H, $J = 9.8$, 4.7 Hz), 4.10 (dd, 1H, $J = 9.8$, 7.5 Hz), 2.44 (s, 3H), 0.83 (s, 9H), 0.05 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.4, 144.8, 142.2, 132.9, 129.8, 127.9, 110.2, 107.7, 71.8, 66.7, 25.6, 21.6, 18.0, −5.17, −5.20; IR (film): 2955, 2930, 2887, 2856, 1519, 1366 cm^{-1}; Anal. Calcd for $C_{19}H_{28}O_5SSi$: C, 57.54; H, 7.12; S, 8.09; Si, 7.08. Found: C, 57.61; H, 7.13; S, 8.07.

4.36. (*R*)-[2-Azido-1-(furan-2-yl)ethoxy](*tert*-butyl)dimethylsilane 41

To a solution of **40** (3.49 g, 9.94 mmol) in DMF (20 mL), NaN_3 (0.969 g, 14.9 mmol) was added under a nitrogen atmosphere. The reaction was heated at 95 °C for 16 h, then cooled at room temperature and quenched by water (200 mL) addition. The mixture was extracted with Et_2O (3 × 50 mL), and the combined ether solution washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. After solvent evaporation at a reduced pressure, the crude was flash chromatographed ($R_f = 0.22$, petroleum ether) to give azide **41** (2.44 g, 91%) as a colorless oil: $[\alpha]_D^{22} = +89.6$ (*c* 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.41 (dd, 1H, $J = 1.8$, 0.8 Hz), 6.38 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.34–6.32 (m, 1H), 4.90 (dd, 1H, $J = 7.4$, 4.3 Hz), 3.55 (dd, 1H, $J = 12.5$, 7.4 Hz), 3.42 (dd, 1H, $J = 12.5$, 4.3 Hz), 0.95 (s, 9H), 0.17 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 154.0, 142.0, 110.3, 107.3, 68.6, 56.1, 25.6, 18.1, −5.1, −5.2; IR (film): 29.30, 2858, 2104 cm^{-1}; Anal. Calcd for $C_{12}H_{21}N_3O_2Si$: C, 53.90; H, 7.92; N, 15.71; Si, 10.50. Found: C, 53.83; H, 7.90; N, 15.67.

4.37. (*R*)-2-Amino-1-(furan-2-yl)ethanol 42

To a suspension of $LiAlH_4$ (0.656 g, 0.0172 mol) in dry THF (20 mL), a solution of azido **41** (3.08 g, 0.0115 mol), dissolved in dry THF (90 mL), was added dropwise and under nitrogen. The reaction was stirred before at room temperature for 2 h, then at reflux for 1 h. After cooling at −10 °C the hydride excess was quenched with a 15% aqueous NaOH (2.8 mL). The mixture was left to warm at room temperature and stirred until a gray solid material was decanted from the organic solvent. The solid material was removed by filtration on a Büchner and washed many times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, and after solvent evaporation the crude was bulb to bulb distilled to give the amino alcohol **42** (1.22 g, 83%) as a white solid: mp 86–88 °C; $[\alpha]_D^{23} = +38.7$ (*c* 1.1, $CHCl_3$) {lit. (*S*)-isomer mp 79 °C,[24] $[\alpha]_D^{27} = -40$ (*c* 2, CH_3CN);[24] $[\alpha]_D^{20} = -32$ (*c* 1, $CHCl_3$)}.[25] ^1H NMR spectrum agrees with those previously published.[24–26] ^{13}C NMR ($CDCl_3$): δ 155.4, 141.9, 110.1, 106.2, 68.1, 46.0.[†]

4.38. General procedure for the preparation of 2-(dialkylamino)-1-(furan-2-yl)ethanols 43–48[17]

Amino alcohol **42** (1 mmol) was alkylated with alkyl iodide (2.10 mmol), K_2CO_3 (2.10 mmol) in refluxing CH_3CN (1 mL) for 24–36 h. It was then cooled at room temperature, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash

[†] ^{13}C NMR does not agree with that previously reported by Demir et al.[35] In particular the resonance at 96.7 ppm assigned to *exo* cyclic CHOH.

chromatography on silica gel to give, after bulb to bulb distillation, the desired dialkylated amino alcohol.

4.38.1. (*R*)-2-(Dipropylamino)-1-(furan-2-yl)ethanol 43. Yield 75%; colorless oil: $R_f = 0.5$ in petroleum ether/EtOAc 1:1; $[\alpha]_D^{21} = +95.3$ (*c* 1.29, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38 (dd, 1H, $J = 1.8$, 0.9 Hz), 6.33 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.30–6.28 (m, 1H), 4.66 (dd, 1H, $J = 10.2$, 3.8 Hz), 3.84 [br s, 1H (OH)], 2.83 (dd, 1H, $J = 12.8$, 10.2 Hz), 2.65 (dd, 1H, $J = 12.8$, 3.8 Hz), 2.59–2.38 (m, 4H), 1.62–1.38 (m, 4H), 0.90 (t, 6H, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.8, 142.0, 110.0, 106.5, 63.4, 58.8, 56.0, 20.2, 11.6; IR (film): 3428 cm^{-1}; Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.08; H, 9.99; N, 6.64.

4.38.2. (*R*)-2-(Dibutylamino)-1-(furan-2-yl)ethanol 44. Yield 64%; colorless oil: $R_f = 0.3$ in petroleum ether/Et_2O 3:2; $[\alpha]_D^{24} = +82.1$ (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37 (dd, 1H, $J = 1.8$, 0.9 Hz), 6.32 (dd, 1H, $J = 3.3$, 1.8 Hz), 6.29–6.27 (m, 1H), 4.65 (dd, 1H, $J = 10.1$, 3.8 Hz), 3.98 [br s, 1H (OH)], 2.82 (dd, 1H, $J = 12.8$, 10.1 Hz), 2.64 (dd, 1H, $J = 12.8$, 3.8 Hz), 2.63–2.52 (m, 2H), 2.50–2.39 (m, 2H), 1.56–1.22 (m, 8H), 0.92 (t, 6H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.8, 142.0, 110.0, 106.6, 63.4, 58.8, 53.8, 29.3, 20.5, 14.0; IR (film): 3432, 2958, 2862 cm^{-1}; Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.41; H, 10.56; N, 5.84.

4.38.3. (*R*)-2-(Di-*iso*-butylamino)-1-(furan-2-yl)ethanol 45. Yield 71%; colorless oil: $R_f = 0.3$ in petroleum ether/Et_2O 17:3; $[\alpha]_D^{22} = +128.6$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.36 (dd, 1H, $J = 1.8$, 0.9 Hz), 6.32 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.29–6.27 (m, 1H), 4.67 (dd, 1H, $J = 10.3$, 3.6 Hz), 3.83 [br s, 1H (OH)], 2.84 (dd, 1H, $J = 12.7$, 10.3 Hz), 2.53 (dd, 1H, $J = 12.7$, 3.6 Hz), 2.23 (d, 4H, $J = 7.2$ Hz), 1.90–1.70 (m, 2H), 0.95 (d, 6H, $J = 6.5$ Hz), 0.88 (d, 6H, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.6, 142.0, 110.1, 106.8, 64.0, 63.7, 60.3, 26.3, 21.1, 20.9; IR (film): 3437 cm^{-1}; Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.11; H, 10.54; N, 5.87.

4.38.4. (*R*)-2-(Dipentylamino)-1-(furan-2-yl)ethanol 46. Yield 61%; colorless oil: $[\alpha]_D^{23} = +78.4$ (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37 (dd, 1H, $J = 1.8$, 0.8 Hz), 6.32 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.29–6.27 (m, 1H), 4.65 (dd, 1H, $J = 10.1$, 3.7 Hz), 4.11 [br s, 1H (OH)], 2.82 (dd, 1H, $J = 12.7$, 10.2 Hz), 2.64 (dd, 1H, $J = 12.7$, 3.8 Hz), 2.62–2.51 (m, 2H), 2.50–2.39 (m, 2H), 1.58–1.18 (m, 12H), 0.90 (t, 6H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.9, 142.0, 110.1, 106.6, 63.4, 58.8, 54.0, 29.6, 26.8, 22.6, 14.0; IR (film): 3436, 2956, 2930, 2860, 1466 cm^{-1}; Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.86, H, 10.93; N, 5.24. Found: C, 72.02; H, 10.96; N, 5.23.

4.38.5. (*R*)-2-(Dihexylamino)-1-(furan-2-yl)ethanol 47. Yield 75%; colorless oil: $R_f = 0.3$ in petroleum ether/Et_2O 7:3; $[\alpha]_D^{21} = +71.0$ (*c* 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38 (dd, 1H, $J = 1.8$, 0.8 Hz), 6.33 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.30–6.27 (m, 1H), 4.65 (dd, 1H, $J = 10.2$, 3.7 Hz), 3.95 [br s, 1H (OH)], 2.82 (dd, 1H, $J = 12.7$, 10.2 Hz), 2.64 (dd, 1H, $J = 12.7$, 3.8 Hz), 2.60–2.51 (m, 2H), 2.50–2.39 (m, 2H), 1.55–1.40 (m, 4H), 1.36–1.22 (m, 12H), 0.89 (t, 6H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.9, 142.0, 110.1, 106.7, 63.4, 58.8, 54.1, 31.7, 27.07, 27.05, 22.6, 14.0; IR (film): 3420, 2955, 2929, 2858, 1467 cm^{-1}; Anal. Calcd for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26; N, 4.74. Found: C, 73.40; H, 11.23; N, 4.75.

4.38.6. (*R*)-1-(Furan-2-yl)-2-(pyrrolidin-1-yl)ethanol 48. Amino alcohol **42** (0.138 g, 1.09 mmol) was alkylated with 1,4-dibromobutane (0.257 g, 1.19 mmol), K_2CO_3 (0.323 g, 2.34 mmol) in refluxing acetonitrile (1.1 mL) and under nitrogen. After 20 h, the reaction mixture was cooled to room temperature, filtered, and the filtrate concentrated. The residue was purified by flash chromatography ($R_f = 0.13$ CH_2Cl_2/MeOH 9:1) on silica gel to give, after bulb to bulb distillation the amino alcohol **48** (0.101 g, 51%) as a colorless oil: $[\alpha]_D^{19} = +35.8$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.36 (m, 1H), 6.34–6.32 (m, 1H), 6.31–6.28 (m, 1H), 4.78 (dd, 1H, $J = 10.1$, 3.5 Hz), 4.62 [br s, 1H (OH)], 3.10 (dd, 1H, $J = 12.2$, 10.2 Hz), 2.82–2.70 (m, 2H), 2.62 (dd, 1H, $J = 12.2$, 3.5 Hz), 2.62–2.52 (m, 2H), 1.87–1.76 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 154.8, 142.0, 110.1, 106.5, 64.6, 60.0, 53.9, 23.5; IR (film): 344, 2958, 2930, 2854, 1466 cm^{-1}; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27, H, 8.34; N, 7.73. Found: C, 66.08; H, 8.36; N, 7.72.

4.39. (3*S*,3a*R*,6*S*,6a*S*)-6-Chlorohexahydrofuro[3,2-*b*]furan-3-yl acetate 50

To a well-stirred solution of **49**[27] (7.76 g, 0.0412 mol) in pyridine (8.6 mL), $SOCl_2$ (3.46 mL, 0.0474 mol) was added dropwise at 0 °C and under nitrogen, in accordance to the Stross' procedure.[27] The temperature was left to rise at room temperature and after 15 min heated at 100 °C; during this time the reaction mixture became dark. After 1 h the reaction mixture was cooled at room temperature then poured into water/ice (50 mL) and extracted with Et_2O (2 × 50 mL). The ether solution was washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. After solvent evaporation the crude was purified by flash chromatography and bulb to bulb distilled to give chloride **50** (8.162 g, 96%) as a colorless oil: $[\alpha]_D^{22} = +87.0$ (*c* 1.36, $CHCl_3$); {lit.: $[\alpha]_D^{20} = +79.5$ (*c* 1.0, MeOH);[27] $[\alpha]_D^{20} = 99.0$ (*c* 1.0, $CHCl_3$)[23]}; ^1H NMR and IR spectra were identical to those previously reported.[23] ^{13}C NMR ($CDCl_3$): δ 169.72, 88.25, 84.96, 77.18, 74.74, 73.19, 60.32, 20.76.

4.40. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(furan-2-yl) ethanol *ent*-39

To *t*-BuOK (53.1 mL 1 M in THF, 0.053 mol) a solution of **50** (4.11 g, 0.020 mol) in dry THF (3 mL) was added at room temperature and under argon. The reaction was stirred for 30 min at room temperature, then heated to 50 °C for 30 min. After cooling at room temperature a solid *t*-BuMe_2SiCl (3.3 g, 0.0219 mol) was added, in one portion, to the basic reaction mixture (pH $\geqslant$ 9 by universal paper). The resulting reaction mixture was stirred at room temperature for 30 min, then filtered through Florisil plug and

washed with dry THF (the pH of filtered THF solution was ≈7). After solvent evaporation,[‡] the crude was dissolved in $PhCH_3$ (30 mL) and pyridinium *p*-toluensulfonate (0.120 g, 2.5 mol %) added. The resultant solution was gently warmed at 50–55 °C and when the PTSA was completely dissolved, 40–60 min, the reaction was completed. The reaction mixture was cooled at room temperature, $NaHCO_3$ (0.168 g, 2 mmol) added, and stirred for 15 min. After solvent evaporation, the crude was purified by flash chromatography and bulb to bulb distilled to give the alcohol *ent*-**39** (3.47 g, 72%) as a colorless oil: $[\alpha]_D^{22} = -62.2$ (*c* 1.0, $CHCl_3$); ^1H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **39**.

4.41. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(furan-2-yl)ethyl 4-methylbenzenesulfonate *ent*-40

Alcohol *ent*-**39** (2.74 g, 0.0113 mol) was esterified, with TsCl, under the same conditions of the corresponding enantiomer **39**. The *p*-toluensulfonate *ent*-**40** (4.137 g, 92%) was isolated as a colorless oil: $[\alpha]_D^{20} = -42.1$ (*c* 1.07, $CHCl_3$); ^1H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **40**.

4.42. (*S*)-[2-Azido-1-(furan-2-yl)ethoxy](*tert*-butyl)dimethylsilane *ent*-41

Ester *ent*-**40** (4.10 g, 0.0103 mol) was subjected to react with NaN_3 under the same condition of the corresponding enantiomer **40** to give *ent*-**41** (2.34 g, 85%) as a colorless oil. $[\alpha]_D^{21} = -87.3$ (*c* 1.06, $CHCl_3$). ^1H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **41**.

4.43. (*S*)-2-Amino-1-(furan-2-yl)ethanol *ent*-42

Azido *ent*-**41** (2.34 g, 8.75 mmol) was reduced under the same conditions of the corresponding enantiomer **41** to give, after bulb to bulb distillation, the amino alcohol *ent*-**42** (0.912 g, 82%) as a hygroscopic white solid: mp 86–87 °C; $[\alpha]_D^{21} = -38.6$ (*c* 1.8, $CHCl_3$), [lit. mp 79 °C,[24] $[\alpha]_D^{27} = -40$ (*c* 2, CH_3CN);[24] $[\alpha]_D^{20} = -32$ (*c* 1, $CHCl_3$)[25]]. ^1H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **42**.

4.44. (*S*)-2-(Dibutylamino)-1-(furan-2-yl)ethanol *ent*-44

Amino alcohol *ent*-**42** (0.190 g, 1.5 mmol) was alkylated under the same conditions of the corresponding enantiomer **42** to give, after flash chromatography and bulb to bulb distillation, the alkylated amine *ent*-**44** (0.226 g, 63%) as a colorless oil: $[\alpha]_D^{21} = -84.8$ (*c* 1.0, $CHCl_3$); ^1H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **44**.

4.45. (*R*)-1-(Furan-2-yl)ethane-1,2-diol 54

To a solution of *t*-BuOK (104 mL 1 M in THF, 0.104 mmol), chlorohydrin **36** (8.2 g, 0.0493 mol) dissolved in dry THF (15 mL) was added at room temperature, under argon, and warmed at 50–55 °C. After 2 h, the reaction mixture was cooled at room temperature, quenched with water (10 mL), and stirred for 15 min. The organic phase was separated and the aqueous one extracted with CH_2Cl_2. The combined organic phases were dried before on K_2CO_3 and then filtered through a Florisil plug ($\varnothing = 2$ cm, $h = 3$ cm) and washed with THF (3 × 50 mL). After solvent evaporation, under reduced pressure,[§] the residue was dissolved in dry THF (150 mL) and treated with pyridinium *p*-toluensulfonate (PTSA, 0.3 g, 2.5 mol %). The mixture was warmed at 45 °C and when PTSA was completely dissolved, after 40 min, the reaction was completed. $NaHCO_3$ (0.168 g, 2 mmol) was added and THF distilled under reduced pressure. The crude after flash chromatography[¶] and after bulb to bulb distillation gave diol **54** (5.93 g, 94%) as a colorless oil ($R_f = 0.2$, petroleum ether/EtOAc 2:3): $[\alpha]_D^{24} = +34.3$ (*c* 1, $CHCl_3$); {lit.[14] $[\alpha]_D^{24} = +32.3$ (*c* 0.5, $CHCl_3$) with an enantiomeric excess of 90% ee}; ^1H and ^{13}C NMR spectra were identical to those previously reported.[14]

4.46. (*R*)-2-(Furan-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate 56

Following a published procedure[29] a mixture of **54** (1.3 g, 0.0101 mol) and Bu_2SnO (2.61 g, 0.0105 mol), in dry toluene (128 mL) and under nitrogen, was heated and the water was removed by azeotropic distillation in a Dean–Stark apparatus. After 2 h, the reaction mixture was cooled at room temperature and the solvent removed under reduced pressure. To the residue, dissolved in $CHCl_3$ (40 mL, filtered on neutral aluminum oxide), TsCl (2.0 g, 0.0105 mmol) was added in one portion. After 150 min at room temperature, the solvent was distilled and the residue supported on silica gel. From flash chromatography ($R_f = 0.3$, petroleum ether/EtOAc 3:2), diol mono ester **56** (2.57 g, 90%) was obtained as a colorless oil: $[\alpha]_D^{24} = +25.0$ (*c* 1.0, $CHCl_3$); ^1H NMR spectrum was identical to that previously reported for the racemic mixture;[30] ^{13}C NMR ($CDCl_3$): δ 151.4, 145.1, 142.6, 132.4, 129.9, 127.9, 110.4, 107.9, 71.4, 65.8, 21.6.

[‡] A small amount of crude was purified by flash chromatography to obtain the intermediate enol ether *tert*-butyldimethyl{(3*S*,3a*S*,6a*R*)-2,3,3a,6a-tetrahydrofuro[3,2-*b*]furan-3-yloxy}silane **51** as a colorless oil: $[\alpha]_D^{22} = -2.8$ (*c* 1.4, C_6H_6); ^1H NMR (C_6H_6): δ 6.16 (d, 1H, $J = 2.6$ Hz), 5.32–5.28 (m, 1H), 4.85–4.82 (m, 1H), 4.55 (d, 1H, $J = 6.5$ Hz), 4.21–4.18 (m, 1H), 3.70 (dt, 1H, $J = 9.8$, 1.0 Hz), 3.41 (dd, 1H, $J = 9.8$, 3.1 Hz), 0.88 (s, 9H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (C_6H_6): δ 149.9, 101.6, 90.7, 84.5, 78.3, 71.3, 26.6, 18.9, −4.10, −4.14; IR (film): 2965, 2931 2857, and 1612 cm^{-1}.

[§] A small sample was flash chromatographed to isolate (3*R*,3a*R*,6a*R*)-2,3,3a,6a-tetrahydrofuro[3,2-*b*]furan-3-ol **53**: $[\alpha]_D^{24} = -75.1$ (*c* 1.0, C_6H_6); ^1H NMR (C_6D_6): δ 6.15 (d, 1H, $J = 2.6$ Hz), 4.98 (dd, 1H, $J = 6.4$, 2.7 Hz), 4.80–4.77 (m, 1H), 4.22 (t, 1H, $J = 6.0$ Hz), 4.07–3.95 (m, 1H), 3.81 (dd, 1H, $J = 8.7$, 6.5 Hz), 3.08–3.01 (m, 1H), 2.44 [d, 1H, $J = 10.2$ Hz (OH)]; ^{13}C NMR (C_6D_6): δ 150.2, 101.5, 84.1, 82.1, 73.0, 67.3.

[¶] Moreover the 1,4:2,5:3,6-trianhydro-D-mannitol **55** (0.128 g, 2%) was isolated: mp = 67–68 °C; $[\alpha]_D^{23} = 167.2$ (*c* 1, $CHCl_3$), [lit.;[28] mp = 65–67 °C; $[\alpha]_D^{23} = 171.5$ (*c* 2.8, $CHCl_3$)]; ^1H NMR (C_6D_6): δ 4.32 (dd, 4H, J = 12.8, 0.9 Hz,), 4.05 (dd, 2H, J = 8.4, 0.9 Hz), 3.61 (d, 2H, J = 8.4 Hz,); ^{13}C NMR (C_6D_6): δ 81.8, 77.1, 73.2.

4.47. (*R*)-1-(Furan-2-yl)-2-(tosyloxy)ethyl pivalate 57

To alcohol **56** (2.57 g, 9.1 mmol) dissolved in CH_2Cl_2 (7 mL) were added at 0 °C Et_3N (1.38 g, 13.6 mmol) and, dropwise, trimethylacetyl chloride (1.43 g, 11.8 mmol) dissolved in CH_2Cl_2 (2 mL) over 10 min. After 2 h at 0 °C, the reaction was left overnight at room temperature and quenched with Et_2O (70 mL) addition. The resulting solution was washed with 1 M HCl (10 mL), water (3 × 10 mL), brine (5 mL), and dried over $MgSO_4$. The residue, after solvent evaporation, was supported on silica gel and purified by flash chromatography ($R_f = 0.24$ in petroleum ether/Et_2O 5:1) to give pivaloyl ester **57** (3.14 g, 94%) as a colorless oil: $[\alpha]_D^{21} = +60.8$ (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.76 (d, 2H, $J = 8.2$ Hz), 7.37–7.31 (m, 3H), 6.36–6.33 (m, 1H), 6.32 (dd, 1H, $J = 3.3$, 1.8 Hz), 6.02 (dd, 1H, $J = 7.7$, 4.3 Hz), 4.42 (dd, 1H, $J = 10.6$, 7.7 Hz), 4.30 (dd, 1H, $J = 10.6$, 4.3 Hz), 2.44 (s, 3H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 177.4, 148.7, 145.4, 143.4, 133.1, 130.3, 128.2, 110.8, 110.0, 68.6, 66.1, 39.2, 27.3, 22.0; IR (film): 2975, 1738, 1599 cm^{-1}; Anal. Calcd for $C_{18}H_{22}O_6S$: C, 59.00, H, 6.05; S, 8.75. Found: C, 58.88, H, 6.03; S, 8.78.

4.48. (*R*)-2-(Dimethylamino)-1-(furan-2-yl)ethyl pivalate 58

In a sealed tube, **57** (1.34 g, 3.65 mmol) and Me_2NH (4.3 mL ~5.6 M in EtOH) were warmed at 50 °C. After 24 h, the reaction was cooled at room temperature filtered on paper and the solid washed with CH_2Cl_2 (2 × 5 mL). The combined organic phases were filtered on a Florisil plug ($\varnothing = 1$ cm, $h = 2$ cm) washing with Et_2O. The crude, after solvent evaporation, was flash chromatographed ($R_f = 0.2$, light petroleum/EtOAc 3:2) to give the dimethyl amine **58** (0.598 g, 68%) as a colorless oil: $[\alpha]_D^{22} = +96.8$ (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.36 (m, 1H), 6.34–6.31 (m, 2H), 5.97 (dd, 1H, $J = 7.1$, 6.2 Hz), 2.84 (dd, 1H, $J = 13.1$, 6.2 Hz), 2.77 (dd, 1H, $J = 13.1$, 7.1 Hz), 2.28 (s, 6H), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 177.4, 152.1, 142.3, 110.2, 108.2, 66.4, 61.0, 45.8, 38.7, 27.0; IR (film): 2974, 2771, 1731, 1461 cm^{-1}; Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25, H, 8.84; N, 5.85. Found: C, 65.40, H, 8.83; N, 5.87.

4.49. (*R*)-2-(Dimethylamino)-1-(furan-2-yl)ethanol 59

To a solution of **58** (0.540 g, 2.25 mmol) in MeOH (2 mL) a 15% aqueous NaOH (0.6 mL, 2.25 mmol) was added. After 18 h the reaction was diluted with CH_2Cl_2 (10 mL) in a separator funnel. The separated organic phase was dried on K_2CO_3 and the solvent distilled. After bulb to bulb distillation the amino alcohol **59** (0.321 g, 92%) was obtained as a colorless oil: $[\alpha]_D^{21} = +44.4$ (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38 (dd, 1H, $J = 1.8$, 0.8 Hz), 6.34 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.31–6.29 (m, 1H), 4.75 (dd, 1H, $J = 10.5$, 3.5 Hz), 4.12 [br s, 1H (OH)], 2.85 (dd, 1H, $J = 12.3$, 10.5 Hz), 2.48 (dd, 1H, $J = 12.3$, 3.5 Hz), 2.36 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 154.6, 142.1, 110.1, 106.8, 63.5, 63.3, 45.3; IR (film): 3391, 2948, 2827, 1463 cm^{-1}; Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91, H, 8.44; N, 9.03. Found: C, 62.04, H, 8.46; N, 9.05.

4.50. (*R*)-4-(Furan-2-yl)-1,3-dioxolan-2-one 60

Diol **54** (1.43 g, 0.0112 mol) was subjected to react with dimethyl carbonate following the Zhou's procedure.[15] Carbonate **60** (1.48 g, 86%) was obtained as a colorless oil: $[\alpha]_D^{21} = -72.3$ (*c* 0.8, EtOH) {corresponding (*S*)-enantiomer[15] $[\alpha]_D^{20} = +63.4$ (*c* 1.1, EtOH)}; ^1H NMR and IR spectra were identical to those previously reported;[15] ^{13}C NMR ($CDCl_3$): δ 154.4, 147.1, 144.6, 111.9, 110.8, 71.0, 67.3.

4.51. (*S*)-2-Azido-2-(furan-2-yl)ethanol 61

Carbonate **60** (0.880 g, 5.71 mmol) was reacted with NaN_3 following Zhou's procedure.[15] Azido alcohol **61** (0.725 g, 83%) was obtained as a colorless oil: $[\alpha]_D^{21} = -128.8$ (*c* 1.55, EtOH), {corresponding (*R*)-enantiomer lit.[15] $[\alpha]_D^{21} = +95.3$ (*c* 1.3, EtOH)}; ^1H NMR and IR spectra were identical to those previously reported;[15] ^{13}C NMR ($CDCl_3$): δ 149.5, 143.2, 110.4, 108.8, 63.4, 60.4.

4.52. (*S*)-2-Amino-2-(furan-2-yl)ethanol 62

Azido alcohol **61** (0.217 g, 1.42 mmol) dissolved in MeOH (8 mL) was added to a pre-hydrogenated suspension of 5 wt % Pd(0) on $CaCO_3$ (75 mg,) poisoned with lead, and hydrogenated (H_2, 1 atm). After 6 h, the mixture was filtered on Celite, after which the solvent was distilled under reduced pressure, and the residue bulb to bulb distilled to give the amino alcohol **62** (0.157 g, 87%) as a waxy solid: $[\alpha]_D^{22} = -11.8$ (*c* 1.1, $CHCl_3$); {lit.[31] $[\alpha]_D^{20} = -7.4$ (*c* 0.8, MeOH) for ee ≈ 91%}; ^1H and ^{13}C NMR spectra were identical to those previously reported.[31]

4.53. (*S*)-2-(Dibutylamino)-2-(furan-2-yl)ethanol 63

Amino alcohol **62** (0.244 g, 1.92 mmol) was alkylated with *n*-BuI under the same condition of the corresponding isomer **42**. After flash chromatography ($R_f = 0.28$, petroleum ether/Et_2O 5:1) and bulb to bulb distillation, the alkylated amine **63** (0.340 g, 74%) was obtained as a colorless oil: $[\alpha]_D^{25} = -84.0$ (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37 (dd, 1H, $J = 1.9$, 0.7 Hz), 6.32 (dd, 1H, $J = 3.2$, 1.9 Hz), 6.13–6.10 (m, 1H), 3.99 (dd, 1H, $J = 10.8$, 5.4 Hz), 3.75 (dd, 1H, $J = 10.8$, 10.3 Hz), 3.62 (dd, 1H, $J = 10.3$, 5.4 Hz), 3.15 [br s, 1H (OH)], 2.63–2.52 (m, 2H), 2.32–2.22 (m, 2H), 1.50–1.18 (m, 8H), 0.92 (t, 6H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 152.4, 141.9, 109.8, 107.8, 59.1, 58.6, 50.3, 30.9, 20.6, 14.1; IR (film): 3486 cm^{-1}; Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.05; H, 10.50; N, 5.86.

4.54. (3*S*,3a*R*,6*S*,6a*S*)-6-Chlorohexahydrofuro[3,2-*b*]furan-3-ol 64

Acetate **50** (8.0 g, 0.0387 mol) was saponified as the corresponding pivalate epimer **35**. From flash chromatography and bulb to bulb distillation, chlorohydrin **64** (6.21 g, 97%) was isolated as a white solid: mp 61–62 °C; $[\alpha]_D^{23} = +43.9$ (*c* 1.0, $CHCl_3$), {lit.[27] mp 68–69 °C; $[\alpha]_D^{23} = +60.0$ (*c* 1.0, MeOH); lit.[23] mp 64.6–65.5 °C; $[\alpha]_D^{20} = +52.0$ (*c* 0.5, $CHCl_3$)}; ^1H, ^{13}C NMR, and IR spectra were identical to those previously reported.[23]

4.55. (*S*)-1-(Furan-2-yl)ethane-1,2-diol *ent*-54

To a solution of *t*-BuOK (30 mL 1 M in THF, 0.030 mmol) a dry THF (4 mL) solution of chlorohydrin **64** (1.46 g, 0.010 mol) was added at room temperature under argon. The reaction was warmed at 50–55 °C for 4 h, then cooled at room temperature and quenched with water (1.5 mL). The organic phase was separated and the aqueous one extracted with CH_2Cl_2. Combined organic phases were dried before on K_2CO_3, then filtered through a Florisil plug ($\varnothing = 3$ cm, $h = 3$ cm) washed with Et_2O/THF 4:1 (2×50 mL). The colorless and neutral filtrate was concentrated under reduced pressure to give the enol alcohol **65** as hygroscopic white solid.[‖] To a solution of enol alcohol **65**, in dry THF (30 mL), pyridinium *p*-toluensulfonate (0.057 g, 2.5 mol %) was added and warmed at 50–55 °C. After 60 min the reaction was cooled at room temperature then $NaHCO_3$ (0.084 g, 1 mmol) added and stirred for 15 min. The solution was concentrated under reduced pressure and the residue purified by flash chromatography. From bulb to bulb distillation the diol *ent*-**54** (1.035 g, 80%) was isolated as a colorless oil: $[\alpha]_D^{23} = -35.4$ (*c* 1.5, $CHCl_3$); ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **54**.

4.56. (*S*)-2-(Furan-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate *ent*-56

Diol *ent*-**54** (1.05 g, 8.19 mmol) was esterified under the same conditions of the corresponding enantiomer **54**. Purification by flash chromatography gave ester *ent*-**56** (2.15 g, 93%) as a colorless oil: $[\alpha]_D^{21} = -24.6$ (*c* 1.35, $CHCl_3$); ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **56**.

4.57. (*S*)-1-(Furan-2-yl)-2-(tosyloxy)ethyl pivalate *ent*-57

Alcohol *ent*-**56** (2.08 g, 7.37 mmol) was esterified under the same conditions of the corresponding enantiomer **56**. Purification by flash chromatography gave diester *ent*-**57** (2.15 g, 93%) as a colorless oil: $[\alpha]_D^{21} = -59.6$ (*c* 1.1, $CHCl_3$); ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **57**.

4.58. (*S*)-2-(Dimethylamino)-1-(furan-2-yl)ethyl pivalate *ent*-58

Toluensulfonate *ent*-**57** (1.13 g, 3.08 mmol) was subjected to reaction with Me_2NH under the same conditions of the corresponding enantiomer **57**. After flash chromatography and bulb to bulb distillation, amine *ent*-**58** (0.479 g, 65%) was obtained as a colorless oil: $[\alpha]_D^{21} = -97.7$ (*c* 1.10, $CHCl_3$); ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **58**.

[‖] (3*S*,3a*R*,6a*R*)-2,3,3a,6a-Tetrahydrofuro[3,2-*b*]furan-3-ol **65**: ($R_f = 0.17$ petroleum ether/EtOAc 3:2); ^{1}H NMR ($CDCl_3$): δ 6.40 (d, 1H, $J = 2.7$ Hz), 5.38 (dd, 1H, $J = 6.3$, 2.6 Hz), 4.96–4.94 (m, 1H), 4.65 (d, 1H, $J = 6.3$ Hz), 4.17 (dd, 1H, $J = 6.3$, 2.7 Hz), 3.74 (d, 1H, $J = 10.3$ Hz), 3.39 (dd, 1H, $J = 10.3$, 2.7 Hz), 2.85 (d, 1H, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 149.6, 99.7, 88.5, 83.7, 75.6, 69.8; IR (film): 3348 cm^{-1}.

4.59. (*S*)-2-(Dimethylamino)-1-(furan-2-yl)ethanol *ent*-59

Pivalate *ent*-**58** (0.450 g, 1.88 mmol) was saponified under the same conditions as the corresponding enantiomer **58**. Bulb to bulb distillation gave amino alcohol *ent*-**59** (0.271 g, 93%) as a colorless oil: $[\alpha]_D^{21} = -54.3$ (*c* 0.50, $CHCl_3$); ^{1}H, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **59**.

4.60. (*S*)-4-(Furan-2-yl)-1,3-dioxolan-2-one *ent*-60

Diol *ent*-**54** (1.58 g, 0.0136 mol) was esterified under the same conditions as the corresponding enantiomer **54** (the following the Zhou's procedure[15]). The carbonate *ent*-**60** (1.58 g, 75%) was obtained as colorless oil: $[\alpha]_D^{22} = +74.6$ (*c* 1.2, EtOH); {lit.[15] $[\alpha]_D^{20} = +63.4$ (*c* 1.1, EtOH)}. ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **60.**

4.61. (*R*)-2-Azido-2-(furan-2-yl)ethanol *ent*-61

Carbonate *ent*-**60** (1.58 g, 0.0102 mol) was subjected to reaction with NaN_3 following Zhou's procedure.[15] The azido alcohol *ent*-**61** (1.36 g, 85%) was obtained as a colorless oil. $[\alpha]_D^{24} = +135.3$ (*c* 1.51, EtOH); {lit.[15] $[\alpha]_D^{21} = 95.3$ (*c* 1.3, EtOH)}. ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **61.**

4.62. (*R*)-2-Amino-2-(furan-2-yl)ethanol *ent*-62

Azido *ent*-**61** (0.145 g, 0.947 mmol) was hydrogenated under the same conditions as the corresponding enantiomer **61**. Bulb to bulb distillation gave amino alcohol *ent*-**62** (0.113 g, 93%) as a waxy solid: $[\alpha]_D^{26} = +15.9$ (*c* 2.41, $CHCl_3$); {lit.[31] $[\alpha]_D^{20} = +7.8$ (*c* 0.8, MeOH), ee $\approx$ 96%}; ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **62.**

4.63. (*R*)-2-(Dibutylamino)-2-(furan-2-yl)ethanol *ent*-63

Amine *ent*-**62** (0.168 g, 1.32 mmol) was alkylated under the same conditions of the corresponding enantiomer **42**. After flash chromatography and bulb to bulb distillation the alkylated amine *ent*-**63** (0.193 g, 61%) was obtained as a colorless oil: $[\alpha]_D^{25} = +83.9$ (*c* 1.51 $CHCl_3$). ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **63.**

4.64. (*R*)-2-(Dibutylamino)-2-phenylethanol 67

(*R*)-(−)-2-Amino-2-phenyl-1-ethanol, (*R*)-**66,** (0.549 g, 4 mmol) was alkylated under the same condition of the corresponding furanyl **42** derived above to give, after flash chromatography (petroleum ether/Et_2O 3:2) and bulb to bulb distillation, the alkylated amine **67** (0.580 g, 58%) as colorless oil: $[\alpha]_D^{24} = -64.4$ (*c* 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.37–7.27 (m, 3H), 7.21–7.16 (m, 2H), 3.98–3.87 (m, 2H), 3.66–3.56 (m, 1H), 3.24 [br s, 1H (OH)], 2.65–2.54 (m, 2H), 2.24–2.14 (m, 2H), 1.55–1.20 (m, 8H), 0.92 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 136.5, 128.9, 128.1, 127.6, 64.6, 60.3, 49.4, 30.7, 20.6, 14.1; IR

(film): 3390 cm^{-1}; Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 76.77; H, 10.93; N, 5.61.

4.65. (*S*)-2-(Dibutylamino)-2-phenylethanol *ent*-67

(*S*)-(−)-2-Amino-2-phenyl-1-ethanol, (*S*)-**66,** (0.548 g, 3.99 mmol) was alkylated under the same conditions of the corresponding above enantiomer. Alkylated amine *ent*-**67** (0.423 g, 43%) was isolated as a colorless oil: $[\alpha]_D^{22} = 65.3$ (*c* 1.10, $CHCl_3$); ^1H NMR, ^{13}C NMR, and IR spectra were identical to the corresponding enantiomer **67.**

4.66. (*R*)-2-(Dimethylamino)-2-phenylethanol 68

A mixture of **66** (0.535 g, 3.9 mmol), formic acid (0.6 mL, 15.9 mmol), and 40% formaldehyde (0.6 mL, 8 mmol) was heated at 80 °C for 8 h. Cooled at room temperature the reaction mixture was basified with 30% aqueous NH_4OH (0.5 mL) and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 5 mL) and the organic phase dried on $MgSO_4$. The crude, after solvent evaporation, was purified by flash chromatography ($MeOH/CH_2Cl_2$ 1:20) and after bulb to bulb distillation gave **68** (0.548 g, 85%) as solid: mp 102–103 °C; $[\alpha]_D^{24} = -25.6$ (*c* 1.20, $CHCl_3$); {lit.[32] mp 104–105 °C; $[\alpha]_D^{25} = -30.8$ (*c* 0.85, H_2O)}; ^1H NMR and IR spectra coincided with those previously reported for the racemic mixture;[33] ^{13}C NMR ($CDCl_3$): δ 135.8, 128.9, 128.1, 127.8, 70.2, 61.4, 41.4.

4.67. (*S*)-2-(Dibutylamino)-1-phenylethanol 70

(*S*)-2-Phenyloxirane **69** (0.240 g, 2 mmol) was subjected to reaction with lithium dibutylamide as described in the literature.[16] The amino alcohol **70** (0.320 g, 64%) was isolated as a colorless oil: $[\alpha]_D^{22} = +103.9$ (*c* 1.05, $CHCl_3$); ^1H and ^{13}C NMR spectra coincided with those previously reported for the racemic mixture.[16]

4.68. (*S*)-2-(Dibutylamino)propan-1-ol 72

A mixture of L-alanine methyl ester hydrochloride **71** (3.3 g, 0.0238 mol), $NaHCO_3$ (12 g, 0.142 mol), and *n*-BuI (8.76 g, 0.0476 mol) in THF/DMSO 4:1 (64 mL) was heated at reflux for 36 h. After cooling, the solid materials were removed by filtration and the resulting filtrate concentrated under reduced pressure. The residue, diluted with EtOAc (50 mL), was washed with water (5 mL) and dried over $MgSO_4$. After solvent evaporation, the crude product was purified by flash chromatography (petroleum ether/Et_2O 9:1) to give *N*,*N*-dialkylated amines as a viscous oil (2.4 g).[††] To a suspension of $LiAlH_4$ (0.415 g, 0.011 mol) in dry THF (26 mL), the above *N*,*N*-dialkylated product, in dry THF (60 mL), was added dropwise over 45 min at 20 °C. After 30 min at room temperature and 1 h at reflux, the reaction mixture was cooled at −10 °C, then the excess of the hydride quenched with a saturated aqueous solution of NH_4Cl (5 mL). The mixture was left to warm at room temperature and stirred until a gray solid material decanted from the organic solvent. The solid material was removed by filtration on a Büchner funnel and washed with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried over K_2CO_3 and the solvent evaporated under reduced pressure. From bulb to bulb distillation, amino alcohol **72** (1.89 g, 42% overall) was obtained as a colorless oil: $[\alpha]_D^{24} = +112.3$ (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.52 [br s, 1H (OH)], 3.40–3.29 (m, 1H), 3.26–3.18 (m, 1H), 3.00–2.87 (m, 1H), 2.52–2.40 (m, 2H), 2.35–2.23 (m, 2H), 1.50–1.15 (m, 8H), 0.91 (t, 6H, $J = 7.2$ Hz), 0.85 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 62.6, 56.0, 48.7, 31.1, 20.5, 14.0, 9.0; IR (film): 3436, 2959, 2932, 2862, 1467 cm^{-1}. Anal. Calcd for $C_{11}H_{25}NO$: C, 70.53; H, 13.45; N, 7.48. Found: C, 70.68; H, 13.48; N, 7.49.

4.69. (1*S*,2*S*)- and (1*R*,2*S*)-2-(dibutylamino)-1-(furan-2-yl)propan-1-ol *anti*-73 and *syn*-73

To a solution of oxalyl chloride (1.40 g, 11 mmol) in dichloromethane (25 mL), DMSO (1.87 g, 24 mmol) in dichloromethane (5 mL) at −70 °C was added. The mixture was stirred at −70 °C for 10 min, then a solution of the amino alcohol **72** (1.89 g, 10 mmol) in dichloromethane (5 mL) was added. The mixture was stirred at −70 °C for 15 min, then triethylamine (6.97 mL, 50 mmol) was added and the reaction mixture allowed to warm to room temperature. After 15 min at room temperature the reaction was quenched with water (15 mL) addition. The organic layer was separated and the aqueous one washed with dichloromethane (2 × 20 mL). The combined organic phases were washed with water (2 × 8 mL), brine (8 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde (1.9 g) was used in the next step without purification. To furan (2.72 g, 40 mmol) in dry THF (50 mL), BuLi (19 mL, 1.6 M in hexane, 30 mmol) was added at −40 °C.[18] The reaction mixture was warmed at room temperature for 3 h, then cooled at −78 °C and a solution of the above aldehyde in dry THF (3 mL), added. After 3 h, the reaction was quenched, at −78 °C, with saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated and the aqueous one washed with ether (2 × 25 mL). The combined organic phases were dried over $MgSO_4$ and the solvents distilled under reduced pressure. The crude was purified by flash chromatography (petroleum ether/EtOAc 4:1) to give *syn*-**73** and *anti*-**73** (1.88 g, 74%).

4.69.1. (1*R*,2*S*)-2-(Dibutylamino)-1-(furan-2-yl)propan-1-ol *syn*-73.

syn-**73** (76 mg, 3%) as a colorless oil: ($R_f = 0.33$, petroleum ether/EtOAc 9:1); $[\alpha]_D^{21} = +15.0$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38 (dd, 1H, $J = 1.6$, 0.8 Hz), 6.34–6.30 (m, 2H), 4.26 (d, 1H, $J = 10.0$ Hz), 3.06 (dq, 1H, $J = 10.0$, 6.7 Hz), 2.59–2.47 (m, 2H), 2.40–2.29 (m, 2H), 1.60–1.20 (m, 9H), 0.94 (t, 6H, $J = 7.4$ Hz), 0.79 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.5, 142.2, 110.1, 108.2, 67.9, 59.6, 49.4, 31.1, 20.6, 14.1, 8.7; IR (film): 3370, 2959, 2929, 2873, 1466 cm^{-1}; Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 70.89; H, 10.71; N, 5.51.

[††] As mixture of (*S*)-methyl and (*S*)-butyl 2-(dibutylamino)propanoate in a 4:1 ratio.

4.69.2. (1*S*,2*S*)-2-(Dibutylamino)-1-(furan-2-yl)propan-1-ol *anti*-73. *anti*-**73** (1.88 g, 74%) as a colorless oil: ($R_f = 0.2$, petroleum ether/EtOAc 9:1); $[\alpha]_D^{22} = +31.9$ (*c* 1.22, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.33 (dd, 1H, $J = 1.7$, 0.8 Hz), 6.31 (dd, 1H, $J = 3.2$, 1.7 Hz), 6.24–6.21 (m, 1H), 4.53 (d, 1H, $J = 5.6$ Hz), 4.32 [br s, 1H (OH)], 3.14–3.04 (m, 1H), 2.34–2.19 (m, 4H), 1.50–1.12 (m, 8H), 1.03 (d, 3H, $J = 7.0$ Hz), 0.88 (t, 6H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 156.4, 141.2, 110.1, 106.3, 68.6, 59.5, 50.8, 31.0, 20.5, 14.1, 9.9; IR (film): 3345, 2958, 2932, 2974, 1466 cm^{-1}; Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 70.94; H, 10.76; N, 5.53.

4.70. (*S*)-2-(Dibutylamino)-3-methylbutan-1-ol 75

A mixture of amine alcohol **74**[34] (0.945 g, 9.13 mmol), *n*-BuI (5.04 g, 27.4 mmol), K_2CO_3 (3.78 g, 27.4 mmol) in MeCN (9.2 mL) was refluxed for 26 h. The reaction mixture was cooled, diluted with CH_2Cl_2 (92 mL) and filtered. The residue after solvent evaporation was dissolved in Et_2O (100 mL), washed with water (2 × 5 mL) brine, and dried on K_2CO_3 dry. The solvent was evaporated, the residue supported on silica gel and flash chromatographed ($R_f = 0.45$, EtOAc/petroleum ether 1:5) to give, after distillation at 110 °C/1 mm, amine **75** (1.72 g, 87%) as colorless oil: $[\alpha]_D^{23} = 31.3$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.78 (br s, 1H), 3.55 (dd, 1H, $J = 10.2$, 5.2 Hz), 3.09 (t, 1H, $J = 10.2$ Hz), 2.69–2.50 (m, 4H), 2.42 (ddd, 1H, $J = 10.5$, 9.1, 5.1 Hz), 1.82 (dhept, 1H, $J = 9.1$, 6.7 Hz), 1.56–1.20 (m, 8H), 1.00 (d, 3H, $J = 6.7$ Hz), 0.91 (t, 6H, $J = 7.1$Hz), 0.83 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$): δ 68.6, 59.8, 51.4, 32.8, 28.6, 22.4, 20.5, 20.0, 14.0; IR (film): 3436, 2957, 2931, 2873, 1467 cm^{-1}; Anal. Calcd for $C_{13}H_{29}NO$: C, 70.50; H, 13.57; N, 6.50. Found: C, 70.71; H, 13.55; N, 6.51.

4.71. (1*S*,2*S*)- and (1*R*,2*S*)-2-(dibutylamino)-1-(furan-2-yl)-3-methylbutan-1-ol *anti*-76 and *syn*-76

The amino alcohol **75** (1.59 g, 5.65 mmol) was first oxidized and then added to a 1-lithiofuran solution under the same conditions as described above for **72**. From flash chromatography and bulb to bulb distillation, *anti*-**76** ($R_f =$ 0.2, Et_2O/petroleum ether 1:20) and *syn*-**76** ($R_f = 0.3$, Et_2O/petroleum ether 1:5) were isolated as colorless oils.

4.71.1. (1*S*,2*S*)-2-(Dibutylamino)-1-(furan-2-yl)-3-methylbutan-1-ol *anti*-76. *anti*-**76** (0.975 g, 61%): $[\alpha]_D^{21} = -25.1$ (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.32 (dd, 1H, $J = 1.8$, 0.9 Hz), 6.30 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.26–6.24 (m, 1H), 4.75 (br s, 1H), 4.71 (d, 1H, $J = 5.0$ Hz), 2.60–2.45 (m, 3H), 2.33–2.21 (m, 2H), 2.05 (dhept, 1H, $J = 10.9$, 6.5 Hz), 1.59–1.40 (m, 2H), 1.40–1.25 (m, 2H), 1.24–1.11 (m, 4H), 1.09 (d, 3H, $J = 6.5$ Hz), 1.01 (d, 3H, $J = 6.5$ Hz), 0.87 (t, 6H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 156.6, 141.0, 110.0, 106.4, 73.1, 65.4, 53.6, 33.1, 28.2, 22.3, 21.0, 20.3, 14.0; IR (film): 3414, 2958, 2930, 2872, 1469 cm^{-1}; Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.40; H, 11.07; N, 4.99.

4.71.2. (1*R*,2*S*)-2-(Dibutylamino)-1-(furan-2-yl)-3-methylbutan-1-ol *syn*-76. *syn*-**76** (0.075 g, 5%): $[\alpha]_D^{21} = +47.3$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.39–7.37 (m, 1H), 6.33–6.30 (m, 2H), 5.34 [br s, 1H (OH)], 4.43 (d, 1H, $J = 9.8$ Hz), 2.94 (dd, 1H, $J = 4.8$, 9.8 Hz), 2.73–2.62 (m, 2H), 2.60–2.50 (m, 2H), 1.92 (dhept, 1H, $J = 6.9$, 4.8 Hz), 1.62–1.23 (m, 8H), 0.94 (t, 6H, $J = 7.2$ Hz), 0.78 (d, 3H, $J = 6.9$ Hz), 0.74 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 155.3, 141.6, 110.3, 108.5, 68.7, 64.0, 51.0, 31.9, 27.3, 23.0, 20.6, 19.4, 14.1; IR (film): 3340, 2958, 2931, 2873, 1468 cm^{-1}; Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.38; H, 11.08; N, 4.98.

4.72. (*S*)-2-(Dibutylamino)-3,3-dimethylbutan-1-ol 78

Amino alcohol **77**[34] (1.12 g, 9.56 mmol) was alkylated under the same conditions as described above for **74**. From flash chromatography ($R_f = 0.2$, in Et_2O/petroleum ether 1:10) and distillation at 125 °C/3 mm the amino alcohol **78** (1.74 g, 79%) was obtained as a colorless oil: $[\alpha]_D^{23} = +35.2$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.56 (dd, 1H, $J = 10.4$, 4.6 Hz), 3.49–3.39 (m, 1H), 3.13 [br s, 1H (OH)], 2.83–2.63 (m, 4H), 2.57 (dd, 1H, $J = 10.5$, 4.6 Hz), 1.56–1.17 (m, 8H), 0.97 (s, 9H) 0.91 (t, 6H, $J = 7.1$Hz); ^{13}C NMR ($CDCl_3$): δ 70.9, 58.2, 52.2, 36.5, 33.3, 29.2, 20.5, 14.1; IR (film): 3401, 2957, 2872, 1467 cm^{-1}; Anal. Calcd for $C_{14}H_{31}NO$: C, 73.30; H, 13.62; N, 6.11. Found: C, 73.52; H, 13.59; N, 6.09.

4.73. (1*S*,2*S*)- and (1*R*,2*S*)-2-(dibutylamino)-1-(furan-2-yl)-3,3-dimethylbutan-1-ol *anti*-79 and *syn*-79

The amino alcohol **78** (1.50 g, 6.54 mmol) was first oxidized and then added to a 1-lithiofuran solution under the same conditions as described above for **72**. From flash chromatography *anti*-**79** ($R_f = 0.26$, Et_2O/petroleum ether 1:20) and *syn*-**79** ($R_f = 0.3$, Et_2O/petroleum ether 1:5) were isolated as colorless oil.

4.73.1. (1*S*,2*S*)-2-(Dibutylamino)-1-(furan-2-yl)-3,3-dimethylbutan-1-ol *anti*-79. *anti*-**79** (1.25 g, 64.7%): $[\alpha]_D^{23} = -1.2$ (*c* 2.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.32 (dd, 1H, $J = 1.8$, 0.9 Hz), 6.31 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.21–6.19 (m, 1H), 4.82 (d, 1H, $J = 5.9$ Hz), 4.08 [br s, 1H (OH)], 2.82 (d, 1H, $J = 5.9$ Hz), 2.69–2.60 (m, 4H), 1.56–1.33 (m, 4H), 1.33–1.19 (m, 4H), 0.96 (s, 9H), 0.91 (t, 6H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 157.0, 140.6, 110.4, 106.8, 72.9, 65.9, 54.0 (br), 37.2, 33.0, 29.6, 20.5, 14.1; IR (film): 3422, 2957, 2872, 1467 cm^{-1}; Anal. Calcd for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26; N, 4.74. Found: C, 72.99; H, 11.28; N, 4.75.

4.73.2. (1*R*,2*S*)-2-(Dibutylamino)-1-(furan-2-yl)-3,3-dimethylbutan-1-ol *syn*-79. *syn*-**76** (0.075 g, 5%): $[\alpha]_D^{24} = +40.6$ (*c* 2.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.37 (m, 1H), 6.33–6.29 (m, 2H), 5.34 [br s, 1H (OH)], 4.52 (d, 1H, $J = 9.7$ Hz), 2.97 (d, 1H, $J = 9.7$ Hz), 2.89–2.71 (m, 4H), 1.68–1.50 (m, 2H), 1.50–1.38 (m, 2H), 1.38–1.24 (m, 4H), 0.94 (t, 6H, $J = 7.1$ Hz), 0.81 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 155.0, 141.5, 110.3, 108.7, 72.8, 63.5, 52.4 (br), 36.8, 33.4, 29.3, 20.5, 14.0; IR (film): 3400, 2957, 2931, 2872, 1468 cm^{-1}; Anal. Calcd for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26; N, 4.74. Found: C, 72.95; H, 11.29; N, 4.71.

4.74. (1*R*,2*R*)- and (1*S*,2*R*)-2-(dibutylamino)-1-(furan-2-yl)-2-phenylethanol *anti*-80 and *syn*-80

Amino alcohol **67** (1.43 g, 5.73 mmol) was first oxidized and then added to a 1-lithiofuran solution under the same conditions as described above for **72**. From flash chromatography *syn*-**80** ($R_f = 0.4$, Et_2O/petroleum ether 1:20) and *anti*-**80** ($R_f = 0.2$, Et_2O/petroleum ether 1:20) were isolated.

4.74.1. (1*S*,2*R*)-2-(Dibutylamino)-1-(furan-2-yl)-2-phenylethanol *syn*-80. *syn*-**80** (0.068 g, 3.8%), white semisolid material; $[\alpha]_D^{24} = -13.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.29–7.18 (m, 4H), 7.17–7.11 (m, 2H), 6.12 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.09–6.07 (m, 1H), 5.06 (d, 1H, $J = 10.6$ Hz), 5.02 [br s, 1H (OH)], 4.13 (d, 1H, $J = 10.6$ Hz), 2.69–2.60 (m, 2H), 2.21–2.11 (m, 2H), 1.61–1.22 (m, 8H), 0.95 (t, 6H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 153.6, 142.0, 134.5, 129.4, 127.9, 127.6, 109.9, 108.5, 67.5, 64.5, 49.6, 30.7, 20.6, 14.1; IR (film): 3350, 2957, 2931, 2872, 1454 cm^{-1}; Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.34; H, 9.25; N, 4.45.

4.74.2. (1*R*,2*R*)-2-(Dibutylamino)-1-(furan-2-yl)-2-phenylethanol *anti*-80. *anti*-**80** (1.03 g, 56.9%), red light oil; $[\alpha]_D^{24} = +3.3$ (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33–719 (m, 6H), 6.23 (dd, 1H, $J = 3.2$, 1.8 Hz), 6.05–6.02 (m, 1H), 5.21 (d, 1H, $J = 7.1$ Hz), 4.07 (d, 1H, $J = 7.1$ Hz), 2.76 [br s, 1H (OH)], 2.57–2.46 (m, 2H), 2.36–2.25 (m, 2H), 1.44–1.28 (m, 4H), 1.27–1.06 (m, 4H), 0.85 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 154.8, 141.1, 136.8, 129.4, 127.9, 127.4, 110.1, 107.2, 68.9, 67.7, 50.1, 29.5, 20.4, 14.1; IR (film): 3422, 2954, 2921, 2862, 1457 cm^{-1}; Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.30; H, 9.24; N, 4.45.

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