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Asymmetric synthesis of 1,3-aminoketals

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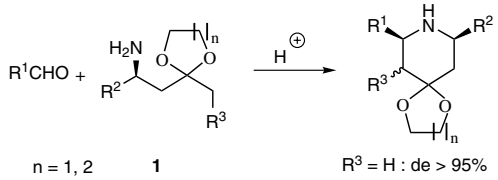
Abstract—The asymmetric synthesis of α-chiral 1,3-aminoketals **1**, useful chiral building blocks for piperidine preparation, was achieved in seven steps involving highly diastereoselective 1,4-addition of Davies' lithium amide to an α,β-unsaturated ester. Problems of partial racemization observed during transformation of the ester moiety into a keto function, via a Weinreb amide, were solved using non-conventional experimental conditions. This procedure allowed the preparation of the title compounds in >90% enantiomeric excess.

1. Introduction

In previous work,[1] we have described a general method for diastereoselective preparation of 2,6-*cis*-disubstituted piperidines based on an intramolecular Mannich-type cyclization[2] involving an aldehyde and chiral β-aminoketal **1** (Scheme 1).

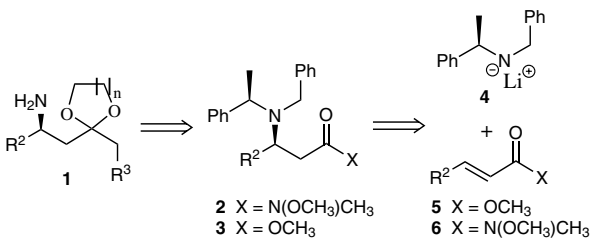
The efficiency of our method was illustrated by achieving the total synthesis of several piperidine[3] and indolizidine[4] alkaloids as well as some trifluoromethylated analogues.[5] However, the generalization of our strategy remains dependent on the preparation of enantiomerically pure ketoprotected 1,3-aminoketones. The development of an enantioselective and versatile route to such compounds proved to be essential.



Scheme 1. Diastereoselective synthesis of piperidines.

2. Results and discussion

Many syntheses of chiral β-aminoketones, useful building blocks for organic synthesis, have been described in the literature. These synthons can, in fact, be obtained from chiral compounds (by reduction and acidic hydrolysis of 1,3-diimines,[6] by ring opening of β-lactams,[7] or by functional modification of β-aminocarbonyls[8]) or, most frequently, by an asymmetric Mannich-type reaction.[9] During this reaction, asymmetry can be induced either by using preformed chiral reagents[10] or by the use of a chiral catalyst.[11] However, only a few methods have been reported, which combine good stereoselectivity and sufficient versatility. In our methodology, which relies on the work of Davies et al.[8a,8d] (Scheme 2), two constraints have to be taken into account: the efficient control of absolute configuration of the created stereogenic centre and the variability of the substituents R^2 and R^3.



Scheme 2. Retrosynthetic pathway to optically pure 1,3-aminoketals.

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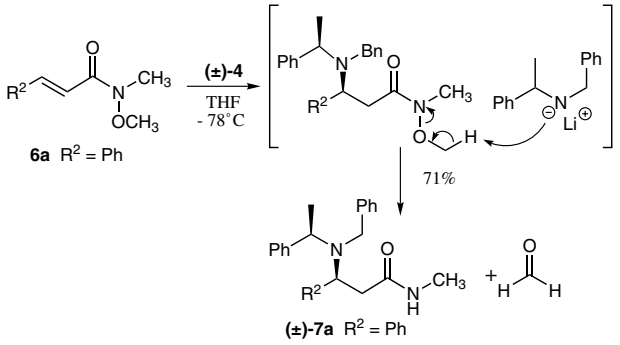
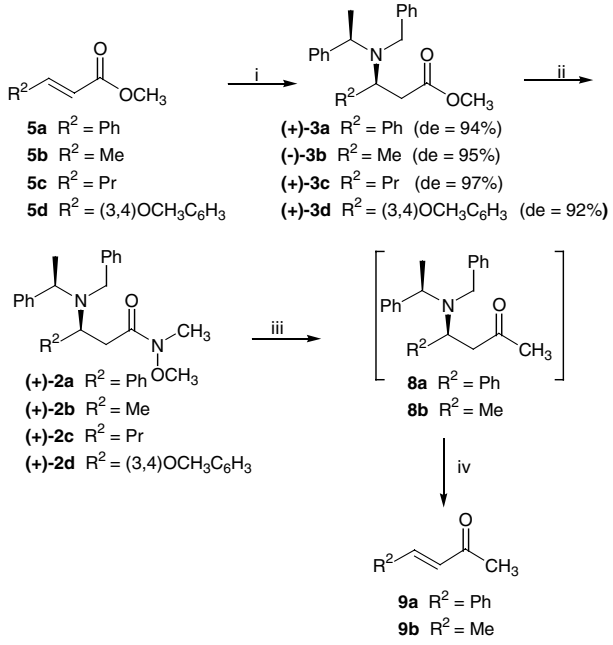
The substituent adjacent to the carbonyl group (R^3CH_2) can be introduced via a Weinreb amide, which is then obtained from the corresponding ester.[12] The synthesis of β-aminoamide **2** or β-aminoester **3** derivatives could be carried out by a hetero-Michael addition of enantiopure lithium *N*-benzyl-*N*-α-methylbenzylamide **4** on an α,β-unsaturated ester **5** or amide **6**, as described by Davies et al.[8a,d,13] which allows control of the absolute configuration of the asymmetric carbon thus formed. Hence, this reaction could be conducted with α,β-unsaturated Weinreb amides, an advantage for our synthetic scheme in terms of reducing the number of steps.[8a,d]

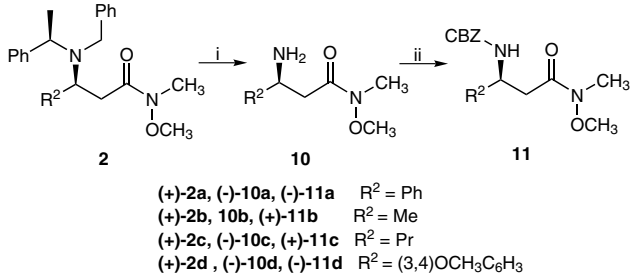
However, in this case, starting from amide **6a** and using lithium Davies' amide (±)-**4**, we obtained β-aminoamide (±)-**7a** in 71% yield, resulting from elimination of the methoxy group (Scheme 3). It is indeed surprising that we obtained this reproducible result, contrary to the published work of Davies et al.[8a,d] However, this type of demethoxylation has been reported in the literature.[14] This unusual reaction, which can occur in some cases, has been mentioned during the use of hindered and/or strongly base lithium amides. The mechanism of this demethoxylation has been postulated to involve an E_2 pathway.[14a] We therefore modified our synthetic pathway as shown in Scheme 4, starting from α,β-unsaturated esters. Treatment of α,β-unsaturated esters **5** with lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide in THF at −78 °C led to the corresponding β-aminoesters **3** in good yields and excellent diastereoisomeric excesses (de >92% from NMR data). The Weinreb amides **2** were then prepared using *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethyl aluminium in dichloromethane,[12] in yields up to 90%. Treatment of amides **2a** and **2b** with methyl magnesium bromide afforded the corresponding ketones **8a** and **b**.[15] However, these compounds proved to be unstable in acidic medium,[16] leading to the α,β-unsaturated ketones **9a** and **b** according to a β-elimination mechanism. Consequently, their purification and the following ketone protection steps were difficult, even under mild conditions.[17] Due to the instability of amino ketones **8**, we modified the synthetic scheme by changing the nitrogen protecting group to a benzyl carbamate (Scheme 5). In fact, the introduction of an electron-withdrawing group caused the nucleophilicity of the nitrogen atom to decrease, thus avoiding β-elimination.



Scheme 3. 1,4-addition of Davies amine to α,β-unsaturated Weinreb amide.



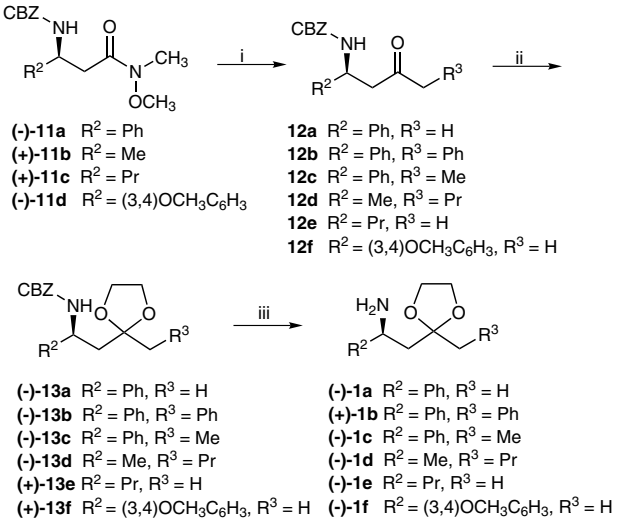
Scheme 4. Reagents: (i) (+)-**4**, THF, −78 °C ((+)-**3a**: 78%; (−)-**3b**: 97%; (+)-**3c**: 77% (+)-**3d**: 86%); (ii) *N*-*O*-dimethylhydoxylamine hydrochloride, trimethylaluminium, CH_2Cl_2, rt ((+)-**2a**: 80%; (+)-**2b**: 87%; (+)-**2c**: 94%; (+)-**2d**: 77%); (iii) 3 equiv CH_3MgBr, THF, 0 °C (**8a**: 64%; **8b**: 85%); (iv) silica gel chromatography or ethylene glycol, *p*TsOH, toluene reflux.



Scheme 5. Reagents: (i) $H_2/Pd(OH)_2/C$ 4 atm, MeOH/AcOH/H_2O ((−)-**10a**: 90%; **10b**: not isolated; (−)-**10c**: 80%; (−)-**10d**: 83%); (ii) 2 equiv CBzCl, CH_2Cl_2/Na_2CO_3 aq 0.4 M, rt ((−)-**11a**: 80%; (+)-**11b**: 70% from (+)-**2b**; (+)-**11c**; 88% (−)-**11d**: 88%).

Thus, the two benzylic groups of amides **2** were cleaved by hydrogenolysis in the presence of Pearlman's catalyst[18] and amines **10** thus obtained were used in the reaction without further purification, with benzyl chloroformate under Schotten–Bauman conditions.[19] Amides **11** were thus obtained in two steps in yields of up to 70%. At this stage, the transformation of Weinreb amides **11** into ketones by the use of a Grignard reagent,[12,15] a critical key step of the synthetic pathway, was tested (Scheme 6).

The experimental conditions of this reaction were shown to be crucial for obtaining the β-aminoketals in good enantiomeric excess, depending mainly on the Grignard reagent used and the reaction temperature (see Table 1). The alkylation of Weinreb amides **11** by methylmagnesium bromide under the usual conditions



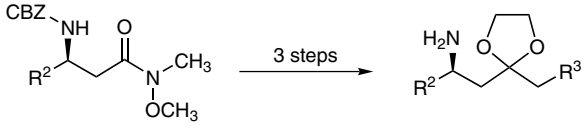
Scheme 6. Reagents: (i) for Grignard reagents and conditions used see Table 1; (ii) ethylene glycol, *p*TsOH, trimethylorthoformate, rt; (iii) HCO_2NH_4, Pd/C, MeOH, reflux. Overall three steps yields are given in Table 1.

(THF, 0 °C) led to expected results (entries 1, 5 and 6). Partial racemization of the stereogenic centre was observed when other Grignard reagents were used (entries 2–4). Diminution of the reaction temperature (THF, −20 °C) moderately improved the enantiomeric excess of the final β-aminoketones, but was prejudicial for the overall yield. These unexpected results could be related to the basicity of the Grignard reagent[20] leading to deprotonation of the molecule, involving three possible mechanisms (Scheme 7). The first one could be due to the deprotonation of carbon at the α-position of the carbonyl group, which in turn led to a β-elimination. The lithium amide thus generated could then react again in an aza-Michael reaction resulting in the racemization of the stereogenic centre. The second one involved deprotonation of the nitrogen atom, which would allow a reversible aldol-type reaction to racemise the substrate. The last mechanism, while unlikely, was related to inversion of the carbanion[21] resulting from the deprotonation of the carbon in the α-position of the nitrogen atom substituted by a carbamate group.[22] One way to lower the basicity of the organometallic reagent was to shift the Schlenk equilibrium towards the formation of a dialkyl magnesium species, which offers a weaker basicity than the corresponding alkylmagnesium halide[23] (Scheme 8). The addition of 1 equiv of dioxane to a solution of commercial Grignard reagent led to the formation of dihalide magnesium salts. The resulting supernatant solution was transferred into a solution of Weinreb amide in THF at room temperature to afford ketones **12**. Treatment of crude ketones **12** with ethylene glycol in trimethylorthoformate led to the keto-protected adducts **13**.[24] Finally, deprotection of the nitrogen atom by ammonium formate in the presence of palladium on charcoal gave the desired ketoprotected 1,3-aminoketones **1** in, three steps, in satisfactory overall yield (see Table 1). The enantiomeric excess of compounds **1** were measured by NMR spectroscopy on benzylisocyanate derivatives[25] by comparison with racemic compounds. The results thus obtained prove that no racemization takes place under these conditions.

3. Conclusion

In conclusion, we have developed an enantioselective and versatile synthesis of ketoprotected 1,3-aminoketones in seven steps. Thus, we have prepared seven amines in about 25% overall yield in very good enantiomeric excess (>90%). Although relatively long, our synthetic pathway has the advantage of being extremely stereoselective and could be generally applied to the preparation of a large number of diversely substituted β-aminoketals. These compounds could be used to obtain enantiomerically pure piperidines with various functional groups, which are useful precursors of complex alkaloids. This work is currently in progress and will be published in due course.

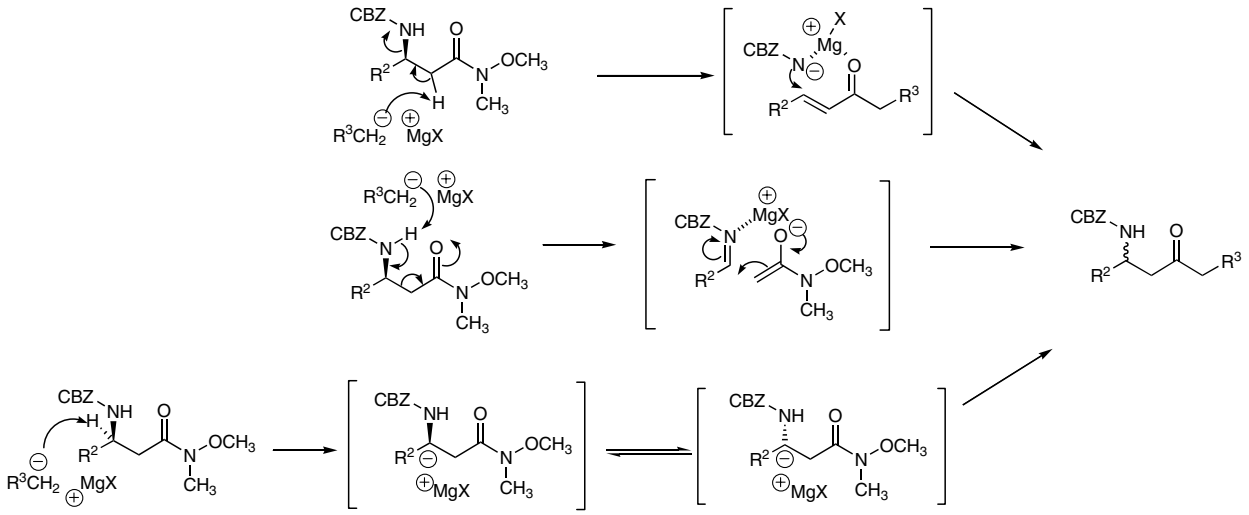
Table 1. Three-step synthesis of ketoprotected β-aminoketones **1** from corresponding β-amido Weinreb amides **11**



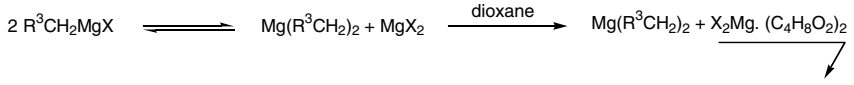
Weinreb amides **11** β-aminoketals **1**

Entry	Grignard reagent	β-Aminoketal	Conditions for alkylation of Weinreb amide with Grignard's reagent					
			THF, 0 °C		THF, −20 °C		THF/dioxane, rt	
			Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	MeMgBr	**1a**	58	92	40	93	57	93
2	BnMgCl	**1b**	60	50	50	90	42	90
3	EtMgCl	**1c**	54	32	45	69	40	92
4	BuMgCl	**1d**	61	46	50	51	49	95
5	MeMgBr	**1e**	49	98	—	—	53	95
6	MeMgBr	**1f**	54	91	—	—	55	92

[a] Overall yields for the three steps from Weinreb amides **11** to ketoprotected β-aminoketones **1**.
[b] Determined by NMR on the benzylisocyanate derivatives of β-aminoketals **1** by comparison with the racemic compounds.[25]



Scheme 7. Three racemization mechanisms of ketones **12** considered.



Scheme 8. Shift of Schlenk equilibrium by forming precipitate salts of magnesium dihalide with dioxane.

4. Experimental

4.1. General information

Unless otherwise specified, reagents were obtained from commercial suppliers. Solvents were dried and freshly distilled following the usual procedures. Product organic solutions were dried over sodium sulfate prior to evaporation of the solvents under reduced pressure on a rotatory evaporator. Thin layer chromatography was performed on TLC precoated aluminium backed silica plates and spots were visualized using UV light (254 nm) before using ethanolic phosphomolybdic acid solution (heating). Column chromatography was carried out on silica gel (70–230 mesh). ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz, respectively. Chemicals shifts are reported in ppm relative to $SiMe_4$. Signals are quoted s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and coupling constant (J) values are given in Hz. Infrared spectra were recorded on a FTIR spectrophotometer. High resolution electro spray impact mass spectra (HR-ESI-MS) were obtained from the Centre Régional de Mesures Physiques de l'Université Blaise Pascal (Clermont II), France. Optical rotations were measured at 589 nm and are given in units of 10^{-1} deg cm^2 g^{-1}.

4.2. 3-Phenyl-(*N*-methoxy-*N*-methyl)propene amide 6a[26]

To a solution of cinnamic acid (3.00 g, 20 mmol) in anhydrous dichloromethane (50 mL), freshly distilled pyridine (1.80 mL, 22 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (2.2 g, 22 mmol) and CBr_4 (7.4 g, 22 mmol) were added. Triphenyl phosphine (5.9 g, 22 mmol) was then added in small portions and the resulting solution stirred at room temperature until TLC indicated that the reaction had gone to completion. The solvent was evaporated under reduced pressure and the crude product purified by column chromatography on silica gel (ethyl acetate/cyclohexane 1:3) to afford 2.6 g (67%) of α,β-unsaturated amide **6a** as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (1H, d, $J = 16$ Hz, C(3)*H*), 7.60–7.55 (2H, m, *Ph*), 7.42–7.36 (3H, m, *Ph*), 7.04 (1H, d, $J = 16$ Hz, C(2)*H*), 3.77 (3H, s, OCH_3), 3.32 (3H, s, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.5, 135.2, 129.9, 128.9, 128.1, 115.8, 62.0, 32.6.

4.3. (±)-(3*S*,α*R*)-3-(*N*-Benzyl-*N*-α-methylbenzylamino)-3-phenyl-(*N*′-methyl)propanamide 7a

To a cold (0 °C) solution of *N*-benzyl-*N*-α-methyl benzylamine (±)-**4** (0.80 mL, 3.9 mmol) in dry THF (10 mL) was slowly added under argon, *n*-butyllithium solution 1.6 M in hexanes (2.60 mL, 4.1 mmol). The resultant pink solution of lithium amide was stirred for 15 min and then cooled to −78 °C before dropwise addition of a solution of α,β-unsaturated amide **6a** (0.48 g, 2.5 mmol) in dry THF (5 mL). The mixture was stirred at −78 °C until TLC showed no starting conjugated amide. A saturated aqueous solution of NH_4Cl was then added dropwise and the resulting solution allowed to warm to room temperature. β-Aminoamide (±)-**7a** was then extracted with diethyl ether. Combined organic extracts were dried, filtered and evaporated. The crude product was purified by column chromatography on silica gel (ethyl acetate/cyclohexane 1:1) to afford 0.72 g (71%) of amide (±)-**7a** as a pale yellow solid: mp 104.5 °C; de = 92% (NMR data); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.20 (15H, m, *Ph*), 5.82 (1H, d, $J = 4.9$ Hz, N*H*), 4.35 (1H, t, $J = 7.5$ Hz, C(3)*H*), 4.15 (1H, q, $J = 6.9$ Hz, C(α)*H*), 3.91 (1H, d,

$J = 14.4$ Hz, CH_2Ph), 3.67 (1H, d, J=14.4 Hz, CH_2Ph), 2.85 (1H, dd, $J = 15.0$ and 7.9 Hz, C(2)H_A), 2.51 (3H, d, $J = 4.9$ Hz, NCH_3), 2.38 (1H, dd, $J = 15.0$ and 6.9 Hz, C(2)H_B), 1.20 (3H, d, $J = 6.9$ Hz, C(α)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 144.1, 141.6, 141.1, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.5, 127.0, 126.8, 60.4, 56.1, 51.0, 40.7, 25.8, 14.0; IR (KBr pellet) ν 3330, 3080, 3050, 3021, 2970, 2934, 2875, 1651, 1558, 1492, 1450, 1302, 1204, 1154, 1119, 1027 cm^{-1}; HR-ESI-MS calculated for $C_{25}H_{29}N_2O$: $(M+H)^+$ 373.2280, found 373.2298.

4.4. General procedure for the preparation of β-amino-esters 3

To a cold (0 °C) solution of (+)-(*R*)-*N*-benzyl-*N*-α-methyl benzylamine **4** (1.1 equiv) in dry THF [5 mL/mmol of (+)-**4**] was added slowly under argon, *n*-butyllithium solution 1.6 M in hexanes (1.2 equiv). The resultant pink solution of lithium amide was stirred for 15 min then cooled to −78 °C before the dropwise addition of a solution of α,β-unsaturated ester **5** (1 equiv) in dry THF (2 mL/mmol of **5**). The mixture was stirred at −78 °C until TLC showed no starting conjugated ester. Then, a saturated aqueous solution of NH_4Cl was added dropwise and the resulting solution was allowed to warm to room temperature. β-Aminoester **3** was then extracted with diethylether. Combined organic extracts were dried, filtered and evaporated. The crude product was purified by column chromatography.

4.4.1. Methyl (+)-(3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-propanoate 3a.[13c] Following the general procedure for preparation of β-aminoester, methyl cinnamate (10 g) and amine (+)-**4** (15.8 mL) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:9), β-aminoester (+)-**3a** as a yellow oil (18 g, 78%): de = 94% (NMR data); $[\alpha]_D^{25} = +5.6$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.20 (15H, m, *Ph*), 4.48 (1H, dd, $J = 5.7$ and 9.4 Hz, C(3)*H*), 4.04 (1H, q, $J = 6.7$ Hz, C(α)*H*), 3.79 (1H, d, $J = 14.6$ Hz, CH_2Ph), 3.70 (1H, d, $J = 14.6$ Hz, CH_2Ph), 3.50 (3H, s, OCH_3), 2.73 (1H, dd, $J = 14.8$ and 5.7 Hz, C(2)H_A), 2.60 (1H, dd, $J = 14.8$ and 9.4 Hz, C(2)H_B), 1.25 (3H, d, $J = 6.7$ Hz, C(α)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 144.1, 141.7, 141.4, 128.8, 128.6, 128.3, 128.1, 127.9, 127.5, 127.3, 126.7, 126.4, 59.3, 56.3, 51.5, 50.8, 37.5, 15.8; IR (neat) ν 3062, 2966, 2931, 1736, 1602, 1494, 1453, 1216 cm^{-1}; HR-ESI-MS calculated for $C_{25}H_{28}NO_2$: $(M+H)^+$ 374.2120, found 374.2116.

4.4.2. Methyl (−)-(3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 3b.[13c] Following the general procedure for the preparation of β-aminoester, methyl crotonate (4.6 mL) and amine (+)-**4** (9.9 mL) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:5), β-aminoester (−)-**3b** as a pale yellow oil (13 g, 97%): de = 95% (NMR data); $[\alpha]_D^{25} = -1.2$ (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.21 (10H, m, *Ph*), 3.92 (1H, q, J=6.9 Hz, C(α)*H*), 3.76 (1H, d, $J = 14.6$ Hz, CH_2Ph), 3.72 (1H, d, $J = 14.6$ Hz, CH_2Ph), 3.53 (3H, s, OCH_3), 3.48 (1H, m, C(3)*H*), 2.40 (1H, dd, $J = 14.3$ and 6.2 Hz, C(2)H_A), 2.15 (1H, dd, $J = 14.3$ and 7.9 Hz, C(2)H_B), 1.38 (3H, d, $J = 6.9$ Hz, C(α)*Me*), 1.17 (3H, d, $J = 6.6$ Hz, C(4)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 144.3, 141.7, 128.4, 128.2, 128.1, 128.0, 127.8, 126.7, 57.6, 51.4, 50.0, 49.6, 39.8, 18.6, 17.6; IR (neat) ν 3061, 3025, 2950, 2920, 1735, 1641, 1492, 1450, 1296, 1201, 1158, 1058; HR-ESI-MS calculated for: $C_{20}H_{26}NO_2$ $(M+H)^+$ 312.1964, found 312.1969.

4.4.3. Methyl (+)-(3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)hexanoate 3c.[27] Following the general procedure for preparation of β-aminoester, methyl hex-2-enoate (5.5 g) and amine (+)-**4** (10.0 mL) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:9), β-aminoester (+)-**3c** as a pale yellow oil (11.2 g, 77%): de = 97% (NMR data); $[\alpha]_D^{25} = +14.9$ (*c* 1.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.25 (10H, m, *Ph*), 3.90 (1H, q, $J = 7.0$ Hz, C(α)*H*), 3.80 (1H, d, J=14.8 Hz, CH_2Ph), 3.62 (1H, d, $J = 14.8$ Hz, CH_2Ph), 3.59 (3H, s, OCH_3), 3.38 (1H, m, C(3)*H*), 2.10 (2H, m, C(2)H_2), 1.70–1.53 (2H, m, C(4)H_2), 1.48 (3H, d, $J = 7.0$ Hz, C(α)*Me*), 1.35–1.23 (2H, m, C(5)H_2), 0.94 (3H, t, $J = 6.9$ Hz, C(6)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 143.0, 141.5, 128.1, 128.0, 127.9, 127.8, 126.7, 126.5, 57.6, 53.6, 51.1, 49.8, 36.4, 35.7, 20.1, 19.2, 14.0; IR (neat) ν 3060, 2958, 1726, 1602, 1494, 1452, 1361, 1303, 1264; HR-ESI-MS calculated for: $C_{22}H_{30}NO_2$ $(M+H)^+$ 340.2277, found 340.2289.

4.4.4. Methyl (+)-(3*S*,α*R*)-3-(3,4-dimethoxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate 3d.[28] Following the general procedure for the preparation of β-aminoester, methyl 3,4-dimethoxycinnamate (5.0 g) and amine (+)-**4** (5.20 mL) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:9), β-aminoester (+)-**3d** as a pale yellow oil (8.5 g, 86%): de = 92% (NMR data); $[\alpha]_D^{25} = +2.0$ (*c* 1.2, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.15 (10H, m, *Ph*), 6.80 (3H, m, Ar*H*), 4.40 (1H, dd, $J = 9.5$ and 5.5 Hz, C(3)*H*), 4.04 (1H, q, $J = 7.0$ Hz, C(α)*H*), 3.94 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.75 (2H, s, CH_2Ph), 3.50 (3H, s, OCH_3), 2.67 (1H, dd, $J = 15.0$ and 5.5 Hz, C(2)H_A), 2.56 (1H, dd, $J = 15.0$ and 9.5 Hz, C(2)H_B), 1.25 (3H, d, $J = 7.0$ Hz, C(α)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 148.7, 148.1, 144.2, 141.5, 134.3, 128.2, 128.1, 127.9, 127.8, 126.9, 126.6, 119.7, 111.7, 110.7, 59.0, 57.1, 56.1, 55.9, 51.5, 50.7, 37.2, 16.6; IR (neat) ν 3061, 3045, 2930, 2834, 1731, 1604, 1514, 1454, 1254, 1143, 1028.

4.5. General procedure for the preparation of β-amino Weinreb amides 2

To a cold (0 °C) stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (2 equiv) in dry dichloromethane (5 mL/mmol of amine), a commercial 3.0 M solution of trimethylaluminium in hexane (2 equiv) was slowly added. The mixture was stirred at room temperature for 2 h and β-aminoester **3** (1 equiv) diluted in dichloromethane (2 mL/mmol of β-aminoester) added. The resulting solution was stirred at room temperature until TLC indicated that the reaction had gone to com-

pletion. Then, the mixture was carefully quenched with a saturated aqueous solution of NH_4Cl and extracted with dichloromethane. The organic extract was dried, filtered and concentrated in vacuo. The crude Weinreb amide **2** thus obtained was purified by column chromatography.

4.5.1. (+)-(3*S*,α*R*)-3-(*N*-Benzyl-*N*-α-methylbenzylamino)-3-phenyl-(*N*′-methoxy-*N*′-methyl)propanamide 2a.[8d] Following the general procedure for the preparation of β-amino Weinreb amide, β-aminoester (+)-**3a** (20 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:3), amide (+)-**2a** as a pale yellow oil (17.3 g, 80%): $[\alpha]_D^{25} = +12.7$ (*c* 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.15 (15H, m, *Ph*), 4.60 (1H, dd, $J = 9.7$ and 4.5 Hz, C(3)*H*), 4.01 (1H, q, $J = 6.7$ Hz, C(α)*H*), 3.78 (1H, d, $J = 15.0$ Hz, CH_2Ph), 3.72 (1H, d, $J = 15.0$ Hz, CH_2Ph), 3.31 (3H, s, OCH_3), 2.97 (3H, s, NCH_3), 2.86 (1H, m, C(2)H_A), 2.55 (1H, dd, $J = 15.6$ and 4.5 Hz, C(2)H_B), 1.30 (3H, d, $J = 6.7$ Hz, C(α)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 144.4, 142.8, 142.1, 128.7, 128.5, 128.3, 128.2, 128.1, 127.1, 126.8, 126.6, 126.4, 61.0, 59.1, 56.8, 51.0, 35.1, 32.1, 15.6; IR (neat) *v* 3064, 2935, 1662, 1602, 1494, 1452; HR-ESI-MS calculated for: $C_{26}H_{31}N_2O_2$ $(M+H)^+$ 403.2386, found 403.2376.

4.5.2. (+)-(3*R*,α*R*)-3-(*N*-Benzyl-*N*-α-methylbenzylamino)-(*N*′-methoxy-*N*′-methyl)butanamide 2b.[8d] Following the general procedure for the preparation of β-amino Weinreb amide, β-aminoester (+)-**3b** (12.8 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:3), amide (+)-**2b** as a pale yellow oil (12.2 g, 87%): $[\alpha]_D^{25} = +28.7$ (*c* 1.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.10 (10H, m, *Ph*), 3.83 (1H, q, $J = 6.9$ Hz, C(α)*H*), 3.73 (1H, d, $J = 14.8$ Hz, CH_2Ph), 3.63 (1H, d, $J = 14.8$ Hz, CH_2Ph), 3.44 (1H, m, C(3)*H*), 3.31 (3H, s, OCH_3), 2.98 (3H, s, NCH_3), 2.33–2.18 (2H, m, C(2)H_2), 1.28 (3H, d, $J = 6.9$ Hz, C(α)*Me*), 1.08 (3H, d, $J = 6.6$ Hz, C(4)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 144.6, 142.1, 128.4, 128.2, 128.1, 128.0, 127.7, 126.5, 61.0, 60.8, 58.0, 49.8, 49.5, 18.6, 18.3; IR (neat) *v* 3023, 2950, 2920, 1665, 1641, 1492, 1450, 1296, 1201, 1158, 1058; HR-ESI-MS calculated for: $C_{21}H_{29}N_2O_2$ $(M+H)^+$ 341.2229, found 341.2214.

4.5.3. (+)-(3*R*,α*R*)-3-(*N*-Benzyl-*N*-α-methylbenzylamino)-(*N*′-methoxy-*N*′-methyl)hexanamide 2c.[8d] Following the general procedure for the preparation of β-amino Weinreb amide, β-aminoester (+)-**3c** (11.5 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:3), amide (+)-**2c** as a yellow oil (11.7 g, 94%): $[\alpha]_D^{25} = +55.3$ (*c* 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.22 (10H, m, *Ph*), 3.88 (2H, m, CH_2Ph and C(α)*H*), 3.60 (1H, d, $J = 14.6$ Hz, CH_2Ph), 3.52 (1H, m, C(3)*H*), 3.43 (3H, s, OCH_3), 3.10 (3H, s, NCH_3), 2.24 (1H, m, C(2)*H*), 1.99 (1H, d, $J = 15.2$ Hz, C(2)*H*), 1.70 (1H, m, C(4)*H*), 1.54–1.38 (5H, m, C(4)*H*, C(5)*H* and C(α)*Me*), 1.28 (1H, m, C(5)*H*), 0.92 (3H, t, $J = 7.0$ Hz, C(6)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 143.2, 141.9, 128.4, 128.2, 128.1, 127.9, 126.7, 126.5, 60.8, 57.7, 52.8, 50.4, 36.3, 33.9, 32.9, 20.3, 20.1, 14.3; IR (neat) *v* 3025, 2957, 2935, 1663, 1584, 1493, 1452, 1218, 1027; HR-ESI-MS calculated for: $C_{23}H_{33}N_2O_2$ $(M+H)^+$ 369.2542, found 369.2538.

4.5.4. (+)-(3*S*,α*R*)-3-(3,4-Dimethoxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-(*N*′-methoxy-*N*′-methyl)propanamide 2d. Following the general procedure for the preparation of β-amino Weinreb amide, β-aminoester (+)-**3d** (8.3 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:3), amide (+)-**2d** as a yellow oil (6.9 g, 77%): $[\alpha]_D^{25} = +54.5$ (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.07 (10H, m, *Ph*), 6.93 (1H, d, $J = 1.8$ Hz, Ar*H*), 6.82 (1H, dd, $J = 8.2$ and 1.8 Hz, Ar*H*), 6.73 (1H, d, $J = 8.2$ Hz, Ar*H*), 4.45 (1H, dd, $J = 10.0$ and 4.4 Hz, C(3)*H*), 3.95 (1H, q, $J = 6.9$ Hz, C(α)*H*), 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.69 (1H, d, $J = 14.5$ Hz, CH_2Ph), 3.65 (1H, d, $J = 14.5$ Hz, CH_2Ph), 3.29 (3H, s, OCH_3), 2.91 (3H, s, NCH_3), 2.79 (1H, m, C(2)H_A), 2.42 (1H, dd, $J = 15.4$ and 4.4 Hz, C(2)H_B), 1.24 (3H, d, $J = 6.9$ Hz, C(α)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 155.5, 136.5, 127.9, 127.7, 128.2, 66.1, 61.0, 44.0, 37.2, 31.7, 20.3; IR (neat) *v* 3071, 3039, 2941, 2801, 1659, 1496, 1417, 1218, 1088, 1065; HR-ESI-MS calculated for: $C_{28}H_{35}N_2O_4$ $(M+H)^+$ 463.2597, found 463.2613.

4.6. General procedure for hydrogenolysis of benzyl groups

A mixture of amide **2** (1 equiv) in methanol (4.5 mL/mmol of **2**), acetic acid (0.12 mL/mmol of **2**) and water (0.45 mL/mmol of **2**) was treated with 20% palladium hydroxide on activated carbon (70 mg/mmol of **2**). The mixture was stirred under a hydrogen atmosphere (4 bar) for 3 days. The reaction mixture was filtered through Celite®, then washed with methanol and the filtrate concentrated under reduced pressure to give a residue which was treated with saturated aqueous bicarbonate solution and then extracted with dichloromethane. The aqueous layer was preserved to be used in the next step for protection of the amino group with benzyl carbamate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo. The crude amine **10** thus obtained was engaged without further purification in the next step.

4.6.1. (−)-(3*S*)-3-Amino-3-phenyl-(*N*-methoxy-*N*-methyl)-propanamide 10a. Following the general procedure for the hydrogenolysis of benzyl and α-methylbenzyl groups, β-amino Weinreb amide (+)-**2a** (16 g) afforded the crude primary amine (−)-**10a** as a yellow oil (7.4 g, 90%): $[\alpha]_D^{25} = -23.8$ (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.18 (5H, m, *Ph*), 4.51 (1H, dd, $J = 8.2$ and 4.9 Hz, C(3)*H*), 3.61 (3H, s, OCH_3), 3.18 (3H, s, NCH_3), 2.76 (2H, m, C(2)H_2), 1.84 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 145.1, 128.5, 127.1, 126.4, 61.1, 52.2, 41.7, 32.5; IR (neat) *v* 3375, 3311, 3065, 3011, 2940, 2868, 2822, 1651, 1587, 1495, 1454, 1381, 1238, 1179; HR-ESI-MS calculated for: $C_{11}H_{17}N_2O_2$ $(M+H)^+$ 209.1290, found 209.1283.

4.6.2. (3*R*)-3-Amino-(*N*-methoxy-*N*-methyl)butanamide 10b. Following the general procedure for the hydrogenolysis of benzyl and α-methylbenzyl groups, β-amino Weinreb amides (+)-**2b** (12 g) afforded crude primary amine **10b** as a yellow oil (4.1 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s, OCH_3), 3.27 (1H, m, C(3)H), 3.30 (2H, br s, NH_2), 3.16 (3H, s, NCH_3), 2.55–2.35 (2H, m, C(2)H_2), 1.18 (3H, d, $J = 6.6$ Hz, C(4)H_3).

4.6.3. (−)-(3*R*)-3-Amino-(*N*-methoxy-*N*-methyl)hexanamide 10c. Following the general procedure for the hydrogenolysis of benzyl and α-methylbenzyl groups, β-amino Weinreb amides (+)-**2c** (9.8 g) afforded crude primary amine (−)-**10c** as a yellow oil (3.7 g, 80%): $[\alpha]_D^{25} = -23.3$ (*c* 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (3H, s, OCH_3), 3.22 (1H, m, C(3)H), 3.14 (3H, s, NCH_3), 2.52 (1H, br d, $J = 15.7$ Hz, C(2)H_A), 2.34 (1H, dd, $J = 15.7$ and 9.7 Hz, C(2)H_B), 2.08 (2H, br s, NH_2), 1.43–1.26 (4H, m, C(4)H_2 and C(5) H_2), 0.89 (3H, t, $J = 7.0$ Hz, C(6)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 61.1, 47.5, 39.6, 31.9, 19.7, 19.6, 14.0; IR (neat) *v* 3392, 3376, 2958, 2927, 2854, 1652, 1492, 1450, 1370, 1265.

4.6.4. (−)-(3*S*)-3-Amino-3-(3,4-dimethoxyphenyl)-(*N*-methoxy-*N*-methyl)propanamide 10d. Following the general procedure for the hydrogenolysis of benzyl and α-methylbenzyl groups, β-amino Weinreb amides (+)-**2d** (6.4 g) afforded crude primary amine (−)-**10d** as a yellow oil (3.1 g, 83%): $[\alpha]_D^{25} = -13.3$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (1H, d, $J =$ 2.0 Hz, ArH), 6.87 (1H, dd, $J =$ 8.2 and 2.0 Hz, ArH), 6.76 (1H, d, $J = 8.2$ Hz, ArH), 4.40 (1H, dd, $J = 9.1$ and 4.2 Hz, C(3)H), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.56 (3H, s, OCH_3), 3.11 (3H, s, NCH_3), 3.00 (2H, br s, NH_2), 2.80–2.66 (2H, m, C(2)H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 148.7, 147.9, 136.8, 118.2, 110.8, 109.4, 60.9, 55.6, 51.6, 40.8, 31.7; IR (neat) *v* 3368, 3301, 3013, 2935, 2834, 1659, 1591, 1453, 1235.

4.7. General procedure for protection of amine 10 by a benzyl carbamate group

Amine **10** (1 equiv) was dissolved in dichloromethane (4 mL/mmol of 10) and 0.4 M aqueous sodium carbonate (2 equiv). The aqueous layer of the previous step was then added and the mixture cooled to 0 °C before the addition of benzylchloroformate (2 equiv). The ice bath was removed and the solution stirred at room temperature. After three hours, the solution was diluted with dichloromethane and the combined organic material washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. The crude amide **11** thus obtained was purified by column chromatography.

4.7.1. (−)-(3*S*)-3-(*N*-Benzyloxycarbonylamino)-3-phenyl-(*N*′-methoxy-*N*′-methyl)propanamide 11a. Following the general procedure for the protection of amine **10** by a benzyl carbamate group, β-amino Weinreb amide (−)-**10a** (5.0 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:1), N-protected β-amino Weinreb amide (−)-**11a** as a white solid (6.6 g, 80%): mp 122.0 °C; $[\alpha]_D^{25} = -6.9$ (*c* 1.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.22 (10H, m, *Ph*), 6.43 (1H, br s, NH), 5.18 (1H, dd, $J = 9.7$ and 4.5 Hz, C(3)H), 5.10 (1H, d, $J = 14.0$ Hz, OCH_2Ph), 5.05 (1H, d, $J = 14.0$ Hz, OCH_2Ph), 3.49 (3H, s, OCH_3), 3.09 (4H, m, NCH_3 and C(2)H_A), 2.85 (1H, dd, $J =$ 15.7 and 4.8 Hz, C(2)H_B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 155.6, 141.6, 136.5, 128.4, 128.3, 127.8, 127.3, 127.2, 126.1, 66.5, 61.0, 51.7, 37.4, 31.7; IR (KBr pellet) *v* 3424, 3007, 2882, 1717, 1654, 1503, 1274, 1048; HR-ESI-MS calculated for: $C_{19}H_{22}N_2O_4Na$ $(M+Na)^+$ 365.1477, found 365.1481.

4.7.2. (+)-(3*R*)-3-(*N*-Benzyloxycarbonylamino)-(*N*′-methoxy-*N*′-methyl)butanamide 11b. Following the general procedure for the protection of amine **10** by a benzyl carbamate group, β-amino Weinreb amide **10b** afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:3), N-protected β-amino Weinreb amide (+)-**11b** as a white solid (6.9 g, overall yield from tertiary amine (+)-**2b**: 70%): mp 60.5 °C; $[\alpha]_D^{25} = +8.3$ (*c* 1.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (5H, m, *Ph*), 5.71 (1H, br s, NH), 5.08 (2H, s, OCH_2Ph), 4.13 (1H, m, C(3)H), 3.65 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 2.76 (1H, dd, $J = 15.4$ and 3.5 Hz, C(2)H_A), 2.57 (1H, dd, $J = 15.4$ and 4.2 Hz, C(2)H_B), 1.27 (3H, d, $J = 6.6$ Hz, C(4)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 155.5, 136.6, 128.3, 127.9, 127.8, 66.3, 61.1, 44.0, 37.2, 31.8, 20.4; IR (KBr pellet) *v* 3328, 3052, 3032, 2965, 2937, 2819, 1706, 1649, 1531, 1497, 1458, 1388, 1372, 1279, 1219, 1210, 1053; HR-ESI-MS calculated for: $C_{14}H_{21}N_2O_4$ $(M+H)^+$ 281.1501, found 281.1509.

4.7.3. (+)-(3*R*)-3-(*N*-Benzyloxycarbonylamino)-(*N*′-methoxy-*N*′-methyl)hexanamide 11c. Following the general procedure for the protection of amine **10** by a benzyl carbamate group, β-amino Weinreb amide (−)-**10c** (3.7 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:1), N-protected β-amino Weinreb amide (+)-**11c** as a pale yellow oil (5.8 g, 88%): $[\alpha]_D^{25} = +15.1$ (*c* 2.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (5H, m, *Ph*), 5.62 (1H, br d, $J = 8.2$ Hz, NH), 5.08 (2H, s, OCH_2Ph), 4.00 (1H, m, C(3)H), 3.65 (3H, s, OCH_3), 3.15 (3H, s, NCH_3), 2.75 (1H, br d, $J = 15.0$ Hz, C(2)H_A), 2.59 (1H, d, $J = 15.2$ Hz, C(2)H_B), 1.74–1.21 (4H, m, C(4)H_2 and C(5)H_2), 0.91 (3H, t, $J = 7.0$ Hz, C(6)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 156.0, 136.8, 128.4, 128.0, 127.9, 66.3, 61.2, 48.1, 36.6, 35.9, 31.9, 19.6, 13.8; IR (neat) *v* 3324, 3064, 3033, 2959, 2936, 2873, 1714, 1660, 1538, 1455, 1361, 1303, 1264; HR-ESI-MS calculated for: $C_{16}H_{25}N_2O_4$ $(M+H)^+$ 309.1814, found 309.1824.

4.7.4. (−)-(3*S*)-3-(*N*-Benzyloxycarbonylamino)-3-(3,4-dimethoxyphenyl)-(*N*′-methoxy-*N*′-methyl)propanamide 11d. Following the general procedure for the protection of amine **10** by a benzyl carbamate group, β-amino Weinreb amide (−)-**10d** (3.0 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:1), N-protected β-amino Weinreb amide (−)-**11d** as a white solid (4.0 g, 88%): mp 78.0 °C $[\alpha]_D^{25} = -16.2$ (*c* 1.29, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (5H, m, *Ph*), 6.86 (2H, m, Ar*H*), 6.81 (1H, d, $J = 8.0$ Hz, Ar*H*), 6.37 (1H, br s, N*H*), 5.13–5.05 (3H, m, OCH_2Ph and C(3)*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 3.09 (4H, m, NCH_3 and C(2)H_A), 2.82 (1H, dd, $J = 15.4$ and 5.0 Hz, C(2)H_B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 155.2, 148.8, 148.0, 136.4, 134.3, 128.2, 127.8, 118.2, 111.0, 109.4, 66.4, 61.0, 55.7, 55.6, 51.5, 37.3, 31.7; IR (KBr pellet) ν 3340, 3071, 3049, 2934, 1861, 1713, 1666, 1592, 1515, 1450, 1238, 1142, 1119; HR-ESI-MS calculated for: $C_{21}H_{27}N_2O_6$ $(M+H)^+$ 403.1869, found 403.1878.

4.8. General procedure for the alkylation of amide 11

To a commercial solution of Grignard reagent (3 equiv) in diethyl ether at room temperature, 3 equiv of dry dioxane was added. A white precipitate formed immediately and the mixture stirred at room temperature for 15 min. Then, the mixture was poured off and the solution containing the dialkyl magnesium species transferred dropwise at room temperature into a solution of amide **11** in dry THF (5 mL/mmol of **11**). After 30 min, a saturated aqueous solution of ammonium chloride was added. The mixture was then extracted with diethyl ether. Combined organic extracts were dried, filtered and evaporated. Crude ketone **12** so obtained was directly engaged into the ketoprotection step.

4.8.1. (4*S*)-4-(*N*-Benzyloxycarbonylamino)-4-phenylbutan-2-one 12a. Following the general procedure for the alkylation of amide **11**, N-protected β-amino Weinreb amide (−)-**11a** (0.40 g) treated with methylmagnesium bromide solution afforded crude ketone **12a** as a yellow oil (0.35 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (10H, m, *Ph*), 5.92 (1H, d, $J = 7.8$ Hz, N*H*), 5.18 (1H, dd, $J = 13.3$ and 6.4 Hz, C(4)*H*), 5.12 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 5.07 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 3.16–3.06 (1H, m, C(3)H_A), 2.92 (1H, dd, $J = 16.2$ and 5.9 Hz, C(3)H_B), 2.08 (3H, s, C(1)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 155.6, 141.1, 136.3, 128.6, 128.4, 128.0, 127.8, 127.5, 126.2, 66.7, 51.4, 48.3, 30.5.

4.8.2. (4*S*)-4-(*N*-Benzyloxycarbonylamino)-1,4-diphenylbutan-2-one 12b. Following the general procedure for the alkylation of amide **11**, N-protected β-amino Weinreb amide (−)-**11a** (0.50 g) treated with benzylmagnesium chloride solution afforded crude ketone **12b** as a yellow oil (0.60 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.09 (15H, m, *Ph*), 5.68 (1H, br s, N*H*), 5.07–5.02 (1H, m, C(4)*H*), 5.00 (1H, d, $J = 17.4$ Hz, OCH_2Ph), 4.95 (1H, d, $J = 17.4$ Hz, OCH_2Ph), 3.48 (2H, s, C(1)H_2), 3.03–2.93 (1H, m, C(3)H_A), 2.84–2.78 (1H, m, C(3)H_B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 155.6, 141.8, 136.4, 133.3, 129.4, 128.8, 128.7, 128.5, 128.3, 127.5, 127.2, 126.2, 125.9, 66.8, 51.4, 50.8, 46.9.

4.8.3. (1*S*)-1-(*N*-Benzyloxycarbonylamino)-1-phenylpentan-3-one 12c. Following the general procedure for the alkylation of amide **11**, N-protected β-amino Weinreb amide (−)-**11a** (0.40 g) treated with ethylmagnesium chloride solution afforded crude ketone **12c** as a yellow oil (0.36 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.12 (10H, m, *Ph*), 5.85 (1H, br s, N*H*), 5.05 (1H, m, C(1)*H*), 5.03 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 4.98 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 2.92 (1H, br d, $J = 14.8$ Hz, C(2)H_A), 2.75 (1H, dd, $J = 14.8$ and 4.8 Hz, C(2)H_B), 2.22 (2H, q, $J = 7.2$ Hz, C(4)H_2), 0.84 (3H, t, $J = 7.2$ Hz, C(5)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 155.5, 144.5, 136.4, 128.7, 128.6, 128.5, 127.5, 126.2, 126.1, 66.8, 66.7, 47.6, 36.8, 7.4.

4.8.4. (2*R*)-2-(*N*-Benzyloxycarbonylamino)octan-4-one 12d. Following the general procedure for the alkylation of amide **11**, N-protected β-amino Weinreb amide (+)-**11b** (0.80 g) treated with butylmagnesium chloride solution afforded crude ketone **12d** as a yellow oil (0.79 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m, *Ph*), 5.36 (1H, m, N*H*), 5.00 (2H, s, OCH_2Ph), 3.96 (1H, m, C(2)*H*), 2.60 (1H, m, C(3)H_A), 2.45 (1H, m, C(3)H_B), 2.28 (2H, m, C(5)H_2), 1.45 (2H, m, C(6)H_2), 1.18 (2H, m, C(7)H_2), 1.10 (3H, d, $J = 7.1$ Hz, C(1)H_3); 0.80 (3H, t, $J = 7.5$ Hz, C(8)H_3).

4.8.5. (4*R*)-4-(*N*-Benzyloxycarbonylamino)heptan-2-one 12e. Following the general procedure for the alkylation of amide **11**, N-protected β-amino Weinreb amide (+)-**11c** (1.20 g) treated with methylmagnesium bromide solution afforded crude ketone **12e** as a yellow oil (1.10 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.22 (5H, m, *Ph*), 5.07 (1H, br d, $J = 8.8$ Hz, N*H*), 4.93 (2H, s, OCH_2Ph), 3.89 (1H, m, C(4)*H*), 2.60 (2H, m, C(3)H_2), 2.07 (3H, s, C(1)H_3), 1.51–1.15 (4H, m, C(5)H_2 and C(6)H_2), 0.83 (3H, t, $J = 7.0$ Hz, C(7)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 155.9, 136.6, 128.5, 128.1, 128.0, 66.5, 47.8, 36.6, 30.5, 19.5, 13.8.

4.8.6. (4*S*)-4-(*N*-Benzyloxycarbonylamino)-4-(3,4-dimethoxyphenyl)butan-2-one 12f. Following the general procedure for the alkylation of amide **11**, N-protected β-amino Weinreb amide (−)-**11d** (0.26 g) treated with methylmagnesium bromide solution afforded crude ketone **12f** as a yellow oil (0.24 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (5H, m, *Ph*), 6.88–6.77 (3H, m, Ar*H*), 5.86 (1H, br s, N*H*), 5.14–5.04 (3H, m, OCH_2Ph and C(4)*H*), 3.83 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.03 (1H, br d, $J = 15.0$ Hz, C(3)H_A), 2.88 (1H, dd, $J = 15.0$ and 4.5 Hz, C(3)H_B), 2.07 (3H, s, C(1)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 155.4, 148.7, 148.0, 136.2, 132.4, 128.1, 127.8, 118.0, 111.0, 109.7, 66.4, 55.6, 55.5, 48.9, 41.6, 30.2.

4.9. General procedure for the protection of ketones 12

A solution of ketone **12** (1 equiv), trimethylorthoformate (5 equiv), ethylene glycol (5 equiv) and *para*-toluene sulfonic acid (0.04 equiv) was stirred at room temperature until TLC showed no starting ketone. The mixture was then diluted with dichloromethane and washed with a saturated aqueous solution of sodium hydrogenocarbonate. The organic layer was dried over sodium sulfate, filtered over Celite and concentrated in vacuo to afford crude ketoprotected adducts **13**.

4.9.1. (−)-(2′*S*)-2-[2′-(*N*-Benzyloxycarbonylamino)-2′-phenyl]-ethyl-2-methyl-1,3-dioxolane 13a. Following the general procedure for protection of ketones **12**, β-aminoketone **12a** (0.35 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:3), ketoprotected adduct **(−)-13a** as a colourless oil (0.24 g, 60%): $[\alpha]_D^{25} = -11.4$ (*c* 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (10H, m, *Ph*), 6.00 (1H, d, $J = 3.9$ Hz, N*H*), 5.13 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 5.06 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 4.90 (1H, m, C(2′)*H*), 4.90–3.88 (4H, m, C(4)H_2 and C(5)H_2), 2.11–2.09 (2H, m, C(1′)H_2), 1.36 (3H, s, C(2)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 140.1, 136.6, 128.6, 128.4, 128.3, 127.9, 126.9, 125.8, 109.0, 66.4, 64.8, 64.1, 52.2, 45.2, 24.0; IR (neat) ν 3346, 3060, 3033, 2983, 2882, 1685, 1534, 1496, 1450, 1373, 1253, 1043; HR-ESI-MS calculated for: $C_{20}H_{24}NO_4$ $(M+H)^+$ 342.1705, found 342.1696.

4.9.2. (−)-(2′*S*)-2-Benzyl-2-[2′-(*N*-benzyloxycarbonylamino)-2′-phenyl]-ethyl-1,3-dioxolane 13b. Following the general procedure for protection of ketones **12**, β-aminoketone **12b** (0.60 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:4), ketoprotected adduct **(−)-13b** as a white solid (0.30 g, 50%): mp 111.5 °C; $[\alpha]_D^{25} = -2.5$ (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.23 (15H, m, *Ph*), 5.88 (1H, d, $J = 5.1$ Hz, N*H*), 5.15 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 5.02 (1H, d, $J = 12.3$ Hz, OCH_2Ph), 4.94 (1H, m, C(2′)*H*), 3.90–3.73 (4H, m, C(4)H_2 and C(5)H_2), 2.94 (1H, d, $J = 13.9$ Hz, C(2)CH_2Ph), 2.87 (1H, d, $J = 13.9$ Hz, C(2)CH_2Ph), 2.11–1.97 (2H, m, C(1′)H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 140.1, 136.5, 136.0, 130.6, 128.5, 128.4, 128.1, 127.0, 126.6, 125.9, 110.5, 66.5, 65.6, 64.8, 52.0, 44.3, 44.1; IR (KBr pellet) ν 3333, 3062, 3033, 2959, 1688, 1537, 1497, 1451, 1258, 1027; HR-ESI-MS calculated for: $C_{26}H_{28}NO_4$ $(M+H)^+$ 418.2018, found 418.2009.

4.9.3. (−)-(2′S)-2-Ethyl-2-[2′-(*N*-benzyloxycarbonylamino)-2′-phenyl]-ethyl-1,3-dioxolane 13c. Following the general procedure for the protection of ketones **12**, β-aminoketone **12c** (0.36 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:1), ketoprotected adduct (−)-**13c** as a colourless oil (0.17 g, 42%): $[\alpha]_D^{25} = -7.5$ (*c* 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.16 (m, 10H, *Ph*), 5.88 (1H, br s, N*H*), 5.01 (1H, d, $J = 12.0$ Hz, OCH_2Ph), 4.93 (1H, d, $J = 12.0$ Hz, OCH_2Ph), 4.74 (1H, m, C(2′)*H*), 3.94–3.72 (4H, m, C(4)H_2 and C(5)H_2), 1.93 (2H, m, C(1′)H_2), 1.56 (2H, q, $J = 7.5$ Hz, C(2)CH_2CH$_3$), 0.82 (3H, t, $J = 7.5$ Hz, C(2)CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 143.6, 136.7, 128.9, 128.5, 128.0, 127.6, 127.1, 125.9, 66.5, 65.3, 64.6, 52.3, 43.0, 30.3, 8.1; IR (neat) ν 3428, 3032, 3016, 2976, 2886, 1717, 1507, 1455, 1261, 1236, 1074, 1043; HR-ESI-MS calculated for: $C_{21}H_{25}NO_4Na$ $(M+Na)^+$ 378.1681, found 378.1696.

4.9.4. (−)-(2′*R*)-2-Butyl-2-(2′-*N*-benzyloxycarbonylamino)-propyl-1,3-dioxolane 13d. Following the general procedure for protection of ketones **12**, β-aminoketone **12d** (0.79 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:3), ketoprotected adduct (−)-**13d** as a yellow oil (0.50 g, 54%): $[\alpha]_D^{25} = -3.6$ (*c* 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (5H, m, *Ph*), 5.36 (1H, br s, N*H*), 5.12 (2H, m, OCH_2Ph), 4.00–3.80 (5H, m, C(4)H_2, C(5)H_2 and C(2′)*H*), 1.76 (2H, m, C(1′)H_2), 1.60 (2H, m, C(2)CH_2C$_3$H$_7$), 1.40–1.28 (4H, m, C(2)CH_2C$_2$$H_4CH_3$), 1.24 (3H, d, $J = 6.4$ Hz, C(3′)H_3), 0.91 (3H, t, $J = 7.1$ Hz, C(2)C$_3$H$_6$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 136.9, 128.4, 128.0, 127.9, 111.0, 66.3, 65.0, 64.5, 43.9, 43.1, 42.7, 37.14, 25.9, 22.9, 22.3, 14.0; IR (neat) ν 3344, 3032, 2955, 2872, 1720, 1512, 1454, 1375, 1340, 1238, 1157, 1090; HR-ESI-MS calculated for: $C_{18}H_{28}NO_4$ $(M+H)^+$ 322.2018, found 322.2017.

4.9.5. (+)-(2′R)-2-methyl-2-(2′-*N*-benzyloxycarbonylamino)-pentyl-1,3-dioxolane 13e. Following the general procedure for protection of ketones **12**, β-aminoketone **12e** (1.10 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:6), ketoprotected adduct (+)-**13e** as a yellow oil (0.65 g, 54%): $[\alpha]_D^{25} = +2.2$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (5H, m, *Ph*), 5.11 (3H, m N*H* and OCH_2Ph), 3.98–3.82 (5H, m, C(4)H_2, C(5)H_2 and C(2′)*H*), 1.87 (1H, br d, $J = 14.6$ Hz, C(1′)H_A), 1.75 (1H, dd, $J = 14.6$ and 9.3 Hz, C(1′)H_B), 1.54–1.45 (2H, m, C(3′)H_2), 1.40–1.25 (5H, m, C(4′)H_2 and C(1)*Me*), 0.92 (3H, t, $J = 7.2$ Hz, C(5′)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 136.9, 128.4, 128.0, 127.5, 109.4, 66.3, 64.7, 64.1, 47.8, 42.9, 38.4, 24.0, 18.8, 14.0; IR (neat) ν 3338, 3033, 2958, 2934, 2874, 1704, 1537, 1455, 1379, 1253, 1102; HR-ESI-MS calculated for: $C_{17}H_{26}NO_4$ $(M+H)^+$ 308.1862, found 308.1858.

4.9.6. (+)-(2′S)-2-[-2′-(*N*-benzyloxycarbonylamino)-2′-(3,4-dimethoxyphenyl)]-ethyl-2-methyl-1,3-dioxolane 13f. Following the general procedure for protection of ketones **12**, β-aminoketone **12f** (0.20 g) afforded, after purification on silica gel (ethyl acetate/cyclohexane 1:1), ketoprotected adduct (+)-**13f** as a white solid (0.13 g, 60%): mp 88.0 °C; $[\alpha]_D^{25} = +0.9$ (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (5H, m, *Ph*), 6.87–6.76 (3H, m, Ar*H*), 5.87 (1H, m, C(2′)*H*), 5.11–5.01 (2H, m, OCH_2Ph), 4.79 (1H, br s, N*H*), 4.01–3.80 (10H, m, Ar(OCH_3)$_2$, C(4)H_2 and C(5)H_2), 2.08–1.99 (2H, m, C(1′)H_2), 1.32 (3H, s, C(1)*Me*); IR (KBr pellet) ν 3385, 3063, 3033, 2980, 2960, 2948, 2878, 1693, 1592, 1535, 1517, 1452, 1375, 1260, 1237, 1141, 1037; HR-ESI-MS calculated for: $C_{22}H_{28}NO_6$ $(M+H)^+$ 402.1917, found 402.1932.

4.10. General procedure for hydrogenolysis of a carbamate group

To a stirred solution of aminoketal **13** (1 equiv) in anhydrous methanol (5 mL/mmol of **13**) was added 10% Pd/C (40 mg/mmol of **13**) then ammonium formate (5 equiv). The resulting suspension was heated at reflux for 5 h. After cooling at room temperature, the catalyst was removed by filtration on Celite®. The residue obtained after evaporation of the solvent was diluted with dichloromethane. This organic phase was washed with a saturated aqueous solution of sodium hydrogenocar-

bonate. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried, filtered and then concentrated to afford pure β-aminoketal **1**.

4.10.1. (−)-(2′S)-2-(2′-Amino-2′-phenyl)-ethyl-2-methyl-1,3-dioxolane 1a. Following the general procedure for the hydrogenolysis of carbamates **13**, compound (−)-**13a** (0.24 g) afforded ketoprotected β-aminoketone (−)-**1a** as a yellow oil (0.14 g, 96%): $[\alpha]_D^{25} = -13.5$ (*c* 2.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.26 (5H, m, *Ph*), 4.29 (1H, dd, $J = 8.8$ and 3.4 Hz, C(2′)*H*), 4.09–4.01 (4H, m, C(4)H_2 and C(5)H_2), 2.40 (2H, br s, NH_2), 2.15–2.05 (2H, m, C(1′)H_2), 1.45 (3H, s, C(1)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 128.3, 126.8, 126.2, 109.6, 64.5, 64.1, 52.0, 47.5, 24.1; IR (neat) *v* 3382, 3310, 3086, 3065, 3029, 2986, 2956, 2888, 1602, 1493, 1453, 1378, 1224, 1043; HR-ESI-MS calculated for: $C_{12}H_{18}NO_2$ $(M+H)^+$ 208.1338, found 208.1347.

4.10.2. (+)-(2′S)-2-Benzyl-2-(2′-amino-2′-phenyl)-ethyl-1,3-dioxolane 1b. Following the general procedure for the hydrogenolysis of carbamates **13**, compound (−)-**13b** (0.25 g) afforded ketoprotected β-aminoketone (+)-**1b** as a yellow oil (0.15 g, 85%): $[\alpha]_D^{25} = +1.9$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–6.97 (10H, m, *Ph*), 4.07 (1H, m, C(2′)*H*), 3.80–3.73 (2H, m, C(4)H_2 or C(5)H_2), 3.61–3.51 (2H, m, C(5)H_2 or C(4)H_2), 2.80 (1H, d, $J = 13.9$ Hz, C(1)CH_2Ph), 2.73 (1H, d, $J = 13.9$ Hz, C(1)CH_2Ph), 1.88–1.73 (4H, m, C(1′)H_2 and NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 136.7, 128.4, 128.0, 126.9, 126.5, 126.4, 111.2, 65.2, 64.9, 51.9, 44.1, 39.9; IR (neat) *v* 3384, 3305, 3087, 3065, 3032, 3011, 2957, 2890, 1686, 1603, 1495, 1455, 1262, 1244, 1117, 1039; HR-ESI-MS calculated for: $C_{18}H_{22}NO_2$ $(M+H)^+$ 284.1651, found 284.1657.

4.10.3. (−)-(2′S)-2-Ethyl-2-(2′-amino-2′-phenyl)-ethyl-1,3-dioxolane 1c. Following the general procedure for the hydrogenolysis of carbamates **13**, compound (−)-**13c** (0.10 g) afforded ketoprotected β-aminoketone (−)-**1c** as a yellow oil (0.06 g, 96%): $[\alpha]_D^{25} = -18.0$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.08 (5H, m, *Ph*), 4.13 (1H, t, $J = 6.1$ Hz, C(2′)*H*), 3.98–3.86 (4H, m, C(4)H_2 and C(5)H_2), 1.90 (2H, d, $J = 6.1$ Hz, C(1′)H_2), 1.77 (2H, br s, NH_2), 1.78–1.63 (2H, m, C(2)CH_2), 0.85 (3H, t, $J = 7.4$ Hz, C(2)CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 128.4, 126.9, 126.3, 111.8, 65.0, 64.6, 52.0, 45.3, 30.1, 8.2; IR (neat) *v* 3380, 3311, 3019, 2976, 2942, 2885, 1602, 1493, 1455, 1380, 1062, 1028; HR-ESI-MS calculated for: $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1492.

4.10.4. (−)-(2′*R*)-2-Butyl-2-(2′-amino)-propyl-1,3-dioxolane 1d. Following the general procedure for hydrogenolysis of carbamates **13**, compound (−)-**13d** (0.50 g) afforded ketoprotected β-aminoketone (−)-**1d** as a yellow oil (0.26 g, 91%): $[\alpha]_D^{25} = -8.6$ (*c* 1.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (4H, m, C(4)H_2 and C(5)H_2), 3.08 (1H, m, C(2′)*H*), 1.63 (2H, m, C(1′)H_2), 1.54 (2H, m, C(2)C$H_2C_3H_7$), 1.25 (4H, m, C(2)CH_2-$C_2H_4CH_3$), 0.99 (3H, d, $J = 6.4$ Hz, C(3′)H_3), 0.83 (3H, t, $J = 7.1$ Hz, C(2) $C_3H_6CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.7, 64.7, 64.4, 45.7, 43.0, 37.1, 26.0, 24.9, 22.9, 14.0; IR (neat) *v* 3384, 3310, 2920, 2908, 2865, 1567, 1380, 1240, 1221, 1156, 1077; HR-ESI-MS calculated for: $C_{10}H_{22}NO_2$ $(M+H)^+$ 188.1651, found 188.1660.

4.10.5. (−)-(2′*R*)-2-Methyl-2-(2′-amino)-pentyl-1,3-dioxolane 1e. Following the general procedure for the hydrogenolysis of carbamates **13**, compound (+)-**13e** (0.59 g) afforded ketoprotected β-aminoketone (−)-**1e** as a yellow oil (0.32 g, 98%): $[\alpha]_D^{25} = -1.7$ (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92–3.88 (4H, m, C(4)H_2 and C(5)H_2), 2.93 (1H, m, C(2′)*H*), 1.77 (2H, br s, NH_2), 1.70 (1H, dd, $J = 14.4$ and 2.2 Hz, C(1′)H_A), 1.52 (1H, dd, $J = 14.4$ and 9.5 Hz, C(1′)H_B), 1.35–1.20 (7H, m, C(3′)H_2, C(4′)H_2 and C(1)*Me*), 0.84 (3H, t, $J = 7.0$ Hz, C(5′)H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.2, 64.6, 64.1, 47.6, 46.0, 41.0, 24.1, 19.1, 14.1; IR (neat) *v* 3367, 3200, 2957, 2931, 2874, 1453, 1379, 1163, 1100, 1044; HR-ESI-MS calculated for: $C_9H_{20}NO_2$ $(M+H)^+$ 174.1494, found 174.1500.

4.10.6. (−)-(2′*S*)-2-[2′-Amino-2′-(3,4-dimethoxyphenyl)]-ethyl-2-methyl-1,3-dioxolane 1f. Following the general procedure for the hydrogenolysis of carbamates **13**, compound (+)-**13f** (0.12 g) afforded ketoprotected β-aminoketone (−)-**1f** as a yellow oil (0.08 g, 97%): $[\alpha]_D^{25} = -24.5$ (*c* 1.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, d, $J = 1.8$ Hz, Ar*H*), 6.88 (1H, dd, $J = 8.2$ and 1.8 Hz, Ar*H*), 6.81 (1H, d, $J = 8.2$ Hz, Ar*H*), 4.19 (1H, dd, $J = 8.8$ and 3.5 Hz, C(2′)*H*), 4.03–3.95 (4H, m, C(4)H_2 and C(5)H_2), 3.88 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.02–1.96 (2H, m, C(1′)H_2), 1.8 (2H, br s, NH_2), 1.36 (3H, s, C(1)*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 147.8, 139.3, 118.2, 110.4, 109.7, 109.5, 64.7, 64.2, 55.8, 51.9, 48.2, 24.7; IR (neat) *v* 3350, 3262, 2945, 2919, 2888, 2837, 1592, 1515, 1466, 1420, 1381, 1261, 1231, 1137, 1108, 1025; HR-ESI-MS calculated for: $C_{14}H_{22}NO_4$ $(M+H)^+$ 268.1549, found 268.1546.

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