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Diastereoselective synthesis of aryl and alkyl *trans*-glycidic amides from pseudoephedrine-derived sulfonium salt. Chemospecific *exo-tet* ring closure for morpholin-3-ones

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ABSTRACT

A regiospecific and high diastereoselective synthesis of *trans*-glycidic amides coming from a common pseudoephedrine sulfonium salt **2** precursor is presented. This is the first example in where the diastereoselectivity is controlled by a chiral noncyclic amide fragment. The epoxidation reaction provides alkyl or aryl glycidic amides in good to excellent yields and exclusive trans selectivity. Finally, through of a chemospecific 6-*exo-tet* ring closure of *trans*-epoxyamides we access to morpholin-3-ones densely functionalized with excellent chemical and stereochemical yields.

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1. Introduction

Glycidic amides are important building blocks in organic synthesis. There are different methods for their preparation; via an oxidation route of the corresponding α,β-unsaturated amide,[1] by a direct oxidation of tertiary allylamine,[2] by a Darzens condensation of α-haloacetamides,[3] α-diazoacetamides,[4] ammoniumacetamides[5] with carbonyl compounds or by a condensation of an amide-stabilized sulfonium ylide with an aldehyde.[6]

Specifically, amide-stabilized sulfonium ylides, have attracted great attention because react with aldehydes to give glycidic amides with high degree of trans selectivity.[7] The induction of chirality may be achieved either at the aldehyde,[7b,8] at the sulfide fragment,[6c,d,9] or at the chiral cyclic sulfur ylide type.[10]

The reaction is general for aromatic aldehydes, but aliphatic aldehydes gave more variable enantioselectivities and a mixture of cis- and trans-isomers has been obtained.[9b,10b]

In this way, we previously reported that stabilized sulfur ylides derived from (*S*)- or (*R*)-phenylethylamine afford aliphatic or aromatic *trans*-glycidic amides in good to excellent yields, however, with very low diastereoselectivity.[11]

In order to improve the diastereomeric excess we turned our attention to explore other chiral amines. In this sense, (*S*,*S*)-(+)-pseudoephedrine, which is a commercially and inexpensive chiral available reagent, has provided excellent results as chiral auxiliary in several C–C and C–X bond-forming reactions. Specifically, amides derived from this amino alcohol have been employed as nucleophiles via their corresponding enolates.[12]

Taking into account this impressive precedent, herein we report the first example in where, the asymmetric epoxidation is controlled by a chiral acyclic amide fragment, precisely sulfur ylide derived from (*S*,*S*)-(+)-pseudoephedrine gives aliphatic and aromatic *trans*-glycidic amides in good to excellent yields and high diastereoselectivity.

Finally, in order to demonstrate the valuable utility of these glycidic amides, we make the chemospecific 6-*exo-tet* ring closure obtaining the corresponding morpholin-3-one compounds densely functionalized.

2. Results and discussion

Chiral sulfonium salt **2** was synthesized in two steps starting from pseudoephedrine in 95% overall yield (Scheme 1).

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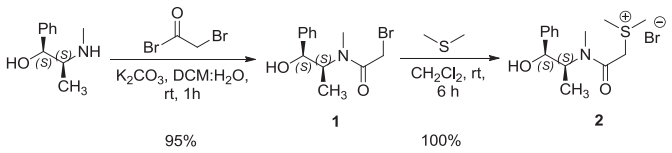
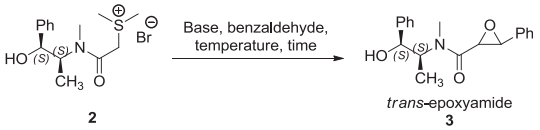


Scheme 1.

With chiral sulfonium salt **2** in hand we proceeded to investigate the asymmetric epoxidation with benzaldehyde (Table 1).

Table 1
Effect of the base, solvent, temperature, and time on conversion



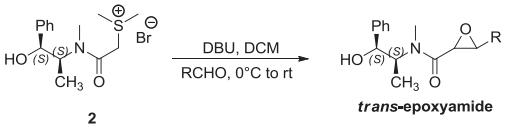
Entry	Base	Solvent	Temperature (°C)	Time (h)	Yield (%)	de[a] (%)
1	KOH	THF	0 °C to rt	36	60	90
2	KOH	THF/H_2O	0 °C to rt	24	80	90
3	KOH	EtOH	0 °C	12	85	90
4	KOH	DCM	0 °C	24	73	90
5	DBU	THF	0 °C to rt	72	50	90
6	DBU	DCM	0 °C to rt	24	95	90

[a] Calculated by HPLC analysis of the crude reaction mixture (Chiralcel OD column, UV detector, *n*-hexane/2-propanol 50:50, t_R for the major diastereoisomer, 5.67 min, t_R for the minor diastereoisomer 6.35 min, flow rate 1.00 mL/min).

Diverse reaction conditions were tested giving in general good to excellent yields. The best result was obtained when sulfonium salt **2** was treated with DBU as a base, in DCM, benzaldehyde (2 equiv) from 0 °C to room temperature, giving the desired epoxyamide in 95% (entry 6, Table 1). Exclusive formation of *trans*-adducts was confirmed by the magnitude of the coupling constants (J=2.1 and 1.6 Hz).[13] ^{1}H NMR determination of diastereomeric ratios was complicated by the presence of *E* versus *Z* amide rotamers in solution.[12b,14] However, HPLC analysis of the crude reaction showed a de≥90% in all entries.

The asymmetric epoxidation of chiral sulfonium salt **2** with several aromatic aldehydes was then investigated giving in all entries good to excellent yields despite of the presence of deactivating or activating groups at aromatic ring (Table 2, entries 1–4) or the presence of chlorine atoms (entries 5 and 6). The asymmetric epoxidation with aliphatic aldehydes was tested giving exclusively the trans-adducts in good yields (entries 7–9).

Table 2
Asymmetric epoxidation with aromatic and aliphatic aldehydes



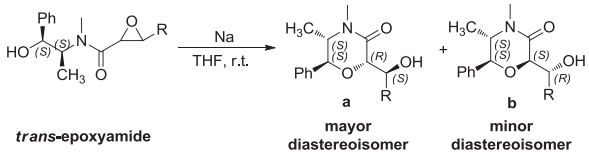
Entry	R	Product	Yield (%)	de[a] (%)
1	2-$O_2NC_6H_4$	**4**	85	80
2	3-$O_2NC_6H_4$	**5**	93	70
3	4-$O_2NC_6H_4$	**6**	90	94
4	3,4-$(CH_3)_2C_6H_3$	**7**	83	94
5	2,6-ClC_6H_3	**8**	75	60
6	3,5-ClC_6H_3	**9**	80	80
7	Pr	**10**	73	86
8	*i*-Pr	**11**	75	70
9	*i*-Bu	**12**	84	33

Reaction conditions: aldehyde (2 equiv), 0 °C to rt, 12 h.
[a] Calculated by HPLC (Chiralcel OD column, UV detector, *n*-hexane/2-propanol 50:50, 1.00 mL/min).

As the determination of the absolute or relative stereochemistry at epoxide function proved to be difficult at this stage, the regiospecific 6-*exo-tet* ring closure was tested following the procedure previously described by us based on the in situ sodium alkoxide formation accessing to the morpholinone ring.[11b]

Firstly, *trans*-epoxyamide **3** was treated with sodium in anhydrous tetrahydrofuran giving the desired cyclic compound after 30 min. The NMR analysis of the crude reaction showed exclusively the presence of the corresponding diastereomeric mixture of morpholin-3-ones **13a**/**13b** in a 95:5 ratio and 95% yield (entry 1, Table 3). Diastereomers were easily separated by chromatographic column. Fortunately, the major diastereoisomer **13a** crystallized, enabling the determination of its absolute configuration and the confirmation of the presence of the morpholinone ring by X-ray diffraction analysis (Fig. 1).[15]

Table 3
Intramolecular 6-*exo-tet* ring-closure reaction



Entry	*trans*-Epoxyamide	Time (min)	Ratio of **a**/**b**[a]	Product	Isolated yield of **a**[b] (%)
1	**3**	30	9.5:0.5	**13**	81
2	**4**	30	9:1	**14**	77
3	**5**	20	8.5:1.5	**15**	72
4	**6**	25	9.5:0.5	**16**	76
5	**7**	30	9.5:0.5	**17**	78
6	**8**	30	8:2	**18**	58
7	**9**	10	9:1	**19**	80
8	**10**	25	9:1	**20**	40
9	**11**	20	8.5:1.5	**21**	70
10	**12**	25	7:3	**22**	33

[a] Determined by ^{1}H NMR of the unpurified reaction mixture.
[b] Isolated yield of the major diastereoisomer.

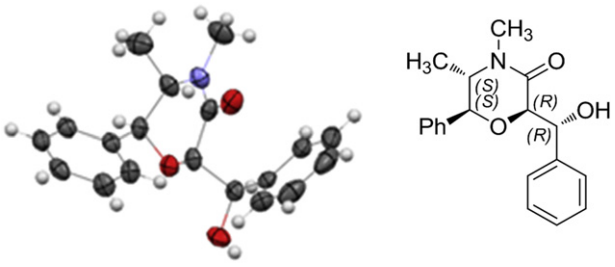
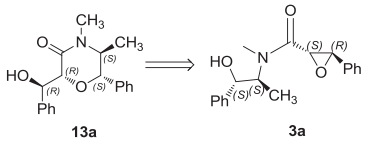


Fig. 1. X-ray ORTEP diagram of compound **13a**.

As a correlation, we concluded that the morpholinone comes from the (*S*,*R*)-epoxyamide, this is the mainly diastereoisomer formed in the asymmetric epoxidation process (Scheme 2).

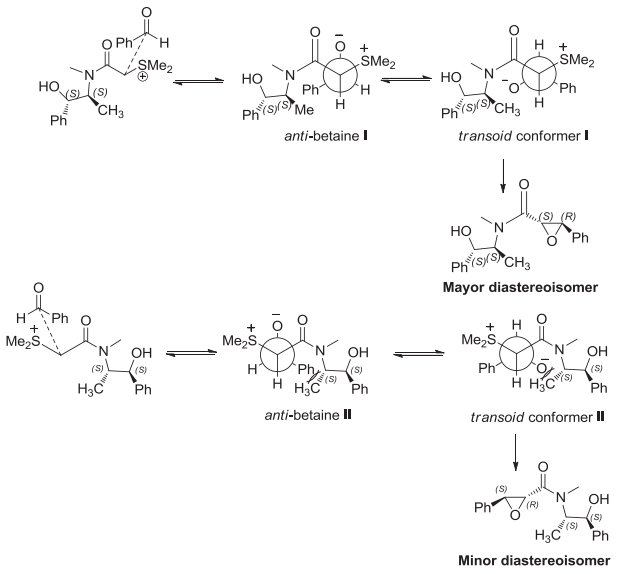


Scheme 2.

Epoxyamides containing deactivating or activating groups at aromatic ring were reacted with sodium, affording the corresponding morpholinones in good to excellent yields. However, epoxyamide **8** gave low yield; this result was attributed to the

presence of chlorine atoms at *ortho* position, which represents a combination of unfavorable steric and electronic effects (entry 6, Table 3). Epoxyamides containing an aliphatic group gave the corresponding morpholinones in excellent yields.[16]

Finally, the diastereoselective outcomes in asymmetric epoxidation reaction could be explains as follows. The addition of the ylide onto the aldehyde results in a formation of reversible two possible *anti*-betaine intermediates **I** and **II**, followed by the reversible rotation around the newly formed C–C bond giving the *transoid* conformers **I** and **II**, in agreement with Aggarwal's postulated mechanism,[9b] in where the *transoid* **II** shows a greater steric interactions between oxy and methyl groups destabilizing this rotamer, while *transoid* **I** disposes the oxy and methyl groups in an opposite side favoring the ring closure, giving the *trans*-(*S*,*R*)-diastereoisomer as a mayor compound (Scheme 3)



Scheme 3. Suggested mechanism.

3. Conclusion

We have shown that chiral non-racemic amide-stabilized sulfur ylide **2** is a valuable starting material for the preparation of alkyl or aryl *trans*-epoxyamides. These intermediates were utilized to build in a high yielding, highly functionalized morpholin-3-ones. This new, short, versatile, and scalable strategy opens the route to the six-membered *N*,*O*-heterocycles for further pharmacological investigations.

4. Experimental section

4.1. General methods

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were acquired on Varian VX400 (400 MHz), chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on Nicolet FT-IR Magna 750. Mass spectra were recorded on JEOL JEM-AX505HA at a voltage of 70 eV. Optical rotations were measured on Perkin–Elmer 341polarimeter at room temperature. Column chromatography was performed on silica gel (60, 0.063–0.2 mm/70–230 mesh ASTM). All reagents and solvents were analytically pure.

4.2. Synthesis of (+)-2-bromo-*N*-((1*S*,2*S*)-1-hydroxy-1-phenyl propan-2-yl)-*N*-methylacetamide, 1

To a stirred solution of (1*S*,2*S*)-pseudoephedrine (2.5 g, 15.1 mmol, 1.0 equiv) in DCM, at room temperature, was added an aqueous solution of K_2CO_3 (4.18 g, 2 equiv) and bromoacetyl bromide (15.1 mmol, 3.05 g, 1.3 mL, 1 equiv). The resulting mixture was stirred for 1 h. After, the reaction was quenched by the successive addition of brine solution (25 mL) and the organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by evaporation. The resulting mixture was purified via flash column chromatography. Compound **1** was obtained as a white solid in a 95% yield (spectroscopic details of the major rotamer of compound **1**); $[\alpha]_D^{20}$ +81.0 (*c* 1.0, CH_2Cl_2); IR (film) 3383, 1632, 1454, 1086 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J*=7.2 Hz, 3H), 2.90 (s, 3H), 3.72 (d, *J*=10.4 Hz, 1H), 3.95 (qd, *J*=7.2, 6.6 Hz, 1H), 4.11 (m, 1H), 4.16 (d, *J*=10.4 Hz, 1H), 4.53 (br, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 27.0, 59.4, 74.6, 75.3, 126.2, 127.9, 128.7, 141.2, 168.1. HRMS (FAB): calcd for $C_{12}H_{16}BrNO_2$: 285.0364; found: 285.0366.

4.3. Synthesis of (+)-(2-(((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)dimethylsulfonium bromide, 2

To a stirred solution of *N*-methylacetamide **1** (2.27 mmol, 0.65 g), in DCM (2 mL), at room temperature was added dimethyl sulfide (0.35 g, 0.42 mL, 5.63 mmol). Then, the mixture was stirred until total formation of the corresponding sulfonium salt (6 h). Later, the excess of dimethyl sulfide was eliminated by evaporation, and the solvent was removed under reduce pressure giving the desired sulfonium salt **2** in a quantitative yield.

The NMR spectra show the presence of a rotameric mixture of *E* versus *Z* isomers, only the major rotamer is described. $[\alpha]_D^{20}$ +69.1 (*c* 1.0, CH_2Cl_2); IR (film) 3378, 1633, 1453, 1045, 704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J*=6.4 Hz, 3H), 2.87 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 3.90 (qd, *J*=6.4, 9.2 Hz, 1H), 4.46 (d, *J*=9.2 Hz, 1H), 5.22 (br, OH), 5.31 (br, 2H), 7.23–7.76 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 24.8, 25.2, 27.1, 49.8, 59.1, 74.7, 126.8, 128.0, 128.4, 140.9, 164.2. HRMS (FAB): calcd for $C_{14}H_{22}BrNO_2S$: 347.0555; found: 347.0554.

4.4. Representative procedure for asymmetric epoxidation of (2-(((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)dimethylsulfonium bromide 2 with benzaldehyde

To a stirred solution of sulfonium salt **2** (0.35 g, 1.0 mmol) in DCM (20 mL) at 0 °C were added DBU (0.39 g, 2 equiv) and benzaldehyde (0.26 mL, 0.274g, 2 equiv). The resulting mixture was stirred from 0 °C to room temperature until the total consumption of sulfonium salt **2** (24 h). Finally the reaction was quenched by a successive addition of a brine solution. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by evaporation. The resulting mixture was purified via flash column chromatography. Compound **3** was obtained as a colorless oil in a 95% yield. The NMR spectra show the presence of a rotameric mixture of *E* versus *Z* isomers of each diastereomer.

4.5. Representative procedure for intramolecular 6-*exo-tet* ring-closure reaction

To a solution of the corresponding trans-diastereomeric mixture of epoxyamide (0.38mmol) in anhydrous THF (6 mL) at room temperature was added Na (14–18 mg). The resulting mixture was stirred until the total conversion of the starting material (30 min). Finally, the reaction mixture was filtered and quenched by addition of a brine solution, and the organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by evaporation. The

resulting diastereomeric mixture was purified via flash column chromatography. Only the mayor diastereoisomer is described.

4.5.1. (+)-(2R,5S,6S)-2-((R)-Hydroxy(phenyl)methyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***13a****.* Mp=154–156 °C; $[\alpha]_D^{20}$ +100.3 (*c* 1.0, CH_2Cl_2); IR (film) 3384, 1635, 1449, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J*=6.4 Hz, 3H), 2.92 (s, 3H), 3.41 (qd, *J*=6.6, 9.2 Hz, 1H), 4.18 (d, *J*=9.2 Hz, 1H), 4.23 (d, *J*=7.2 Hz, 1H), 5.02 (d, *J*=7.6 Hz, 1H), 5.30 (br, OH), 7.17–7.45 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 30.3, 58.5, 74.3, 78.8, 81.6, 127.2, 127.5, 127.9, 128.4, 137.7, 140.0, 169.8. HRMS (FAB): calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1520.

4.5.2. (+)-(2R,5S,6S)-2-((R)-Hydroxy(2-nitrophenyl)methyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***14a****.* $[\alpha]_D^{20}$ +91.6 (*c* 1.0, CH_2Cl_2); IR (film) 3379, 1634, 1520, 1346 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J*=6.8 Hz, 3H), 2.99 (s, 3H), 3.53 (qd, *J*=6.8, 9.6 Hz, 1H), 3.99 (d, *J*=8.8 Hz, 1H), 4.10 (d, *J*=9.6 Hz, 1H), 5.94 (br, OH), 5.99 (d, *J*=8.8 Hz, 1H), 7.15–7.37 (m, 6H), 7.52 (td, *J*=1.2, 7.6 Hz, 1H), 7.65 (dd, *J*=1.2, 8.0 Hz, 1H), 7.95 (dd, *J*=1.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 30.4, 58.5, 68.2, 78.8, 82.4, 123.8, 126.9, 127.3, 128.8, 132.6, 134.6, 136.9, 149.1, 170.1. HRMS (FAB): calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1370.

4.5.3. (+)-(2R,5S,6S)-2-((R)-Hydroxy(3-nitrophenyl)methyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***15a****.* $[\alpha]_D^{20}$ +83.3 (*c* 1.0, CH_2Cl_2); IR (film) 3380, 1652, 1524, 1350 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J*=6.8 Hz, 3H), 2.97 (s, 3H), 3.51 (qd, *J*=6.8, 9.6 Hz, 1H), 4.18 (d, *J*=7.6 Hz, 1H), 4.21 (d, *J*=9.6 Hz, 1H), 5.10 (d, *J*=7.6 Hz, 1H), 5.67 (d, *J*=2.4 Hz, 1H), 7.25–7.41 (m, 6H), 7.76 (d, *J*=7.6 Hz, 1H), 8.03 (m, 1H), 8.37 (t, *J*=2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 30.2, 58.2, 73.2, 78.3, 81.6, 122.5, 127.1, 128.3, 133.4, 137.2, 142.0, 169.2. HRMS (FAB): calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1371.

4.5.4. (+)-(2R,5S,6S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***16a****.* $[\alpha]_D^{20}$ +119.6 (*c* 1.0, CH_2Cl_2); IR (film) 3393, 1646, 1524, 1344 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J*=6.0 Hz, 3H), 2.98 (s, 3H), 3.52 (qd, *J*=6.0, 9.6 Hz, 1H), 4.17 (d, *J*=7.6 Hz, 1H), 4.20 (d, *J*=9.6 Hz, 1H), 5.11 (d, *J*=7.6 Hz, 1H), 5.71 (br, OH), 7.23–7.35 (m, 5H), 7.60 (d, *J*=8.6 Hz, 2H), 8.07 (d, *J*=8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 30.4, 58.6, 73.5, 78.3, 81.9, 122.7, 127.1, 128.4, 128.7, 137.2, 147.2, 147.4, 169.4. HRMS (FAB): calcd for $C_{19}H_{20}N_2O_5$: 356.1372; found: 356.1370.

4.5.5. (+)-(2R,5S,6S)-2-((R)-(3,4-Dimethylphenyl)(hydroxy)methyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***17a****.* $[\alpha]_D^{20}$ +61.6 (*c* 1.0, CH_2Cl_2); IR (film) 3385, 1642, 1575, 1120, 770 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J*=6.6 Hz, 3H), 2.19 (s, 3H), 2.21 (s, 3H), 2.95 (s, 3H), 3.45 (m, *J*=6.6, 9.2 Hz, 1H), 4.20 (d, *J*=9.2 Hz, 1H), 4.25 (d, *J*=7.5 Hz, 1H), 4.95 (d, *J*=7.5 Hz, 1H), 5.18 (br, OH), 7.01–7.42 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 19.4, 19.7, 29.6, 58.7, 74.3, 78.9, 81.7, 124.9, 127.4, 128.3, 128.5, 135.7, 137.5, 138.0, 170.1. HRMS (FAB): calcd for $C_{21}H_{25}NO_3$: 339.1834; found: 339.1832.

4.5.6. (+)-(2R,5S,6S)-2-((R)-(2,6-Dichlorophenyl)(hydroxy)methyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***18a****.* $[\alpha]_D^{20}$ +51.5 (*c* 1.0, CH_2Cl_2); IR (film) 3385, 1642, 1575, 1120, 770 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J*=6.8 Hz, 3H), 3.03 (s, 3H), 3.52 (m, *J*=6.8, 9.6 Hz, 1H), 4.25 (d, *J*=9.6 Hz, 1H), 5.03 (d, *J*=9.6 Hz, 1H), 5.71 (s, OH), 5.80 (d, *J*=9.6 Hz, 1H), 6.98 (t, *J*=8 Hz, 1H), 7.18–7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 30.4, 59.0, 71.4, 74.4, 81.7, 127.1, 127.4, 128.0, 128.3, 128.9, 133.7, 137.8, 171.0. HRMS (FAB): calcd for $C_{19}H_{19}NO_3$: 379.0742; found: 379.0740.

4.5.7. (+)-(2R,5S,6S)-2-((R)-(3,5-Dichlorophenyl)(hydroxy)methyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***19a****.* $[\alpha]_D^{20}$ +115.7 (*c* 1.0, CH_2Cl_2); IR (film) 3381, 1634, 1432, 1125, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J*=6.8 Hz, 3H), 2.98 (s, 3H), 3.49 (qd, *J*=6.8, 9.6 Hz, 1H), 4.16 (d, *J*=7.6 Hz, 1H), 4.22 (d, *J*=9.6 Hz, 1H), 4.97 (d, *J*=7.6 Hz, 1H), 5.48 (br, OH), 7.18–7.40 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 30.4, 58.6, 73.4, 78.3, 81.7, 125.9, 126.0, 127.0, 127.2, 127.6, 128.4, 128.7, 134.0, 137.3, 143.4, 169.4. HRMS (FAB): calcd for $C_{19}H_{19}NO_3$: 379.0742; found: 379.0740.

4.5.8. (2R,5S,6S)-2-((R)-1-Hydroxybutyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***20a****.* $[\alpha]_D^{20}$ +58.8 (*c* 1.0, CH_2Cl_2); IR (film) 3417, 1632 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.2 Hz, 3H), 1.10 (d, *J*=6.4 Hz, 3H), 1.49 (m, 3H), 1.68 (m, 1H), 2.97 (s, 3H), 3.89 (qd, *J*=6.8, 7.2 Hz, 1H), 3.97 (m, 2H), 4.28 (d, *J*=9.6 Hz, 1H), 4.61 (br, OH), 7.28–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 15.9, 18.1, 30.2, 34.6, 58.6, 71.6, 78.9, 82.1, 127.1, 127.4, 128.7, 137.9, 170.5. HRMS (FAB): calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1675.

4.5.9. (+)-(2R,5S,6S)-2-((R)-1-Hydroxy-2-methylpropyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***21a****.* $[\alpha]_D^{20}$ +50.7 (*c* 1.0, CH_2Cl_2); IR (film) 3418, 2955, 1634, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J*=7.2 Hz, 3H), 0.97 (d, *J*=6.8 Hz, 3H), 1.08 (d, *J*=6.8 Hz, 3H), 2.04 (m, J=2.8, 6.8 Hz, 1H), 2.95 (s, 3H), 3.57 (m, *J*=7.2, 9.6 Hz, 1H), 3.79 (qd, *J*=2.8, 8.4 Hz, 1H), 3.99 (d, *J*=8.4 Hz, 1H), 4.25 (d, *J*=9.6 Hz, 1H), 7.31–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 15.9, 28.38, 30.3, 58.6, 75.3, 76.8, 82.2, 127.1, 128.4, 128.7, 137.9, 171.4. HRMS (FAB): calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1676.

4.5.10. (+)-(2R,5S,6S)-2-((R)-1-Hydroxy-3-methylbutyl)-4,5-dimethyl-6-phenylmorpholin-3-one, ***22a****.* $[\alpha]_D^{20}$ +54.3 (*c* 1.0, CH_2Cl_2); IR (film) 3418, 2958, 1633, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J*=6.4 Hz, 3H), 0.94 (d, *J*=6.4 Hz, 3H), 1.09 (d, *J*=6.0 Hz, 3H), 1.46 (m, 2H), 1.91 (m, 1H), 2.96 (s, 3H), 3.59 (m, 1H), 3.96 (d, *J*=6.8 Hz, 1H), 4.04 (m, 1H), 4.27 (d, *J*=9.6 Hz, 1H), 7.29–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 21.1, 23.7, 30.2, 41.5, 58.5, 70.0, 79.3, 82.1, 127.3, 128.6, 128.7, 137.8, 170.3. HRMS (FAB): calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 291.18933.

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15. Crystal structure of compound **13a** was deposited at the Cambridge Crystallographic Data Centre. Deposit number: CCDC 885086.
16. We assumed that in all morpholinones the majority diastereoisomers have the same stereochemistry than morpholinone **13a**, because they have the same optical rotation sign.