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Sequenced elimination-reduction and elimination-cyclopropanation reactions of 2,3-epoxyamides promoted by samarium diiodide. Synthesis of 2,3-dideuterioamides and cyclopropanamides

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Abstract—An easy and general sequenced elimination/reduction or elimination/cyclopropanation process promoted by samarium diiodide or/and CH_2I_2/Sm provide an efficient method for synthesising 2,3-dideuterioamides **3** or cyclopropanamides **8**, respectively. The transformations take place in high yields and with total or high selectivity from the easily available 2,3-epoxyamides. © 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Samarium diiodide is a polyvalent reducing agent and constitutes an effective reagent for sequential reactions,¹ which present a high potential because less time, effort, and material are required. Epoxides are useful intermediates in organic synthesis and have been widely used because of their chemical reactivity.² However, the reduction of epoxides to hydrocarbons has been scarcely reported,³ and to the best of our knowledge, transformation of 2,3-epoxyamides into saturated or 2,3dideuterioamides has not been published. Other possible alternative to reduce 2,3-epoxyacid derivatives can be performed by its transformation into α,β -unsaturated acid derivatives and subsequent reduction to corresponding saturated compounds. In this sense, selective conjugated reduction of α,β -unsaturated carboxylic acid derivatives has been achieved by using several methodologies.⁴ However, the conjugated reduction of α , β unsaturated amides with deuterium instead of hydrogen has been scarcely reported.⁵ To the best of our knowledge, only two examples have hitherto been described,⁶ both of wich involved catalytic addition of D₂. Taking into account the utility of isotopically labelled compounds to establish the mechanisms of organic reactions and the biosynthesis of many natural

products,⁷ the development of an effective general method for the synthesis of 2,3-dideuterioamides would seem to be a valuable goal.

Moreover, the use of cyclopropanes in mechanistic studies,⁸ their utility as synthetic intermediates,⁹ and their presence in a great number of natural products¹⁰ warrants interest in these carbocycles from various fields in organic chemistry. The majority of the methodologies developed for the synthesis of cyclopropanes¹¹ rely on variants of the following reactions: Simmons–Smith cyclopropanation,¹² transition-metal catalyzed cyclopropanation of alkenes with diazomethane¹³ or diazoesters,¹⁴ and cyclopropanation of Michael acceptors.¹⁵ However, these methods have some disadvantages: total control of diastereoselectivity in the synthesis of cyclopropanes from unsaturated compounds in which the C=C bond is tri- or tetrasubstituted cannot be carried out.¹⁶ Consequently, new methods for the diastereoselective construction of cyclopropanamides, in which the cyclopropane ring is polysubstituted, are of significant interest.¹⁷

Previously, we reported the transformation of 2,3-epoxyesters into saturated esters by using SmI₂¹⁸ and 2-chloro-3hydroxyamides into cyclopropanamides promoted by CH₂I₂/Sm.¹⁹ More recently, we have also reported a β -elimination reaction of aromatic²⁰ and aliphatic²¹ α , β epoxyamides, obtaining (*Z*)- or (*E*)- α , β -unsaturated amides with total or very high diastereoselectivity.

Keywords: Samarium diiodide; Sequenced reactions; Deuterium; Saturated amides; Cyclopropanamides.

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Now, we describe a method to obtain saturated amides and cyclopropanamides from 2,3-epoxyamides by an efficient SmI₂-promoted elimination-reduction or eliminationcyclopropanation sequential reaction, respectively. We have also performed sequenced elimination-reduction reactions to obtain 2,3-dideuterioamides by using D₂O instead of H₂O.

2. Results and discussion

The starting compounds 1 were easily obtained by reaction of aldehydes or ketones with lithium or potassium enolates derived from chloroacetamides, by using standard methods.^{20,21} Thus, epoxyamides **1** were obtained as a mixture *cis/trans* and with the yields showed in Table 1.

2.1. Synthesis of saturated 2 or 2,3-dideuterioamides 3

The reaction of different di- or tetrasubstituted 2,3epoxyamides 1a-c with SmI₂ (5 equiv.) afforded the corresponding α,β -unsaturated amides. After treatment with H_2O or D_2O gave the corresponding saturated amides 2 or 2,3-dideuterioamides 3, respectively (Scheme 1, Table 2).

Starting from trisubstituted 2,3-epoxyamides 1, (Table 2, entries 2, 3 and 7,8) a complex mixture of products was obtained. We have overcome this problem by adding samarium diiodide in two times. Thus, the succesive treatment of trisubstituted 2,3-epoxyamides 1 with a solution of SmI₂ in THF and HMPA (exclusively in the case of aliphatic α,β -epoxyamides) and further treatment with additional SmI₂ and H₂O or D₂O, afforded the corresponding saturated amides 2 or 2,3-dideuterioamides 3 respectively, in good yield (Scheme 1, Table 2).

Table 1.	Synthesis	of epox	yamides	1
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Scheme 1.

This proposed methodology to obtain saturated amides 2 or 2,3-dideuterioamides **3** is general. Thus, R^1 and R^3 can be aliphatic or aromatic, and can be performed from 2,3epoxyamides in which the oxirane ring is di-, tri- or tetrasubstituted. No significant differences were observed in the reaction when D₂O was used instead of H₂O.

The position of deuteration was established by ${}^{1}H$ and ${}^{13}C$ NMR spectrometry of compounds 3, while complete deuterium incorporation (>99%) was determined by mass spectroscopy.²² The obtained 2,3-dideuterioamides $\mathbf{3}$ were isolated as mixture of diastereoisomers (ranging between 1:1 and 2:1) due to the fact that incorporation of deuterium generates two new stereogenic centres. It is noteworthy that D_2O is the most widely available deuteration reagent for obtaining organic compounds isotopically labelled with deuterium.

A postulated mechanism is illustrated in Scheme 2. In the first step, the metalation of 1 by SmI₂ generates an enolate intermediate 4, which suffers a β -elimination reaction affording α,β -unsaturated amides 5.^{20,21} In the second step, the 1,4-reduction of 5, is initiated by a single electron transfer from SmI₂ to generate the enolate radical 6^{23} which, upon reaction with a second equivalent of SmI₂ produces the dianion 7. Subsequent protonation of 7 by D₂O or H₂O, affords the corresponding compound 3 or 2, respectively.

Entry	1 ^a	R^1	R^2	R ³	Yield (%) ^b	trans /cis ^c
1	1a	Ph	Н	Н	62	2/1
2	1b	pMeO–C ₆ H ₄	Н	Н	69	1.4/1
3	1c	Bu	Н	Ph	74	1.6/1
4	1d	Cyclohexyl	Н	Me	85	1.7/1
5	1e	C ₇ H ₁₅	Н	Me	92	2.7/1
6	1f	Н	Ph	Me	83	1.3/1
7	1g	Н	pMeO-C ₆ H ₄	Me	79	3/1
8	1ĥ	Ph	Et	Me	95	1.5/1

General procedure to obtain compounds **1** is described in references 20 and 21.

Isolated yield after column chromatography. Diastereoisomers ratio determined by ¹³C NMR analysis.

Table 2. Synt	hesis of	saturated	amides 2	and	2,3-dideuterioamides 3
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Entry	Compound ^a	R^1	R^2	R ³	Х	Yield (%) ^b
1	2a	Ph	Н	Н	Н	95
2	2c	Bu	Н	Ph	Н	69
3	2d	Cyclohexyl	Н	Me	Н	82
4	2h	Ph	Et	Me	Н	66
5	3a	Ph	Н	Н	D	94
6	3b	pMeO-C ₆ H ₄	Н	Н	D	71
7	3c	Bu	Н	Ph	D	67
8	3f	Н	Ph	Me	D	61

^a All products were fully characterized by spectroscopic methods [IR, NMR, and MS].

^b Isolated yield after column chromatography based on compound 1.







Scheme 3.

2.2. Preparation of cyclopropanamides 8

The reaction of 2,3-epoxyamides with SmI₂ at room temperature and further treatment with a mixture of Sm/CH_2I_2 afforded the corresponding cyclopropanamide 8 in high yield and with total or very high distereoselectivity (Scheme 3 and Table 3). Starting from trisubstituted aliphatic 2,3-epoxyamides, the elimination reaction was carried out by using HMPA as cosolvent to enhance the diastereoselectivity of the process (Table 3, entries 2 and 3). In the case of trisubstituted aromatic epoxyamides, the use of MeOH as cosolvent in the first step increases the diastereoselectivity of the β -elimination reaction and avoids side reactions (Table 3, entries 4 and 5). In this case, the solvents were eliminated previously to carry out the second step due to no cyclopropanation reaction takes place in the presence of MeOH. Consequently, in these two cases the process is one-pot instead of a sequential reaction. Results in Table 3 show that this elimination-cyclopropanation reaction is general: the starting compounds can be aliphatic or aromatic and the oxirane ring can be di-, tri- or tetrasubstituted.

The stereochemistry of the cyclopropane ring was dependent on the structure starting epoxyamide. Thus, from aliphatic (Table 3, entries 2 and 3) and di- or tetrasubstituted aromatic epoxyamides (entries 1 and 6), *trans*-



Scheme 4.

cyclopropanamides were obtained, while from trisubstituted aromatic epoxyamides *cis*-cyclopropanamides were prepared (Table 3, entries 4 and 5). Taking into account that the cyclopropanation reaction is stereospecific, the stereochemistry of the cyclopropane ring is directly related with the stereochemistry of the double bond C==C formed in the first step.

The diastereoisomeric purity of compounds **8** was determined on the crude reaction products by ¹H NMR spectroscopy (300 MHz) and GC-MS. The relative *trans* or *cis* configuration of substituents on the cyclopropane ring was established by analysis of ¹H NMR coupling constant between the cyclopropane protons of compound **8a**, by NOE experiments (**8h**) and by comparison of their ¹H and ¹³C NMR spectra with authentic samples, as has been previously described.¹⁹

The course of the synthesis of 8 can be thought to occur as shown in Scheme 4, through a sequential eliminationcyclopropanation reaction. Initially, 1 suffers an elimination reaction promoted by SmI₂, affording cis- (from trisubstituted aromatic epoxyamides) or trans- α , β -unsaturated amides 5 (from the rest), with high diastereoselectivity. In the second step, carbenoids of Sm (II) (e.g., ISmCH₂I)²⁴ produce a stereospecific cyclopropanation of 5.25 Tentatively, we propose a transition state model I,²⁶ in which the coordination of the divalent samarium atom with the oxygen atom of the amide group provides cyclopropylamide 8, whilst maintaining the geometry about the C=C bond. The abundance of the zwitterionic specie of the amide seems to be the responsible of the reaction of samarium carbenes with the olefin, in a similar way as this described for allylic alcohols.²

Table 3. Synthesis of cyclopropanamides 8

Table 3. Synthesis of Cyclopropanalitics of						
Entry	8 ^a	R^1	R^2	R ³	d.e. ^b	Yield (%) ^c
1	8a	Ph	Н	Н	>98	73
2	8d	Cyclohexyl	Н	Me	>98	60
3	8e	C ₇ H ₁₅	Н	Me	97	62
4	8f	Н	Ph	Me	>98	88
5	8g	Н	$P \text{meO-C}_6 \text{H}_4$	Me	>98	84
6	8h	Ph	Et	Me	>98	87

^a All products were fully characterized by spectroscopic methods [IR, NMR, and MS].

^b Diastereoisomeric excess determined by GC/MS and 300 MHz ¹H NMR analysis of the crude products.

^c Isolated yield after column chromatography based on compound 1.

3. Conclusion

In conclusion, two efficient sequential methodologies have been described. In the first, the SmI_2 -promoted elimination– reduction sequence (in the presence of D_2O or H_2O) provides an efficient method for synthesising 2,3-dideuterioamides or non-deuterated saturated amides. In the second, elimination–cyclopropanation affords *cis*- or *trans*-cyclopropanamides with total or very high diastereoselectivity.

4. Experimental

4.1. General remarks

Reactions which required an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased from Aldrich or Merck and were used without further purification. Samarium diiodide was prepared by reaction of CH₂I₂ with samarium powder by ultrasonic irradiation.²⁸ Silica gel for flash chromatography was purchased from Merck (230-400 mesh), and compounds were visualized on anlytical thin layer chromatograms (TLC) by UV light (254 nm). ¹H NMR spectra were recorded at 200 or 300 MHz. ¹³C NMR spectra and DEPT experiments were determined at 50 or 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants J are reported in Hz. The diastereoisomeric excesses were obtained from ¹H NMR analysis and GC-MS of crude products. GC-MS and HRMS were measured at 70 eV. Only the most important IR absorptions (cm^{-1}) and the molecular ions and/or base peaks in MS are given.

4.2. General procedure for the synthesis of compounds 2 and 3 from di- or tetrasubstituted 2,3-epoxyamides 1

A solution of SmI₂ (2.3 mmol) in THF (24 mL) was added, under nitrogen atmosphere, to a stirred solution of the corresponding 2,3-epoxyamide **1** (0.4 mmol) in THF (4 mL) at room temperature. After stirring for 30 min, H₂O or D₂O (1 mL) was added to the reaction. The mixture was stirred for 30 min at room temperature. Then, the reaction was quenched with aqueous HCl (0.1 M, 10 mL). Usual workup afforded crude saturated amides **2** or 2,3-dideuterioesters **3**, which were purified by column flash chromatography over silica gel (hexane/ethyl acetate).

4.3. General procedure for the synthesis of compounds 2 and 3 from trisubstituted 2,3-epoxyamides

A solution of SmI₂ (1.6 mmol) in THF (19 mL) and HMPA (2 mmol), in the case of aliphatic α , β -epoxyamides, was added, under nitrogen atmosphere, to a stirred solution of the corresponding epoxyamide **1** (0.4 mmol) in THF (4 mL) at room temperature. After stirring for 30 min at room temperature, a solution of SmI₂ (1.1 mmol) in THF (12 mL) and H₂O or D₂O (1 mL) was added to the solution and the mixture was stirred for 3 h at room temperature. Then, the reaction was quenched with aqueous HCl (0.1 M, 10 mL). Usual workup afforded crude saturated amides **2** or

2,3-dideuterioamides **3**, which were purified by column flash chromatography over silica gel (hexane/ethyl acetate).

4.3.1. *N*,*N*-Diethyl-3-phenylpropionamide (2a). ¹H RMN (300 MHz, CDCl₃): δ =7.32–7.15 (m, 5H), 3.38 (q, *J*=7.18 Hz, 2H), 3.21 (q, *J*=7.18 Hz, 2H), 3.17–2.94 (m, 2H), 2.65–2.54 (m, 2H), 1.11 (t, *J*=7.18 Hz, 3H), 1.09 (t, *J*=7.18 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ =171.0 (C), 141.4 (C), 128.2 (CH), 125.8 (CH), 41.7 (CH₂), 40.0 (CH₂), 34.9 (CH₂), 31.5 (CH₂), 14.1 (CH₃), 12.9 (CH₃); MS (70 eV): *m/z* (%): 205 (100) [M]⁺, 176 (12), 133 (4), 105 (28), 91 (44), 77 (16); IR 3083, 3059, 3028, 2975, 1640 cm⁻¹; HRMS Calcd for C₁₂H₁₉NO 205.1466; found 205.1468; *R*_f 0.2 (hexane/AcOEt 5/1).

4.3.2. *N*,*N*-Diethyl-2-phenylheptanamide (2c). ¹H NMR (200 MHz, CDCl₃): δ =7.41–7.17 (m, 5H), 3.52–3.01 (m, 4H), 2.67–2.56 (m, 1H), 2.22–1.53 (m, 2H), 1.49–1.11 (m, 6H), 1.08–0.65 (m, 9H); ¹³C NMR (75 MHz, CDCl₃): δ = 172.0 (C), 140.8 (C), 128.3 (CH), 127.5 (CH), 126.4 (CH), 48.7 (CH), 41.4 (CH₂), 40.1 (CH₂), 35.2 (CH₂), 31.6 (CH₂), 27.4 (CH₂), 22.3 (CH₂), 14.2 (CH₃), 13.8 (CH₃), 12.6 (CH₃); IR 2939, 1636, 1456, 1380 cm⁻¹. Anal. Calcd for C₁₇H₂₂NO: C, 78.11; H, 10.41; N, 5.36; found: C, 78.06; H, 10.39; N, 5.44; *R*_f 0.3 (hexane/AcOEt 3/1).

4.3.3. 3-Cyclohexyl-*N*,*N***-diethyl-2-methylpropanamide** (**2d**). ¹H NMR (200 MHz, CDCl₃): $\delta = 3.63 - 3.29$ (m, 4H), 1.88–0.72 (m, 14H), 2.19 (t, *J*=7.2 Hz, 6H), 1.09 (d, *J*= 7.4 Hz, 3H); ¹³C RMN (75 MHz, CDCl₃): $\delta = 176.2$ (C), 41.9 (CH₂), 41.7 (CH₂), 40.2 (CH₂), 35.3 (CH), 33.9 (CH₂), 33.1 (CH₂), 32.5 (CH), 26.5 (CH₂), 26.3 (CH₂), 26.2 (CH₂), 18.1 (CH₃), 14.8 (CH₃), 13.0 (CH₃); IR 2924, 1624, 1448, 1380 cm⁻¹. Anal. Calcd for C₁₄H₂₇NO: C, 74.61; H, 12.08; N, 6.21; found: C, 74.58; H, 12.07; N, 5.38; *R*_f 0.3 (hexane/ AcOEt 3/1).

4.3.4. *N*,*N*-Diethyl-3-phenyl-2-methylpentanamide (2h). (Diastereoisomeric mixture); ¹H NMR (200 MHz, CDCl₃): δ =7.35–7.09 (m, 10H), 3.54–2.63 (m, 16H), 1.27 (t, *J*=7.1 Hz, 6H), 1.15 (t, *J*=7.1 Hz, 6H), 1.04 (t, *J*=7.1 Hz, 6H), 0.83 (d, *J*=5.9 Hz, 6H), 0.74–0.61 (m, 6H); ¹³C NMR (50 MHz, CDCl₃): δ =175.3 (C), 174.8 (C), 143.2 (C), 142.8 (C), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 126.0 (CH), 125.8 (CH), 51.4 (CH), 50.4 (CH), 42.0 (CH), 41.9 (CH), 41.5 (CH₂), 41.4 (CH₂), 40.5 (CH₂), 39.8 (CH₂), 27.1 (CH₂), 23.9 (CH₂), 17.2 (CH₃), 16.2 (CH₃), 14.8 (CH₃), 14.3 (CH₃), 12.9 (CH₃), 12.3 (CH₃), 12.1 (CH₃), 11.9 (CH₃); IR 2968, 1635, 1456, 1380 cm⁻¹. Anal. Calcd for C₁₆H₂₅N: C, 77.68; H, 10.19; N, 5.66; found: C, 77.75; H, 10.09; N, 5.67; *R*_f 0.4, 0.3 (hexane/AcOEt 3/1).

4.3.5. 2,3-Dideuterio-*N*,*N***-diethyl-3-phenylpropanamide** (**3a**). ¹H NMR (300 MHz, CDCl₃): $\delta = 7.34-7.19$ (m, 5H), 3.38 (q, J = 7.18 Hz, 2H), 3.23 (q, J = 7.18 Hz, 2H), 3.00– 2.94 (m, 1H), 2.61–2.55 (m, 1H), 1.12 (t, J = 7.18 Hz, 3H), 1.11 (t, J = 7.18 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): $\delta =$ 171.0 (C), 141.2 (CH), 128.2 (CH), 125.8 (CH), 41.6 (CH₂), 39.9 (CH₂), 34.4 (t, J = 19.7 Hz, CHD), 31.0 (t, J = 19.7 Hz, CHD), 14.0 (CH₃), 12.8 (CH₃); MS (70 eV): m/z (%): 207 (42) [M]⁺, 178 (7), 149 (10), 135 (4), 107 (18), 92 (53), 77 (50); IR 3083, 3060, 3025, 2973, 2932, 1638 cm⁻¹; HRMS Calcd for $C_{13}H_{17}D_2NO$ 207.1466; found 207.1589; R_f 0.2 (hexane/AcOEt 5/1).

4.3.6. 2,3-Dideuterio-*N*,*N***-diethyl-3-[4-(methoxy)phenyl]propanamide (3b).** ¹H NMR (300 MHz, CDCl₃): $\delta =$ 7.14 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.37 (q, J = 7.2 Hz, 2H), 3.21 (q, J = 7.2 Hz, 2H), 2.98–2.78 (m, 1H), 2.62–2.44 (m, 1H), 1.11 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃): $\delta =$ 171.2 (C), 157.8 (C), 133.4 (C), 129.2 (CH), 113.7 (CH), 55.1 (CH₃), 41.7 (CH₂), 40.0 (CH₂), 34.8 (CHD, t, J = 19.2 Hz), 30.2 (CHD, t, J = 19.2 Hz), 14.1 (CH₃), 12.9 (CH₃); MS (70 eV): m/z (%): 227 (2) [M]⁺, 222 (2), 147 (35), 72 (100); IR 3060, 1636, 1514, 1458 cm⁻¹; $R_{\rm f}$ 0.3 (hexane/AcOEt 3/1).

4.3.7. 2,3-Dideuterio-*N*,*N*-diethyl-2-phenylheptanamide (**3c**). ¹H NMR (200 MHz, CDCl₃): δ =7.39–7.19 (m, 5H), 3.56–3.06 (m, 4H), 2.18–1.53 (m, 2H), 1.49–1.10 (m, 5H), 1.17–0.78 (m, 9H); ¹³C NMR (50 MHz, CDCl₃): δ =172.1 (C), 140.8 (C), 128.5 (CH), 127.7 (CH), 126.5 (CH), 48.3 (CD, t, *J*=19.4 Hz), 41.5 (CH₂), 40.3 (CH₂), 34.9 (CHD, t, *J*=19.4 Hz), 31.7 (CH₂), 27.4 (CH₂), 22.4 (CH₂), 14.4 (CH₃), 13.9 (CH₃), 12.8 (CH₃); IR 2939, 1636, 1456, 1380 cm⁻¹. Anal. Calcd for C₁₇H₂₅D₂NO: C, 74.61; H, 11.10; N, 5.32; found: C, 74.60; H, 10.09; N, 5.39; R_f 0.3 (hexane/AcOEt 3/1).

4.3.8. 2,3-Dideuterio-*N*,*N***-diethyl-3-phenyl-2-methyl-propanamide (3f).** (Diastereoisomeric mixture); ¹H NMR (300 MHz, CDCl₃): δ =7.30–7.15 (m, 10H), 3.48–3.36 (m, 2H), 3.25–3.13 (m, 2H), 3.05 (q, *J*=7.18 Hz, 4H), 2.62 (s, 2H), 1.26 (s, 3H), 1.16 (s, 3H), 1.02 (t, *J*=7.18 Hz, 6H), 0.93 (t, *J*=7.18 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 175.0 (C), 140.6 (C), 140.1 (C), 129.0 (CH), 128.9 (CH), 128.1 (CH), 126.0 (CH), 125.7 (CH), 41.6 (CH₂), 40.3 (CH₂), 40.3 (t, *J*=19.8 Hz, CHD), 37.6 (t, *J*=19.8 Hz, CD), 18.0 (CH₃), 14.5 (CH₃), 12.9 (CH₃); MS (70 eV): *m/z* (%): 221 (36) [M]⁺, 206 (22), 121 (19), 92 (100); IR 3062, 3026, 2971, 1636, 1379 cm⁻¹; HRMS Calcd for C₁₄H₁₉D₂NO 221.1735; found 221.1749; *R*_f 0.3 (hexane/AcOEt 3/1).

4.4. General procedure for the synthesis of compounds 8

Over a solution of SmI₂ (1.1 mmol for di- or tetrasubstituted aromatic 2,3-epoxyamides 1 and 1.7 mmol for the rest) in THF (12 and 20 mL, respectively), a solution of the corresponding 2,3-epoxyamide 1 (0.4 mmol) in THF (4 mL) was added, under nitrogen atmosphere, at room temperature. After stirring for 30 min, the complete formation of 5 was checked by TLC. Then, when samarium diiodide remained, iodine pearls were added till colour changed from blue to yellow. The reaction mixture was cooled to -30 °C and 16 mL of dry THF, 2.4 mmol of samarium powder and 2.4 mmol of CH₂I₂ were added. After stirring at -30 °C during 10 h, the excess samarium diiodide was destroyed by oxidation with air, and the reaction was quenched with aqueous HCl (0.1 M, 10 mL). Usual workup afforded crude cyclopropanamides 8, which were purified by short column flash chromatography over silica gel (hexane/ethyl acetate 3:1).

In the case of synthesis of 8b,c or 8d,e, HMPA (0.5 mL) or

MeOH (0.4 mL) were used, respectively, as cosolvent to carry out the first step.^{9,10} In the last case, previously to the addition of CH_2I_2 and Sm, solvents were eliminated to dryness.

In the obtention of **8a**, cyclopropanation took place at 0 $^{\circ}$ C, during 2 h and just with 1.4 mmol of samarium powder and 1.4 mmol of CH₂I₂.

4.4.1. ($1S^*, 2S^*$)-*N*,*N*-Diethyl-2-phenylcyclopropanocarboxamide (8a). ¹H NMR (300 MHz, CDCl₃): δ =7.31–7.10 (m, 5H), 3.44 (q, *J*=7.18 Hz, 2H), 3.43 (q, *J*=7.18 Hz, 2H), 2.49 (ddd, *J*=9.11, 5.98, 4.27 Hz, 1H), 1.93 (ddd, *J*=8.25, 5.41, 4.27 Hz, 1H), 1.65 (ddd, *J*=9.11, 5.41, 3.99 Hz, 1H), 1.25 (ddd, *J*=8.25, 5.98, 3.99 Hz, 1H), 1.19 (t, *J*=7.18 Hz, 3H), 1.14 (t, *J*=7.18 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ =170.9 (C), 141.0 (C), 128.3 (CH), 126.0 (CH), 42.0 (CH₂), 40.8 (CH₂), 25.3 (CH), 23.1 (CH), 16.1 (CH₂), 14.8 (CH₃), 13.2 (CH₃); MS (70 eV): *m*/*z* (%): 217 (37) [M]⁺, 145 (25), 117 (39), 72 (91), 42 (100); IR 3019, 2971, 1627, 1452, 1377 cm⁻¹; HRMS Calcd for C₁₄H₁₉NO 217.1467; found 217.1495; *R*_f 0.3 (hexane/AcOEt 3/1).

4.4.2. $(1S^*, 2R^*)$ -2-Cyclohexyl-*N*,*N*-diethyl-1-methylcyclopropanocarboxamide (8d). ¹H NMR (400 MHz, [D₆]DMSO): $\delta = 3.48$ (q, J = 7.05 Hz, 4H), 1.95–1.69 (m, 5H), 1.45–0.98 (m, 6H), 1.33 (s, 3H), 1.17 (t, J = 7.05 Hz, 6H), 1.06 (dd, J = 8.97, 4.20 Hz, 1H), 0.90 (dd, J = 8.97, 4.77 Hz, 1H), 0.27 (dd, J = 4.77, 4.20 Hz, 1H); ¹³C NMR (100 MHz, [D₆]DMSO): $\delta = 172.7$ (C), 39.1 (CH₂), 36.9 (CH), 32.2 (CH₂), 27.8 (CH), 25.5 (CH₂), 25.3 (CH₂), 25.1 (CH₂), 24.5 (C), 16.9 (CH₂), 15.7 (CH₃), 12.6 (CH₃); MS (70 eV): m/z (%): 237 (10) [M]⁺, 222 (5), 100 (25), 55 (52), 41 (100); IR 2981, 2924, 1627, 1429, 1379 cm⁻¹; HRMS Cald. for C₁₅H₂₇NO 237.2093 found 237.2101; $R_{\rm f}$ 0.4 (hexane/AcOEt 3/1).

4.4.3. (1*S*^{*},2*S*^{*})-*N*,*N*-Diethyl-2-heptyl-1-methylcyclopropanocarboxamide (8e). ¹H NMR (200 MHz, CDCl₃): δ =3.59–3.19 (m, 4H), 1.60–0.95 (m, 17H), 1.20 (s, 3H), 1.09 (t, *J*=7.12 Hz, 3H), 0.83 (t, *J*=6.55 Hz, 3H), 0.13 (dd, *J*=5.41, 4. 84 Hz, 1H); ¹³C RMN (50 MHz, CDCl₃): δ = 174.5 (C), 40.8 (CH₂), 40.1 (CH₂), 31.7 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 24.4 (C), 22.6 (CH₂), 22.3 (CH), 18.5 (CH₂), 16.4 (CH₃), 14.3 (CH₃), 14.0 (CH₃), 13.6 (CH₃); MS (70 eV): *m/z* (%): 253 (18) [M]⁺, 238 (10), 154 (18), 100 (81), 41 (100); IR 2929, 1626, 1425, 1377 cm⁻¹; HRMS Calcd for C₁₆H₃₁NO 253.2406; found 253.2406; *R*_f 0.4 (hexane/AcOEt 3/1).

4.4.4. (1*R*^{*},2*S*^{*})-*N*,*N*-Diethyl-1-methyl-2-phenylcyclopropanocarboxamide (8f). ¹H NMR (300 MHz, CDCl₃): δ =7.28–7.03 (m, 5H), 3.48–3.33 (m, 2H), 2.96–2.87 (m, 1H), 2.74–2.87 (m, 1H), 2.16 (dd, *J*=5.6, 8.8 Hz, 1H), 2.10 (dd, *J*=6.5, 8.8 Hz, 1H), 1.73 (aparent t, *J*=6.0 Hz, 1H), 1.45 (s, 3H), 0.76 (t, *J*=7.1 Hz, 6H); ¹³C RMN (75 MHz, CDCl₃): δ =170.5 (C), 138.6 (C), 127.9 (CH), 126.3 (CH), 125.8 (CH), 40.4 (CH₂), 38.2 (CH₂), 31.7 (CH), 31.5 (C), 23.3 (CH₃), 19.5 (CH₂), 13.2 (CH₃), 11.8 (CH₃); MS (70 eV): *m/z* (%): 231 (64) [M]⁺, 216 (12), 202 (5), 158 (32), 144 (11), 140 (26), 131 (46), 115 (38), 100 (72), 91 (100), 72 (82); IR 3062, 2975, 2931, 2878, 1632, 1461,

1427, 1382, 1253, 1129, 1066 cm⁻¹; R_f (0.2 hexane/AcOEt 3/1).

4.4.5. $(1R^*, 2S^*)$ -*N*,*N*-Diethyl-1-methyl-2-(4-methoxyphenyl)cyclopropanocarboxamide (8g). ¹H NMR (300 MHz, CDCl₃): δ =6.97–6.72 (m, 4H), 3.50 (s, 3H), 3.48–3.29 (m, 2H), 3.07–2.89 (m, 1H), 2.79–2.67 (m, 1H), 2.06–2.01 (m, 1H), 1.65 (aparent t, *J*=6.0 Hz, 1H), 1.42 (s, 3H), 1.01 (dd, *J*=5.5, 8.8 Hz, 1H), 0.86–0.76 (m, 6H); ¹³C RMN (100 MHz, CDCl₃): δ =170.6 (C), 157.7 (C), 130.6 (C), 127.2 (CH), 113.2 (CH), 55.0 (CH₃), 40.4 (CH₂), 38.1 (CH₂), 31.0 (C), 30.9 (CH), 23.2 (CH₃), 19.1 (CH₂), 13.2 (CH₃), 11.8 (CH₃); MS (70 eV): *m/z* (%): 261 (32) [M]⁺, 192 (28), 188 (100), 174 (19), 161 (49), 145 (31), 134 (20), 121 (43), 115 (29), 100 (26), 91 (47), 72 (56); IR 3035, 2947, 2878, 2837, 1628, 1516, 1442, 1381, 1300, 1249, 1129, 1034 cm⁻¹; *R*_f (0. 28 hexane/AcOEt 1/1).

4.4.6. ($1S^*, 2R^*$)-*N*,*N*-Diethyl-2-ethyl-2-phenyl-1-methylcyclopropanocarboxamide (8h). ¹H NMR (300 MHz, CDCl₃): δ = 7.45–7.01 (m, 5H), 3.54–3.27 (m, 4H), 2.75– 2.49 (m, 2H), 2.21 (d, *J* = 5.41 Hz, 1H), 1.46 (s, 3H), 1.03 (t, *J* = 7.12 Hz, 3H), 0.82 (t, *J* = 7.12 Hz, 3H), 0.53 (d, *J* = 5.41 Hz, 1H), 0.32 (t, *J* = 7.12 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃): δ = 171.4 (C), 138.8 (C), 127.6 (CH), 127.5 (CH), 125.7 (CH), 40.8 (CH₂), 37.9 (CH₂), 35.6 (C), 34.3 (C), 25.7 (CH₂), 22.9 (CH₂), 18.8 (CH₃), 13.5 (CH₃), 11.0 (CH₃), 10.8 (CH₃); MS (70 eV): *m/z* (%): 259 (25) [M]⁺, 244 (12), 91 (91), 42 (100); IR 3058, 2968, 1628, 1450, 1381 cm⁻¹; HRMS Calcd for C₁₇H₂₅NO 259.1936; found 259.1933; *R*_f 0.3 (hexane/AcOEt 3/1).

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