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Ni(II)-catalyzed Michael additions. Part 2: Dynamic kinetic resolution in the reduction of chiral α-hydrazino-β-ketoacid derivatives☆

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Abstract—Relative *syn* 1,2-hydrazinoalcohols have been prepared through diastereoselective Ni(II)-catalyzed Michael addition of chiral derivatives of acetoacetic acid and of 3-oxostearic acid to dialkyl azodicarboxylates, followed by stereoselective reduction of the keto function. © 2002 Elsevier Science Ltd. All rights reserved.

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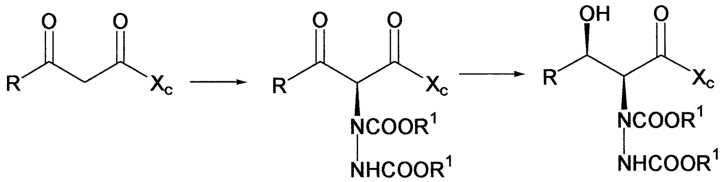
1. Introduction

The Michael reaction is one of the most common methods for the formation of C–C bonds. However, the limitations of conjugate additions caused by basic catalysts are well known. The use of transition metals under essentially neutral conditions normally offer advantages.[2] Furthermore, this approach allows the use of chiral ligands in asymmetric Michael reactions.[3] Of particular significance is the work of Shibasaki[4] based on the use of BINOL and heterobimetallic catalysts, containing two metal centers where one is a lanthanide capable of activating the acceptor, while lithium coordinates to the enolate. Other combinations have been used like Ni(II) and a chiral diamine,[5] Co(II) and a chiral bis(dihydroxazolylphenyl)-oxalamide,[6] and Mg(II) and an aminoindanol derived bis(oxazoline).[7]

An alternative approach relies on the use of a chiral auxiliary in the nucleophile.[8] We are particularly interested in diastereoselective metal-catalyzed Michael reactions using chiral 1,3-dicarbonyl compounds as nucleophiles. Related significant works are the ones by d'Angelo[9] who has reported the use of chiral enamines prepared from β-oxo esters and Christoffers[10] who uses chiral enamino esters which undergo copper-catalyzed asymmetric reactions. Our approximation is based on the use of chiral derivatives of β-ketoacids as nucleophiles (Scheme 1).

We have previously reported that Ni(salicylaldehydate)$_2$ is an efficient catalyst for reactions of a series of Michael acceptors and 3-methyl-2,4-pentanedione and ethyl 2-methyl-3-oxobutanoate with generation of quaternary centers.[1] Moreover, some of these reactions have been performed under organic-perfluorinated biphasic conditions. Reactions were carried out four consecutive times with high yields using the same perfluorinated phase where the catalyst was dissolved. In this case, a Ni(II) complex of the Schiff base of salicylaldehide and 4-perfluorodecylaniline was used.[11]



Scheme 1.

☆ For part 1, see Ref. 1.

Keywords: nickel catalysis; conjugate addition; chiral induction; *syn*-1,2-hydrazinoalcohol; kinetic resolution; β-ketoacid derivatives.

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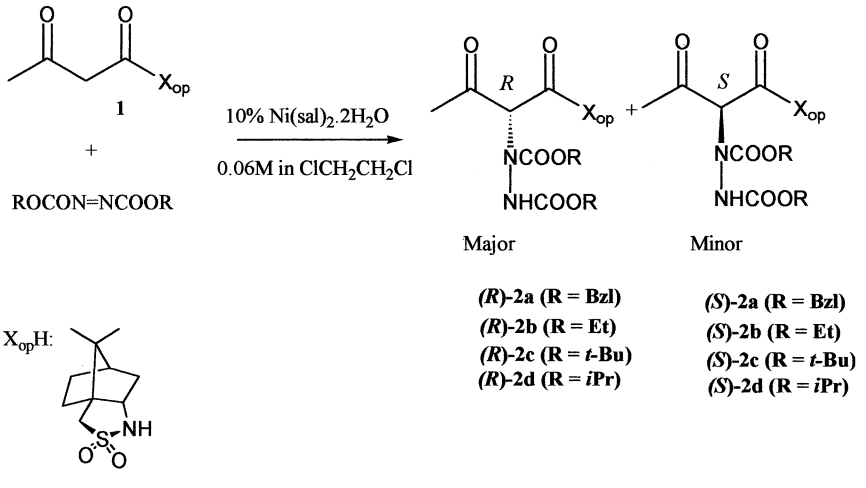


Scheme 2.

Our group has also explored Ni(II)-catalyzed diastereoselective Michael additions of *N*-acetoacetyl derivative of enantiomerically pure Evans oxazolidinone to a broad list of electrophiles. Useful diastereoselectivities have been achieved.[1]

The aim of this work is to establish a new practical methodology to prepare enantiopure 1,2-hydrazynoalcohols based on a diastereoselective Ni(II)-catalyzed Michael addition step followed by stereoselective reduction of the keto function (Scheme 1).

2. Results

Preliminary experiments showed that Oppolzer's sultam was the chiral auxiliary of choice when using chiral derivatives of acetoacetic acid. *N*-Acetoacetyl-(*R*)-bornane-10,2-sultam, **1** (Scheme 2) was prepared as described previously.[12] In adducts **2**, the diastereomeric integrity is compromised by the remaining intercarbonilic active proton, hence we use Ni(salicylaldehyate)$_2$·H$_2$O as catalyst in neutral medium. Ni(II)-catalyzed conjugate additions of **1** to different dialkyl azodicarboxylates gave excellent chemical yields and moderate diastereomeric excesses (Scheme 2 and Table 1). For the reaction of dibenzyl azodicarboxylate, an increase in diastereomeric excesses is observed along time, indicating that an equilibration occurs till it reaches a thermodynamic control which corresponds to a 78% of de (entries 1–4 and entries 5–8 of Table 1). The best result was obtained in the case of diethyl azodicarboxylate affording **2b** in 84% de.

Table 1. Conjugate additions of acetoacetyl derivatives of Oppolzer's sultam to different dialkyl azodicarboxylates promoted by Ni(II) (Scheme 2)

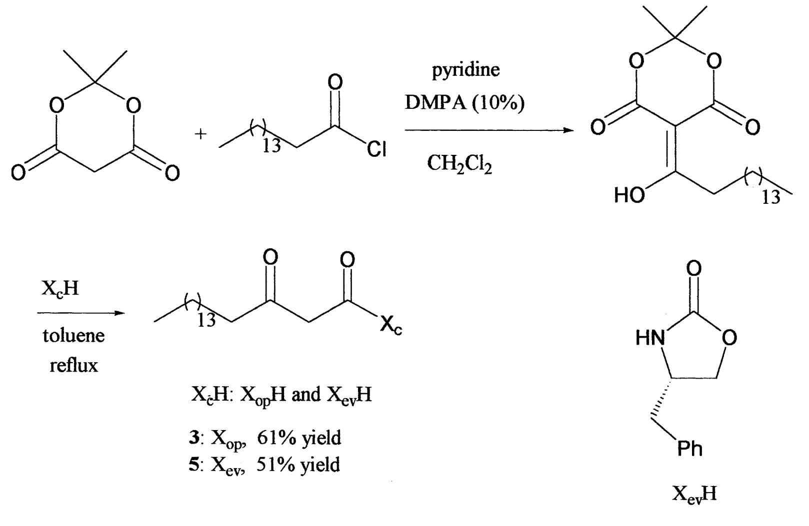
Entry	R	*T* (°C)	*t* (h)	**2**	Yield **2** (%)[a]	de[b] **2** (%)
1	Bzl	Rt	17	**2a**	100[c]	46
2	Bzl	Rt	48	**2a**	100[c]	56
3	Bzl	Rt	72	**2a**	100[c]	68
4	Bzl	Rt	144	**2a**	100[c]	77
5	Bzl	35	7	**2a**	100[c]	30
6	Bzl	35	17	**2a**	100[c]	74
7	Bzl	35	48	**2a**	(77)	76
8	Bzl	35	120	**2a**	100[c]	78
9	Et	35	48	**2b**	67 (60)	84
10	*t*-Bu	35	48	**2c**	75 (66)	80
11	*i*Pr	35	17	**2d**[d]	100[c]	55

[a] Overall yield and, in parentheses, yield of isolated major diastereoisomer (*R*)-**2**.
[b] Diastereomeric excesses were determined by ^{1}H NMR integration of well separated signals.
[c] Conversion yields were determined by ^{1}H NMR.
[d] Not isolated.

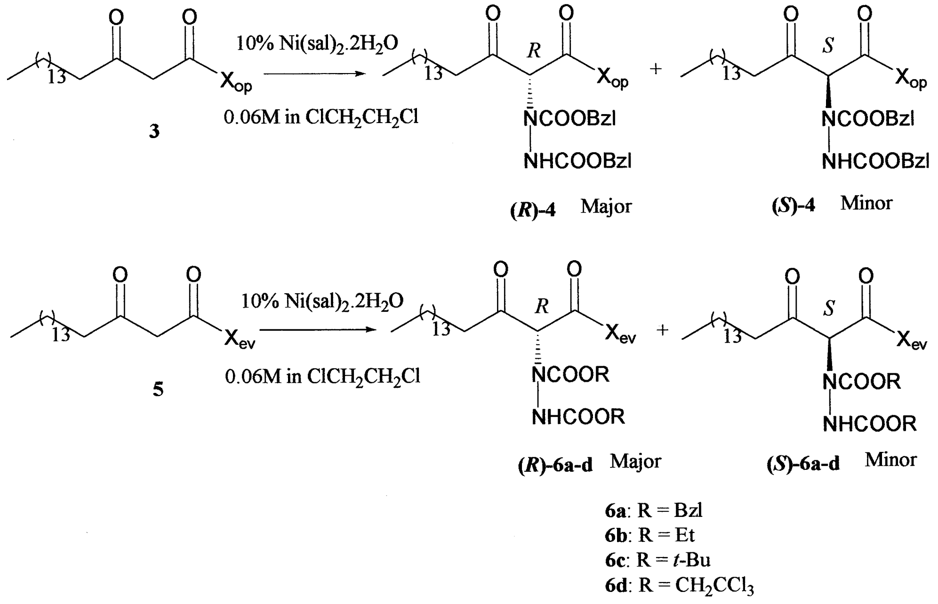
The major diastereoisomers **2** were separated by column chromatography and no epimerization was observed. The reaction of **1** with dibenzyl azodicarboxylate afforded diastereoisomer (*R*)-**2a** with a 77% yield (entry 7 of Table 1). This compound has been previously prepared by our group through a ruthenium-catalyzed Michael addition of **1** and dibenzyl azodicarboxylate.[13] Furthermore, we have noticed that the stereochemical preference using Ni(salycilaldehyate)$_2$ or RuH$_2$(PPh$_3$)$_4$ is the same if the chiral auxiliary is identical. In addition, it is also the same as that previously described for the Oppolzer's sultam in conventional alkylations.[14] Consequently, we assume the same (*R*) configuration for all major diastereoisomers **2b**, **2c**, and **2d**. In related cases where Evans oxazolidinone was used as chiral auxiliary, no isolation was possible without epimerization.[1]

Other chiral β-ketoamides were also studied. Chiral derivatives of 3-oxostearic acid **3** and **5** (Scheme 3) were obtained in 61 and 51% yields, respectively, through acylation of Meldrum's acid with palmitoyl choride and then reaction with the chiral auxiliary (Scheme 3). This methodology has been previously applied only to more simple alcohols and amines.[15] Best yields were obtained by adding a catalytic amount of DMAP (10%) under nitrogen atmosphere in the formation of the acylated Meldrum's acid.

Michael additions of **3** and **5** were carried out with different dialkyl azodicarboxylates. Ni(salycilaldehyate)$_2$ was used as catalyst (Scheme 4). Diastereomeric excesses were only moderate (Table 2). On one hand, we have observed an increase in de with time for compound **4** until thermodynamic equilibrium (entries 2 and 3 of Table 2) has been reached, on the other hand, configurational stability is



Scheme 3.



Scheme 4.

Table 2. Conjugate additions of 3-oxostearic acid derivatives of Oppolzer's sultam to different dialkyl azodicarboxylates promoted by Ni(II) (Scheme 4)

Entry		R	*T* (°C)	*t*		de[a] (%) **4–6**
1	**3**	Bzl	0	24 h	**4**	–[b]
2	**3**	Bzl	Rt	17 h	**4**	60
3	**3**	Bzl	Rt	14 days	**4**	76
4	**5**	Bzl	r.t	18 h	**6a**	20
5	**5**	Et	Rt	17 h	**6b**	64
6	**5**	Et	Rt	6 days	**6b**	60
7	**5**	*t*-Bu	Rt	72 h	**6c**	–[b]
8	**5**	*t*-Bu	50	48 h	**6c**	0
9	**5**	CH_2CCl_3	Rt	18 h	**6d**	–[c]

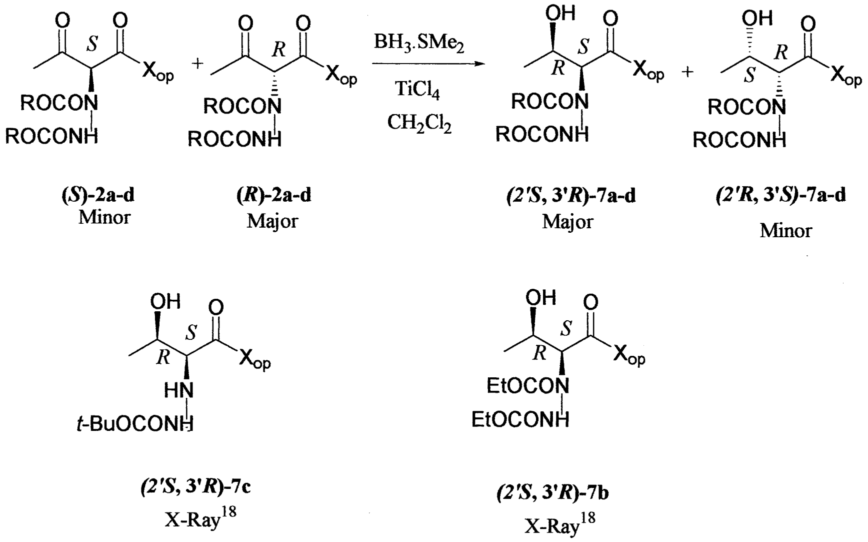
[a] Diastereomeric excesses were determined by ^1H NMR integration of well separated signals.

[b] No reaction under these conditions.

[c] Not determined.

noticed for **6b** (entries 5 and 6 of Table 2). Thereby the stereochemical stability depends on the chiral auxiliary present at the compound.

Conjugate addition diastereoisomers **2**, **4** and **6** were normally not separated and reduction of the keto function was performed in a stereoselective manner. We have initially studied the reduction of a diastereomeric mixture of **2a** (Scheme 5). The use of $Zn(BH_4)_2$ as reductor for chiral β-ketoamides has been reported in the literature.[16] In our group we have previously used it successfully, to reduce the keto group of a similar compound but having Evans' oxazolidinone as chiral auxiliary.[1] Nevertheless, reduction of **2a** failed. Then, we turned our attention to $BH_3·SMe_2$ as reducing agent in the presence of $TiCl_4$ as a chelator Lewis acid.[17] It is worth remarking that under these conditions, practically only one of the four possible stereoisomers



(S)-2a-d Minor

(R)-2a-d Major

(2′S, 3′R)-7a-d Major

(2′R, 3′S)-7a-d Minor

(2′S, 3′R)-7c X-Ray[18]

(2′S, 3′R)-7b X-Ray[18]

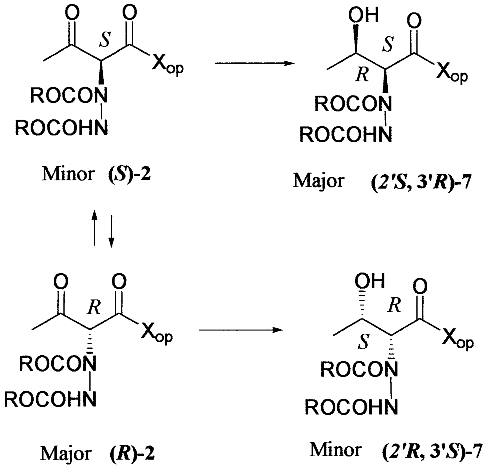
Scheme 5.

Table 3. Reduction of the keto function of Michael adducts from acetoacetyl derivatives of Oppolzer's sultam with BH_3 and $TiCl_4$ (Scheme 5)

Entry	**2**	R	*T* (°C)	*t* (min)	**7**	de[a] **2** (%)	de[a] **7** (%)	Yield[b] **7** (%)
1	**2a**	Bzl	−23	15	**7a**	76	95	67[c]
2	**2a**	Bzl	−23	20	**7a**	40	95	64
3	**2a**	Bzl	−23	60	**7a**	–[d]	95	55
4	**2b**	Et	−23	10	**7b**	56	78	65
5	**2b**	Et	0	10	**7b**	56	97	100[e]
6	**2c**	*t*-Bu	−23	20	**7c**	74	60	32
7	**2d**	*i*Pr	−23	10	**7d**[f]	52	70	100[e]
8	**2d**	*i*Pr	0	10	**7d**[f]	52	94	100[e]

[a] Diastereomeric excesses were determined by ^1H NMR integration of well separated signals.
[b] Yield corresponding to the two consecutive steps (Michael addition and reduction).
[c] Yield corresponding to the reduction step.
[d] Not determined.
[e] Conversion yield determined by ^1H NMR.
[f] Not isolated.

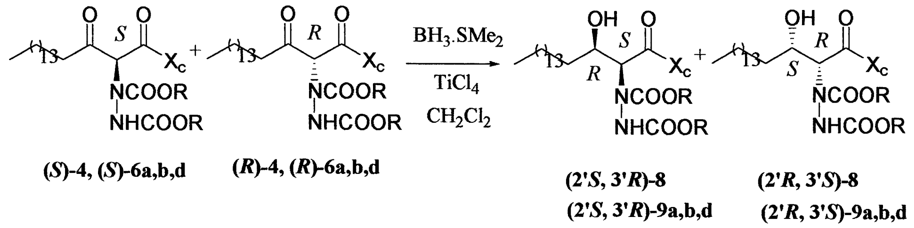
is obtained with a high de of 94–97% (Table 3) in the reduction of **2a**, **2b** and **2d**. For compound **7c**, breaking of one of the amide groups has been observed (Scheme 5). It has been extensively described that this reduction protocol when applied to β-ketoesters and β-ketosulfones gives a high diastereoselectivity in favor of the corresponding *syn* stereoisomer. In our case, we suppose that the same *syn* stereochemistry is obtained in all cases. This was confirmed for **7c** (2′*S*,3′*R*) and **7b** (2′*S*,3′*R*) from X-ray diffraction analysis.[18] The configuration of C-2 for the major diastereoisomer has changed from compounds **2** (*R*) to compounds **7** (*S*). A dynamic kinetic resolution process could explain these results (Scheme 6). If epimerization of diastereoisomers (*R*)-**2** and (*S*)-**2** is rapid enough with respect to the reduction step and their rates of the reduction are substantially different, the reduction would afford only one stereoisomer. In our case, under the reaction conditions, the major diastereoisomer (*R*) of Michael reaction epimerises to the minor (*S*) which is reduced to afford an unique stereoisomer (2′*S*,3′*R*)-**7**. Consequently, from different diasteromeric mixtures of **2a** the same unique alcohol is obtained (entries 1 and 2 of Table 3).



Scheme 6.

Other reductants such as $LiBH_4$ and DIBAL-H gave worst results.

Concerning the reduction of Michael adducts derived from



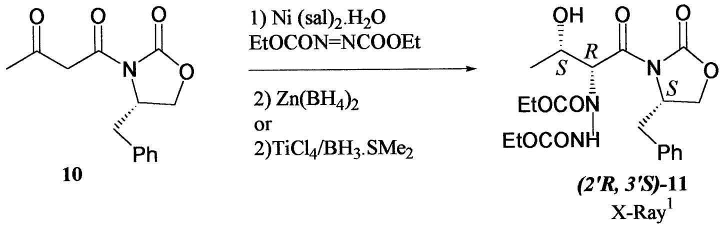
4 and **8** (X_{op} and R = Bzl)
6a and **9a** (X_{ev}, R = Bzl)
6b and **9b** (X_{ev}, R = Et)
6d and **9d** (X_{ev}, R = CH_2CCl_3)

Scheme 7.

Table 4. Reduction of the keto function of Michael adducts from chiral 3-oxostearic acid with BH_3 and $TiCl_4$ (Scheme 7)

Entry		T (°C)	t		de[a] **4–6** (%)	de[a] **8** and **9** (%)	Yield[b] **8** and **9** (%)
1	**4**	−23	10 min	**8**	16	74	–[c]
2	**4**	−23	20 min	**8**	0	74	–[c]
3	**4**	−23	25 min	**8**	76	97	(47)
4	**4**	0	15 min	**8**	–[d]	0	–[c]
5	**6a**	−23	3 h	**9a**	60	60	39 (36)
6	**6b**	−23	1.5 h	**9b**	60	60	60 (47)
7	**6d**	−23	2 h	**9d**	–[d]	20	64 (43)

[a] Diastereomeric excesses were determined by ^{1}H NMR integration of well separated signals.
[b] Overall reaction yield and, in parentheses, yield of major diastereoisomer.
[c] Not isolated.
[d] Not determined.



Scheme 8.

2-oxostearic acid (Scheme 7) we have applied the best conditions found for **2**. Isolation of major alcohols in good yields has been possible. It has to be considered that yields given in Table 4 correspond to the two steps (Michael addition and reduction). In addition, we have observed that the diastereomeric excesses of hydrazinoalcohol **8** (X_{op}) obtained at different reaction times are much higher than the ones of starting ketone, **4** (entries 1–3 of Table 4), and that the major alcohol comes from the minor ketone. This indicates that at −23°C, a kinetic resolution has taken place.

We have observed that selectivity does not increase monotonically with decreasing temperature (entries 4 vs 5 and 7 vs 8 of Table 3, and entries 3 vs 4 of Table 4). This is not unexceptional since there are many examples of such a behavior satisfactorily explained by the isoinversion principle. They are either due to variations in the nature of the rate determining step with temperature, or due to changes in mechanism. An indepth study on this phenomenon has been published.[19]

The absolute configuration of the hydrazinoalcohol **8** (2′*S*,3′*R*) was assigned by comparison of the stereochemistry previously assigned to the hydrazinoalcohols **7** which have the same chiral auxiliary (X_{op}). This is reasonable because all these compounds have been obtained through the same reactions. In addition, comparison of the molar rotation of **8** and (*R*)-**2a** (similar substances with unequal molecular weights) show a great coincidence (for **2a** $[M]=258$ ($CHCl_3$) and for **8** $[M]=209$ ($CHCl_3$)).

Reduction of Michael adducts from *N*-acetoacetyl-4-benzyloxazolidin-2-one using $Zn(BH_4)_2$ allowed the formation of an unique alcohol with a stereochemistry 2′*R*,3′*S* (X-ray diffraction analysis of **11**).[1] Now, we report that when the reduction is carried out with $TiCl_4/BH_3{\cdot}SMe_2$, the same major alcohol is obtained, consequently exhibiting identical specific rotation (Scheme 8). We assume the same chirality for the major diastereoisomers **9a**,**b**,**d** as for **11**. Molar rotations of **11** ($[M]=139$ ($CHCl_3$)) and (2′*R*,3′*S*)-**9b** ($[M]=144$ ($CHCl_3$)) were very similar as expected.

3. Conclusion

Nickel(salycilaldehydate)$_2$ catalyses useful Michael additions of enantiomerically pure acetoacetic and 3-oxostearic acid derivatives of common chiral auxiliaries (X_{op} and X_{ev}). The reduction of the corresponding chiral β-ketoamides can be carried out in a stereoselective manner using BH_3 in the presence of $TiCl_4$. When using X_{op}, a dynamic kinetic resolution is observed in this reduction step. Configurationally opposite enantiopure *syn*-1,2-hydrazinoalcohols have been obtained using Oppolzer sultam (2′*S*,3′*R*) or Evans oxazolidinone (2′*R*,3′*S*).

4. Experimental

4.1. General

Melting points were determined with a Kofler apparatus and are uncorrected. IR spectra were recorded with a Nicolet FT-IR 510 ZDX. NMR spectra were recorded with a Bruker AC 250 or a Bruker AM 244. ^{1}H NMR chemicals shifts are reported relative to tetramethylsilane at $\delta=0.0$. ^{13}C NMR chemical shifts are expressed relative to tetramethylsilane at $\delta=0.0$. Mass spectra were obtained with a Hewlett–Packard 5989A spectrometer and determined at an ionizing voltage of 70 eV. Elemental analyses were performed at the 'Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona'.

4.2. General method for preparation of compounds 3 and 5

4.2.1. (4*S*)-*N*-(3-Oxooctadecanoyl}-4-benzyloxazolidin-2-one (5). Meldrum's acid (2.00 g, 13.8 mmol), dimethylaminopyridine (0.34 g, 2.7 mmol) and anhydrous pyridine (2.23 ml, 27.6 mmol) were dissolved in anhydrous dichloromethane (50 ml) with stirring under nitrogen atmosphere. The solution was cooled to 0°C and palmitoyl chloride (3.53 ml, 20.7 mmol) was then added to the mixture. The mixture was stirred for 2 h at 0°C and for 15 h at room temperature. The solvent was evaporated off and (4*S*)-4-benzyl-2-oxazolidinone (3.67 g, 20.7 mmol) was added to the residue. The mixture was dissolved in anhydrous toluene and was refluxed with stirring for 5 h. The solvent was evaporated and the residue was chromatographed through silica-gel. Compound **5** was eluted with hexanes/ethyl acetate (80:20) and obtained as an orange solid (3.51 g, 51% yield), mp 50–51°C: $[\alpha]_D^{20}=37$ ($c=0.98$, $CHCl_3$). IR (KBr) 2925, 2854, 1792, 1715, 1694, 1398, 1356, 1328, 1229, 1187 cm^{-1}. ^{1}H NMR (d_6-benzene, 400 MHz) δ 0.89 (t, $J=7.0$ Hz, 3H), 1.22–1.32 (m, 24H), 1.57 (t, $J=7.0$ Hz, 2H), 2.25 (dt, $J=7.0$, 1.2 Hz, 2H), 2.44 (dd, $J=11.4$, 9.4 Hz, 1H), 3.14 (dd, $J=13.7$, 3.2 Hz, 1H), 3.25 (t, $J=8.5$ Hz, 1H), 3.46 (dd, $J=9.1$, 1.8 Hz, 1H), 3.82 (s, 2H), 4.21–4.26 (m, 1H), 6.87 (d, $J=6.7$ Hz, 2H), 6.98–7.06 (m, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1, 22.6, 23.3, 29.0, 29.3, 29.4, 29.6 (7C), 31.9, 37.7, 42.9, 50.5, 54.9, 66.3, 127.3, 128.9 (2C), 129.4 (2C), 135.1, 153.6, 166.7, 203.4. ESI-MS (*m/z*): 458.53 $(M+1)^+$, 480.49 $(M+Na)^+$, 496.46 $(M+K)^+$. Anal. calcd for $C_{28}H_{43}O_4N$: C, 73.48; H, 9.47; N, 3.06. Found: C, 73.58; H, 9.57; N, 3.10.

4.2.2. (2*R*)-*N*-(3-Oxooctadecanoyl)bornane-10,2-sultam (3). The title compound was prepared as an oil (61% yield) following the same procedure as for **5**: $[\alpha]_D^{20}=-50$ ($c=1.08$, $CHCl_3$). IR (film) 2924, 2854, 1729, 1694, 1630, 1462, 1335 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.88 (t, $J=6.5$ Hz, 3H), 0.96 (s, 3H), 0.97 (s, 3H enol), 1.16 (s, 3H), 1.17 (s, 3H enol), 1.26 (s broad, 24H), 1.56 (m, 2H), 1.89–2.34 (m, 7H), 2.50 (t, $J=7.3$ Hz, 2H), 3.37 (center AB system, $J=13.8$ Hz, 1H), 3.50 (center AB system, $J=13.8$ Hz, 1H), 3.64 (d, $J=16.8$ Hz, 1H), 3.88 (q, $J=4.0$ Hz, 1H), 4.01 (d, $J=16.8$ Hz, 1H), 5.63 (s, enol), 8.73 (s, enol). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 14.0, 19.8, 20.8, 22.8, 23.3, 26.4, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.6 (4C), 29.4, 31.8, 32.6, 37.9, 43.1, 44.8, 47.7, 48.5, 49.9, 52.6, 64.9, 164.8, 202.3. Anal. calcd for $C_{28}H_{49}NO_4S$: C, 67.84; H, 9.96; N, 2.83; S, 6.47. Found: C, 67.93; H, 10.07; N, 2.76; S, 5.17.

4.3. General method for preparation of compounds 2b and c, 4, 6a–d

4.3.1. (2*R*,2′*R*)-*N*-{2′-[*N*,*N*′-Bis(ethyloxycarbonyl)hydrazino]-3′-oxobutanoyl}bornane-10,2-sultam ((*R*)-2b). Ethylazodicarboxylate (0.418 g, 2.40 mmol) was added to a mixture of **1** (0.600 g, 2.00 mmol) and Ni(salicylaldehyde)$_2$–2H_2O (0.067 g, 0.20 mmol, 0.06 M) in 1,2-dichloroethane (3.3 ml) at 35°C under magnetic stirring during 48 h. The resulting solution was washed with 1 M hydrochloric acid and water. The organic layer was dried and evaporated. The resulting oil was a diastereomeric mixture of (*R*)-**2b** and (*S*)-**2b** in a ratio 92:8 (84% de). The residue was purified by chromatography through silica-gel using hexanes/diethylether (50:50) as eluent to give 0.567 g (60%) of the major diastereoisomer of (*R*)-**2b** as a solid, mp 58–60°C: $[\alpha]_D^{20}=61.2$ ($c=0.85$, $CHCl_3$). IR (KBr) 3446, 1738, 1700, 1331, 1223 cm^{-1}. ^{1}H NMR (d_6-benzene, 336 K, 250 MHz) δ 0.46 (s, 3H), 0.68–0.87 (m, 2H), 0.91 (t, $J=7.3$ Hz, 3H), 1.02 (t, $J=7.3$ Hz, 3H), 1.06 (s, 3H), 1.24–1.41 (m, 3H), 1.81 (dd, $J=13.9$, 8.0 Hz, 1H), 2.26 (dq, $J=13.9$, 5.1 Hz, 1H), 2.50 (s, 3H), 2.77 (center of AB system, 2H), 3.56 (dd, $J=8.0$, 5.1 Hz, 1H), 3.92 (dt, $J=7.3$, 5.1 Hz, 2H), 4.03 (dd, $J=9.5$, 7.3 Hz, 2H), 6.51 (s, 1H); MS-NH_3 (*m/z*, %): 474 (4) $[M^++1]$, 249 (71), 233 (100), 216 (93). ^{13}C NMR (d_6-benzene, 336 K, 62.5 MHz) mixture of conformational isomers δ 14.7, 14.8, 20.3, 20.4, 20.7, 20.8, 27.2, 33.1, 38.3, 38.5, 38.7, 45.5, 48.5, 49.6, 52.8, 52.9, 53.1, 62.3, 62.5, 62.7, 63.9, 64.2, 65.4, 65.5, 71.0, 71.1, 156.6, 157.0, 168.2, 198.4. Anal. calcd for $C_{20}H_{31}N_3O_8S$: C, 50.71; H, 6.60; N, 8.91; S, 6.78. Found: C, 50.78; H, 6.56; N, 8.72; S 6.05.

4.3.2. (2*R*,2′*R*)-*N*-{2′-[*N*,*N*′-Bis(*tert*-butyloxycarbonyl)-hydrazino]-3′-oxobutanoyl}bornane-10,2-sultam ((*R*)-2c). The title compound was prepared as a solid (66% yield), mp 66–69°C, following the same procedure as for **2b**: $[\alpha]_D^{20}=56.1$ ($c=0.82$, $CHCl_3$). IR (KBr) 3412, 1738, 1705, 1334, 1157 cm^{-1}. ^{1}H NMR (d_6-benzene, 336 K, 250 MHz) δ 0.46 (s, 3H), 0.68–0.84 (m, 2H), 1.06 (s, 3H), 1.31 (s, 9H), 1.23–1.38 (m, 3H), 1.43 (s, 9H), 1.80 (dd, $J=13.9$, 7.3 Hz, 1H), 2.25 (dq, $J=13.9$, 3.7 Hz, 1H), 2.49 (s, 3H), 2.76 (center of AB system, $J=13.9$, 2.77 Hz, 2H), 3.53 (dd, $J=7.3$, 4.4 Hz, 1H), 6.44 (s, 1H). ^{13}C NMR (d_6-benzene, 336 K, 250 MHz) mixture of conformational isomers δ 20.3, 20.5, 20.8, 20.9, 27.2, 28.8, 33.1, 38.3, 38.5, 38.7, 45.5, 48.5, 49.6, 52.8, 53.0, 53.2, 65.5, 65.7, 71.2, 71.5, 81.5, 83.5, 155.7, 155.8, 168.4, 198.6. Anal. calcd for $C_{24}H_{39}N_3O_8S$: C, 54.41; H, 7.42; N, 7.97; S, 6.05. Found: C, 54.69; H, 7.49; N, 7.78; S, 5.36.

4.3.3. (2*R*,2′*R*)-*N*-{2′-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]-3′-oxooctadecanoyl}bornane-10,2-sultam ((2′*R*)-4). The title compound was prepared as a liquid following the same procedure as for **2b**, but in this case the reaction was carried out at room temperature and under stirring during 18 h. No purification was required before performing the next reaction. Only an aliquot was purified. IR (film) 3330, 2924, 2854, 1734, 1699, 1332, 1218, 1157, 739, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 336 K, 250 MHz) δ 0.46 (s, 3H), 0.72–0.79 (m, 3H), 0.83 (t, J=7.3 Hz, 3H), 1.06 (s, 3H), 1.27–1.38 (m, 28H), 1.65–175 (m, 2H), 1.81 (dd, J=13.9, 8.0 Hz, 1H), 2.27 (dq, J=13.9, 3.7 Hz, 1H), 2.49 (s, 3H), 2.72 (part B of AB system, J=13.9 Hz, 1H), 2.82 (part A of AB system, J=13.9 Hz, 1H), 3.53 (dd, J=8.0, 5.1 Hz, 1H), 4.94–5.13 (m, 4H), 6.57 (s, 1H), 7.04–7.23 (m, 10H), 7.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 336 K, 62.5 MHz) mixture of conformers 20.2 and 20.4, 20.8, 20.9, 23.5, 27.1, 29.9, 30.3, 30.4, 30.5, 30.6, 30.7, 32.9, 36.7, 42.0, 45.5, 48.5, 49.6, 53.0, 65.5 and 65.7, 68.2 and 68.3, 68.4, 68.5, 69.8 and 69.9, 70.0, 128.0, 128.2, 128.6, 128.9, 129.0, 129.2, 136.5, 137.2, 156.5 and 157.0, 168.3, 201.0. Anal. calcd for $C_{44}H_{63}N_3O_8S$: C, 66.55; H, 8.00; N, 5.29; S, 4.04. Found: C, 66.99; H, 8.14; N, 5.04, S, 3.63.

4.3.4. (4*S*)-*N*-{2′-[*N*,*N*′-Bis(benzyloxycarbonyl) hydrazino]-3′-oxooctadecanoyl}-4-benzyloxazolidin-2-one ((2′*R*)-6a and (2′*S*)-6a). The title compounds were prepared as oils following the same procedure as for **2b**, but in this case, the reaction was carried out at room temperature and under stirring during 18 h. No purification was required before performing the next reaction. An aliquot was purified by chromatography through silica-gel using mixtures of hexanes/ethylacetate as eluent to obtain a mixture of diastereoisomers: IR (film) 3332, 2924, 2854, 1785, 1757, 1722, 1701, 1215 cm^{-1}. ^{1}H NMR (d_6-benzene, 360 K, 250 MHz) δ 0.89 (t, J=6.9 Hz, 3H+3H), 1.29 (s broad, 24H+24H), 1.67–1.87 (m, 2H+2H), 2.30–2.35 (m, 1H), 2.44 (dd, J=13.8, 9.5 Hz, 1H), 2.79 (dd, J=13.2, 2.7 Hz, 1H), 2.86–3.03 (m, 1H+1H), 3.18–3.49 (m, 3H+3H), 4.03–4.13 (m, 1H), 4.17–4.24 (m, 1H), 4.89–5.15 (m, 4H+4H), 6.18–7.08 (m, 15H+15H), 7.37 (s broad, 1H+1H). ^{13}C NMR (d_6-benzene, 336 K, 62.5 MHz) δ 14.7 (2C), 23.5 (2C), 24.2 (2C), 29.9 (2C), 30.2 (2C), 30.4 (2C), 30.4 (2C), 30.5 (2C), 30.6 (2C), 30.7 (2C), 32.8 (2C), 38.3, 38.4, 41.8 (2C), 55.8 (2C), 67.6 (2C), 68.4 (2C), 69.8 (2C), 70.9, 71.8, 127.9–130.3 (30C), 136.0, 136.4, 136.7, 136.8, 137.0 (2C), 154.3, 154.4, 156.6 (2C), 157.4 (2C), 169.3, 169.5, 201.7, 201.9. ESI-MS: 756.37 [M+1]$^+$, 778.40 [M+Na]$^+$, 794.38 [M+K]$^+$. Anal. calcd for $C_{44}H_{57}N_3O_8$: C, 69.91; H, 7.59; N, 5.56. Found: C, 69.73; H, 7.57; N, 5.36.

4.3.5. (4*S*)-*N*-{2′-[*N*,*N*′-Bis(ethyloxycarbonyl)hydrazino]-3′-oxooctadecanoyl}-4-benzyloxazolidin-2-one ((2′*R*)-6b and (2′*S*)-6b). The title compounds were prepared as oils following the same procedure as for **2b**, but in this case the reaction was carried out at room temperature and under stirring during 17 h. No purification was required before performing the next reaction. An aliquot was purified by chromatography through silica-gel using mixtures of hexanes/ethylacetate as eluent to obtain a mixture of diastereoisomers: IR (film) 3289, 2924, 2853, 1785, 1750, 1714, 1693, 1384, 1328, 1215 cm^{-1}. ^{1}H NMR (d_6-benzene, 360 K, 250 MHz) δ 0.89 (t, J=7 Hz, 3H), 0.95–1.06 (m, 6H), 1.29 (s broad, 24H), 1.75–1.91 (m, 2H), 2.38–2.52 (m, 1H), 2.81–3.06 (m, 2H), 3.21–3.51 (m, 3H), 3.92–4.07 (m, 4H), 4.09–4.28 (m, 1H), 6.83–6.91 (m, 2H), 6.99–7.07 (m, 3H), 7.24 (s broad, 1H). ^{13}C NMR (d_6-benzene, 336 K, 62.5 MHz) δ 14.7 (2C), 14.8, 14 9, 23.5 (2C), 24.3 (2C), 30.0 (2C), 30.3 (2C), 30.4 (2C), 30.5 (2C), 30.6 (2C), 30.7 (2C), 32.9 (2C), 38.3, 38.4, 41.7, 41.8, 55.8 (2C), 62.6 (2C), 64.2 (2C), 67.5, 67.6, 70.8, 71.8, 127.8, 128.0, 129.6, 129.7, 130.2 (2C), 135.9, 136.5, 154.2, 154.4, 156.5, 157.5, 169.6, 169.8, 201.9, 202.1. ESI-MS (*m*/*z*): 632.57 [M+1]$^+$, 654.54 [M+Na]$^+$, 670.48 [M+K]$^+$. Anal. calcd for $C_{34}H_{53}N_3O_8$: C, 64.64; H, 8.45; N, 6.65. Found: C, 64.72; H, 8.34; N, 6.47.

4.3.6. (4*S*)-*N*-{2′-[*N*,*N*′-Bis(*tert*-butyloxycarbonyl)hydrazino]-3′-oxooctadecanoyl}-4-benzyloxazolidin-2-one ((2′*R*)-6c and (2′*S*)-6c). The title compound was prepared as an oil following the same procedure as for **2b**, but in this case the reaction was carried out at 50°C and under stirring during 48 h. The crude was purified by chromatography through silica-gel using mixtures of hexanes/ethylacetate as eluent to obtain a mixture of diastereoisomers (63% yield). Pure first eluted diastereoisomer: IR (film) 3368, 2925, 2854, 1785, 1740, 1723, 1703, 1392, 1368, 1153 cm^{-1}. ^{1}H NMR (d_6-benzene, 360 K, 250 MHz) δ 0.88 (t, J=6.8 Hz, 3H), 1.29 (s broad, 24H), 1.37 (s, 9H), 1.43 (s, 9H), 1.68–1.88 (m, 2H), 2.43 (dd, J=13.6, 8.8 Hz, 1H), 2.84–2.97 (m, 2H), 3.25–3.33 (m, 1H), 3.37 (t, J=8.8 Hz, 1H), 3.48 (dd, J=8.9, 3.0 Hz, 1H), 4.20–4.29 (m, 1H), 6.84–6.87 (m, 2H), 6.97–7.10 (m, 3H), 7.11 (s, 1H). ^{13}C NMR (d_6-benzene, 336 K, 250 MHz) δ 14.7, 23.6, 24.3, 28.7 (3C), 28.9 (3C), 30.0, 30.3, 30.4, 30.5, 30.6, 30.7 (5C), 32.9, 38.4, 41.6, 55.9, 67.5, 72.1, 81.5, 83.3, 128.0, 129.6 (2C), 130.2 (2C), 136.1, 154.4, 155.6, 156.4, 170.0, 202.5. Anal. calcd for $C_{38}H_{61}N_3O_8$: C, 66.35; H, 8.94; N, 6.11. Found: C, 65.94; H 9.08; N, 5.98. Pure second diastereoisomer: IR (film) 3369, 2925, 2853, 1785, 1744, 1727, 1703, 1393, 1368, 1153 cm^{-1}. ^{1}H NMR (d_6-benzene, 360 K, 250 MHz) δ 0.88 (t, J=6.8 Hz, 3H), 1.29 (s broad, 24H), 1.37 (s, 9H), 1.44 (s, 9H), 1.68–1.93 (m, 2H), 2.47 (dd, J=13.8, 10 Hz, 1H), 2.88–3.01 (m, 2H), 3.22–3.40 (m, 2H), 3.48 (dd, J=8.6, 2.7 Hz, 1H), 4.09–4.12 (m, 1H), 6.16 (s broad, 1H), 6.88 (d, J=7.0 Hz, 2H), 6.98–7.07 (m, 3H), 7.11 (s, 1H). ^{13}C NMR (d_6-benzene, 336 K, 250 MHz) δ 14.7, 23.6, 24.3, 28.7 (3C), 28.9 (3C), 30.0, 30.3, 30.4, 30.5, 30.6, 30.7 (5C), 32.9, 38.4, 41.6, 55.8, 67.4, 72.2, 81.5, 83.3, 128.0, 129.6 (2C), 130.2 (2C), 136.6, 154.2, 155.6, 156.4, 170.0, 202.3.

4.3.7. (4*S*)-*N*-{2′-[*N*,*N*′-Bis(trifluoroethyloxycarbonyl)-hydrazino]-3′-oxooctadecanoyl}-4-benzyloxazolidin-2-one ((2′*R*)-6d and (2′*S*)-6d). The title compounds were prepared as oils following the same procedure as for **2b**, but in this case the reaction was carried out at room temperature and under stirring during 18 h. No purification was required before performing the next reaction. An aliquot was purified by chromatography through silica-gel using mixtures of hexanes/ethylacetate as eluent to obtain a mixture of diastereoisomers: IR (film) 3306, 2921, 2853, 1784, 1752, 1728, 1702, 1395, 1275, 1210 cm^{-1}. ^{1}H NMR (d_6-benzene, 360 K, 250 MHz) δ 0.94 (t, J=6.8 Hz, 3H), 1.33 (s broad, 24H), 1.71–1.93 (m, 2H), 2.46–2.58 (m, 1H), 2.93–3.09 (m, 1H), 3.21–3.33 (m, 3H), 3.45–3.63 (m, 1H), 4.27–4.35 (m, 1H), 4.54–4.63 (m, H), 6.86–7.22 (m, 5H), 7.72 (broad s, 1H). ^{13}C NMR (d_6-benzene, 336 K, 250 MHz) δ 14.7 (2C), 23.5 (2C), 24.2 (2C), 30.0 (2C), 30.3 (2C), 30.4 (2C), 30.6 (2C), 32.8 (2C), 38.3 (2C), 41.9 (2C), 55.9 (2C), 67.7, 67.9, 70.7, 71.5, 76.1 (2C), 77.1 (2C), 95.7, 95.9, 128.0 (2C), 129.6 (2C), 129.7 (2C), 130.1 (2C), 130.2 (2C), 135.8, 136.2, 154.2, 154.4, 154.7, 155.6, 168.7, 168.9, 200.8, 201.1. Anal. calcd for $C_{34}H_{47}N_3O_8Cl_6$: C, 48.70; H, 5.65; N, 5.01; Cl, 25.37. Found: C, 48.80; H, 5.81; N, 4.81; Cl, 25.74.

4.4. General method for preparation of compounds 7a–c

4.4.1. (2*R*,2′*S*,3′*R*)-*N*-{2-[*N*,*N*′-Bis(ethyloxycarbonyl)hydrazino]-3-hydroxybutanoyl}bornane-10,2-sultam ((2′*S*,3′*R*)-7b). A diasteromeric mixture of **2b** (0.476 g, 1.00 mmol) was dissolved in anhydrous dichloromethane with stirring and under nitrogen atmosphere. The solution was cooled to −23°C and a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1.2 ml, 1.2 mmol) was added. Followed by an immediate slow addition of a 10 M solution of BH_3–Me_2S in CH_2Cl_2 (100 μl, 1 mmol). The resulting mixture was stirred at −23°C during 10 min. Then 1 M HCl was added and the organic layer was washed with a saturated solution of NaCl in H_2O. The organic layer was then dried, evaporated and purified by chromatography on silica-gel, eluting with hexanes/diethylether (3:7). The unique alcohol (2′*S*,3′*R*)-**7b** was obtained a solid in 65% yield, mp 103–105°C: $[\alpha]_D^{20}=-63.5$ (c=0.63, $CHCl_3$). IR (KBr) 3415, 3378, 3295, 2980, 2962, 2933, 1733, 1710, 1686, 1333, 1219 cm^{-1}. ^{1}H NMR (d_6-benzene, 336 K, 250 MHz) δ 0.56 (s, 3H), 0.90–1.50 (m, 5H), 1.07 (s, 3H), 1.21 (t, J=7.3 Hz, 3H), 1.56 (t, J=7.3 Hz, 3H), 1.96 (dd, J=13.9, 8.0 Hz, 1H), 2.09 (dq, J=13.9, 3.7 Hz, 1H), 2.91 (center of AB system, J=25.6, 13.2 Hz, 2H), 3.76 (dd, J=7.3, 5.1 Hz, 1H), 4.03 (m, 2H), 4.19 (m, 2H), 4.62–4.85 (m, 2H), 5.69 (d, J=6.6 Hz, 1H). ^{13}C NMR (d_6-benzene, 336 K, 62.5 MHz) δ 14.7, 14.8, 20.2, 20.3, 21.0, 21.1, 27.1, 33.2, 38.7, 38.8, 39.0, 45.5, 48.4, 49.1, 53.4, 53.5, 53.6, 62.8, 63.1, 63.3, 63.9, 64.2, 65.9, 66.1, 67.6, 68.6, 157.0, 158.7, 170.3. MS-NH_3 (*m/z*, %): 476 (4) [M^++1], 4), 432 (68), 271 (100), 233 (95).

4.4.2. (2*R*,2′*S*,3′*R*)-*N*-{2-[*N*,*N*′-Bis(benzyloxycarbonyl)-hydrazino]-3-hydroxybutanoyl}bornane-10,2-sultam ((2′*S*,3′*R*)-7a). The title compound was prepared following the same procedure as for **7b**, but in this case was purified by chromatography through silica-gel using mixtures of hexanes/ethylacetate (2:3). The unique alcohol was obtained as a white solid in 67% yield (yield corresponding to the two consecutive steps, Michael addition and reduction), mp 177–178°C: $[\alpha]_D^{20}=-43.1$ (c=1.00, $CHCl_3$). IR (KBr) 3435, 3321, 2961, 1735, 1728, 1723, 1691, 1335, 1217, 748, 700 cm^{-1}; ^{1}H NMR (d_6-benzene, 336 K, 250 MHz) δ 0.46 (s, 3H), 0.75–0.91 (m, 2H), 0.97 (s, 3H), 1.15–1.36 (m, 3H), 1.44 (d, J=5.9 Hz, 3H), 1.84 (dd, J=13.9, 8.0 Hz, 1H), 2.00 (dq, J=13.9, 3.7 Hz, 1H), 2.78 (center of AB system, J=24.9, 13.9 Hz, 2H), 3.64 (dd, J=8.0, 5.1 Hz, 1H), 4.46 (broad s, 1H), 4.64 (sext, J=5.9 Hz, 1H), 4.94 (center of AB system, J=17.5, 12.4 Hz, 2H), 5.15 (center of AB system, J=18.3, 12.4 Hz, 2H), 5.63 (d, J=7.3 Hz, 1H), 7.03–7.30 (m, 10H); ^{13}C NMR (d_6-benzene, 336 K, 250 MHz) δ (mixture of conformers) 20.2 and 20.3, 21.2 and 21.3, 27.1, 33.2, 38.6 and 38.8, 39.0, 45.6, 48.5, 49.3, 53.6, 65.9, 66.1, 67.5 and 67.8, 68.7 and 68.8, 68.9, 69.5, 128.8, 129.1, 129.2, 136.9, 137.2, 156.9, 158.5, 169.8. Calcd for $C_{30}H_{37}N_3O_8S$: C, 60.08; H, 6.22; N, 7.01; S, 5.35. Found: C, 60.43; H, 6.13; N, 6.97; S, 5.14.

4.4.3. (2*R*,2′*S*,3′*R*)-*N*-{2-[*N*-*tert*-Butyloxycarbonylhydrazino]-3-hydroxybutanoyl}bornane-10,2-sultam ((2′*S*,3′*R*)-7c). The title compound was prepared following the same procedure as for **7b**, but in this case was purified by chromatography through silica-gel using mixtures of hexanes/diethylether (2:3). The unique alcohol was obtained as a white solid in 32% yield (yield corresponding to the two consecutive steps, Michael addition and reduction), mp 180–182°C: $[\alpha]_D^{20}=-51.7$ (c=0.58, $CHCl_3$). IR (KBr) 3400, 3306, 3268, 2976, 1728, 1686, 1334, 1277, 1139, 1111 cm^{-1}. ^{1}H NMR (d_6-benzene, 336 K, 250 MHz) δ 0.48 (s, 3H), 0.73–0.91 (m, 2H), 0.98 (s, 3H), 1.19–1.38 (m, 3H), 1.31 (d, J=5.9 Hz, 3H), 1.41 (s, 9H), 1.85 (dd, J=13.9, 8.0 Hz, 1H), 2.00 (dq, J=13.9, 5.1 Hz, 1H), 2.81 (center of AB system, J=24.1, 13.9 Hz, 2H), 3.67 (dd, J=8.0, 5.1 Hz, 1H), 4.19–4.23 (m, 2H), 4.65 (broad s, 1H), 6.02 (broad s, 1H)). ^{13}C NMR (d_6-benzene, 336 K, 62.5 MHz) δ (mixture of conformers) 20.1 and 20.2, 20.3, 21.2, 21.4, 27.1, 29.0, 33.4, 39.1, 45.7, 48.3, 49.0, 53.6, 53.7, 66.0, 66.1, 68.2, 68.5, 70.6, 70.9, 80.9, 157.6, 172.3. Calcd for $C_{19}H_{33}N_3O_6S$: C, 52.88; H, 7.71; N, 9.74; S, 7.43. Found: C, 53.12; H, 7.47; N, 9.42; S, 7.00.

4.4.4. (2*R*,2′*S*,3′*R*)-*N*-{2-[*N*,*N*′-Bis(benzyloxycarbonyl)-hydrazino]-3-hydroxyoctadecanoyl}bornane-10,2-sultam ((2′*S*,3′*R*)-8). The title compound was prepared as an oil following the same procedure as for **7b** but in this case the reaction was stirred at −23°C during 25 min. The residue was purified by chromatography through silica-gel using dichloromethane and an unique alcohol was obtained in 47% yield: $[\alpha]_D^{20}=-26.4$ (c=1.06, $CHCl_3$). IR (film) 3446, 3304, 2926, 2853, 1785, 1718, 1703, 1407, 1388, 1217 cm^{-1}. ^{1}H NMR (d_6-benzene, 343 K, 250 MHz) δ 0.47 (s, 3H), 0.79–0.90 (m, 3H), 0.81 (t, J=6.8 Hz, 3H), 1.00 (s, 3H), 1.22–1.32 (m, 28H), 1.40–2.02 (m, 4H), 2.81 (part A, AB system, J=13.8 Hz, 1H), 2.87 (part B, AB system, J=13.8 Hz, 1H), 3.68 (dd, J=7.5, 5.0 Hz, 1H), 4.42–4.47 (m, 1H), 4.85 (part A, AB system, J=12.5 Hz, 1H), 4.93 (part B, AB system, J=12.5 Hz, 1H),), 5.04 (part A, AB system, J=12.3 Hz, 1H), 5.13 (part B, AB system, J=12.3 Hz, 1H), 5.63 (d, J=6.6 Hz, 1H), 6.95–7.27 (m, 10H). ^{13}C NMR (d_6-benzene, 343 K, 250 MHz) δ 14.7, 20.3, 21.2, 23.6, 26.8, 27.1, 30.3, 30.5, 30.6 (2C), 30.7 (7C), 32.8, 33.2, 34.7, 38.8, 45.6, 48.5, 49.2, 53.6, 66.0, 68.0, 68.7, 69.6, 71.7, 128.8 (4C), 129.1 (4C), 129.2 (2C), 137.0, 137.2, 157.1, 158.3, 170.1. MALDI-TOF MS (*m/z*): 820.1 $[M+Na]^+$, 836.1 $[M+K]^+$. Calcd for $C_{44}H_{65}N_3O_8S$: C, 66.39; H, 8.23; N, 5.28; S, 4.03. Found: C, 66.41; H, 8.13; N, 5.53; S, 4.16.

4.4.5. (2*R*,2′*S*,3′*R*)-*N*-{2-[*N*,*N*′-Bis(benzyloxycarbonyl)-hydrazino]-3-hydroxyoctadecanoyl}bornane-10,2-sultam ((2′*R*,3′*S*)-8)). The title compound was isolated as the minor diastereoisomer from reduction of compound **4**: $[\alpha]_D^{20}=-11$ (c=1.01, CHCl$_3$). IR (film) 3437, 3318, 2924, 2853, 1734, 1719, 1691, 1335, 1215 cm^{-1}. ^{1}H NMR (d_6-benzene, 343 K, 250 MHz) δ 0.44 (s, 3H), 0.69–0.82 (m, 3H), 0.80 (t, *J*=6.6 Hz, 3H), 0.94 (s, 3H), 1.21–1.34 (m, 28H), 1.43–2.08 (m, 4H), 2.72 (part A, AB system, *J*=13.6 Hz, 1H), 2.81 (part B, AB system, *J*=13.6 Hz, 1H), 3.69 (dd, *J*=7.3, 4.7 Hz, 1H), 4.40–4.50 (m, 1H), 4.87 (broad s, 2H), 4.98 (part A, AB system, *J*=12.5 Hz, 1H), 5.05 (part B, AB system, *J*=12.5 Hz, 1H),), 5.20 (d, *J*=7.5 Hz, 1H), 6.94–7.19 (m, 10H), 7.18 (broad s, 1H). ^{13}C NMR (d_6-benzene, 343 K, 250 MHz) δ 14.7, 20.3, 21.7, 23.6, 26.8, 27.0, 30.3, 30.6, 30.7 (8C), 32.8, 33.7, 35.2, 39.2, 46.1, 48.3, 49.0, 53.7, 66.6, 67.9, 68.8, 69.5, 70.4, 128.8 (4C), 128.9 (4C), 129.2 (2C), 136.9, 137.1, 156.5, 158.4, 18.8.

4.4.6. (4*S*,2′*R*,3′*S*)-*N*-{2′-[*N*,*N*′-Bis(ethyloxycarbonyl)hydrazino]-3′-hydroxyoctadecanoyl}-4-benzyloxazolidin-2-one ((2′*R*,3′*S*)-9b). The title compound was prepared as an oil following the same procedure as for **7b** but in this case the reaction was stirred at −23°C during 1.30 h. The residue was purified by chromatography through silica-gel using dichloromethane. The major diastereoisomer (2′*R*,3′*S*)-**9b** was obtained in 47% yield: $[\alpha]_D^{20}=22.8$ (c=1.05, CHCl$_3$). IR (film) 3416, 3303, 2924, 2853, 1785, 1700, 1384, 1229 cm^{-1}. ^{1}H NMR (d_6-benzene, 400 MHz) δ 0.89 (t, *J*=6.8 Hz, 3H), 0.96 (t, *J*=7.2 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H), 1.29 (broad s, 24H), 1.55–1.69 (m, 1H), 1.75–1.88 (m, 2H), 1.96–2.03 (m, 1H), 2.41 (dd, *J*=11.5, 9.6 Hz, 1H), 3.11 (dd, *J*=13.4, 3.6 Hz, 1H), 3.39 (t, *J*=8.6 Hz, 1H), 3.52 (dd, *J*=8.9, 3.4 Hz, 1H), 3.91–4.08 (m, 4H), 4.20–4.30 (m, 1H), 4.47–4.52 (m, 1H), 6.38 (d, *J*=6.1 Hz, 1H), 6.90 (dd, *J*=7.9, 1.9 Hz, 2H), 7.00–7.10 (m, 3H). ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ 14.7, 14.8, 14.9, 23.6, 27.0, 30.3, 30.6 (8C), 30.7, 32.9, 34.6, 38.7, 56.2, 62.9, 63.9, 65.4, 66.9, 71.6, 128.0, 129.6 (2C), 130.2 (2C), 136.4, 153.5, 157.6, 158.0, 172.0. Calcd for $C_{34}H_{55}N_3O_8$: C, 64.43; H, 8.75; N, 6.63. Found: C, 64.41; H, 8.72; N, 6.51. The minor diastereoisomer (4*S*,2′*S*,3′*R*)-*N*-{2′-[*N*,*N*′-bis(ethyloxycarbonyl)hydrazino]-3′-hydroxyoctadecanoyl}-4-benzyloxazolidin-2-one, (2′*S*,3′*R*)-**9b**, was obtained in 13% yield: $[\alpha]_D^{20}=23.3$ (c=1.20, CHCl$_3$). IR (film) 3409, 3310, 2924, 2853, 1785, 1708, 1391, 1215 cm^{-1}. ^{1}H NMR (d_6-benzene, 400 MHz) δ 0.89 (t, *J*=8.0 Hz, 3H), 0.94 (t, *J*=7.0 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H), 1.30 (broad s, 24H), 1.59–1.65 (m, 1H), 1.78–1.80 (m, 2H), 1.93–1.97 (m, 1H), 2.36 (dd, *J*=13.5, 9.4 Hz, 1H), 3.11 (broad dd, *J*=13.5 Hz, 1H), 3.28 (t, *J*=8.5 Hz, 1H), 3.48 (dd, *J*=8.8, 2.9 Hz, 1H), 3.93–4.08 (m, 4H), 4.09–4.22 (m, 1H), 4.47–4.49 (m, 1H), 6.30 (broad s, 1H), 7.04 (d, *J*=7.04 Hz, 2H), 6.99–7.09 (m, 3H). ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ 14.7, 14.8, 14.9, 23.6, 27.1, 30.3, 30.6 (8C), 30.7, 32.9, 34.6, 38.6, 56.3, 63.0, 63.9, 66.0, 67.1, 71.1, 128.0, 129.7 (2C), 130.2 (2C), 136.6, 153.5, 157.5, 158.2, 171.5.

4.4.7. (4*S*,2′*R*,3′*S*)-*N*-{2′-[*N*,*N*′-Bis(benzyloxycarbonyl)-hydrazino]-3′-hydroxyoctadecanoyl}-4-benzyloxazolidin-2-one ((2′*R*,3′*S*)-9a). The title compound was prepared as an oil following the same procedure as for **7b** but in this case the reaction was stirred at −23°C during 3 h. The residue was purified by chromatography through silica-gel using dichloromethane. The major diastereoisomer (2′*R*,3′*S*)-**9a** was obtained in 36% yield: $[\alpha]_D^{20}=21.4$ (c=1.15, CHCl$_3$). IR (film) 3446, 3304, 2926, 2853, 1785, 1718, 1703, 1407, 1388, 1217 cm^{-1}. ^{1}H NMR (d_6-benzene, 343 K, 250 MHz) δ 0.99 (t, *J*=6.8 Hz, 3H), 1.40 (broad s, 24H), 1.54–2.02 (m, 4H), 2.57 (dd, *J*=13.4, 9.6 Hz, 1H), 3.20 (dd, *J*=13.4, 3.2 Hz, 1H), 3.57–3.82 (m, 2H), 4.32–4.40 (m, 1H), 4.53–4.55 (m, 1H), 5.02–5.24 (m, 4H), 6.43 (d, *J*=6.1 Hz, 1H), 7.03–7.35 (m, 15H), 7.51 (broad s, 1H). ^{13}C NMR (d_6-benzene, 343 K, 62.5 MHz) δ 14.2, 23.0, 26.4, 29.7, 30.0, 30.1 (8C), 32.3, 34.1, 38.2, 55.7, 64.8, 66.6, 68.1, 69.0, 71.1, 127.4, 128.3 (2C), 128.5 (2C), 128.7 (2C), 128.8 (2C), 129.1 (2C), 129.7 (2C), 135.9, 136.5, 153.0, 156.9, 157.3, 171.1. Calcd for $C_{44}H_{59}N_3O_8$: C, 69.91; H, 7.59; N, 5.56. Found: C, 69.73; H, 7.57; N, 5.36. The minor diastereoisomer (4*S*,2′*S*,3′*R*)-*N*-{2′-[*N*,*N*′-bis(benzyloxycarbonyl)hydrazino]-3′-hydroxyoctadecanoyl}-4-benzyloxazolidin-2-one, (2′*S*,3′*R*)-**9a** was obtained in 3% yield: $[\alpha]_D^{20}=6.6$ (c=0.91, CHCl$_3$). IR (film) 3451, 2926, 2853, 1785, 1718, 1386, 1216, 1113 cm^{-1}. ^{1}H NMR (d_6-benzene, 343 K, 250 MHz) δ 0.88 (t, *J*=6.8 Hz, 3H), 1.30 (broad s, 24H), 1.56–1.90 (m, 4H), 2.26 (dd, *J*=13.4, 9.6 Hz, 1H), 3.02 (dd, *J*=13.4, 3.5 Hz, 1H), 3.32–3.39 (m, 1H), 3.51 (dd, *J*=8.9, 3.5 Hz, 1H), 4.16–4.25 (m, 1H), 4.40–4.42 (m, 1H), 4.98–5.14 (m, 4H), 6.25 (d, *J*=6.3 Hz, 1H), 6.85–7.24 (m, 16H). ^{13}C NMR (d_6-benzene, 343 K, 62.5 MHz) δ 14.7, 23.6, 27.1, 30.3, 30.6, 30.7 (8C), 32.9, 34.6, 38.4, 56.3, 66.3, 67.1, 68.8, 69.5, 71.3, 127.9–130.1 (15C), 136.6, 136.9, 137.1, 153.5, 157.3, 157.9, 171.4.

4.4.8. (4*S*,2′*R*,3′*S*)-*N*-{2′-[*N*,*N*′-Bis(trichloroethyloxycarbonyl)hydrazino]-3′-hydroxyoyl}-4-benzyloxazolidin-2-one ((2′*S*,3′*R*)-9d). The title compound was prepared as an oil following the same procedure as for **7b** but in this case the reaction was stirred at −23°C during 2 h. The residue was purified by chromatography through silica-gel using dichloromethane. The major diastereoisomer (2′*S*,3′*R*)-**9d** was obtained in 43% yield: $[\alpha]_D^{20}=16.0$ (c=0.95, CHCl$_3$). IR (film) 3481, 3255, 2922, 2852, 1788, 1770, 1746, 1703, 1520, 1378, 1332, 1213, 1109 cm^{-1}; ^{1}H NMR (d_6-benzene, 343 K, 250 MHz) δ 0.99 (t, *J*=6.9 Hz, 3H), 1.39 (broad s, 24H), 1.64–2.08 (m, 4H), 2.61 (dd, *J*=13.6, 9.5 Hz, 1H), 3.20 (dd, *J*=13.6, 3.4 Hz, 1H), 3.75–3.77 (m, 2H), 4.43–4.53 (m, 2H), 4.60–4.79 (m, 2H), 4.60–4.79 (m, 4H), 6.41 (d, *J*=5.4 Hz, 1H), 7.07 (d, *J*=6.4 Hz, 2H), 7.51–7.26 (m, 3H), 7.75 (broad s, 1H). ^{13}C NMR (d_6-benzene, 343 K, 62.5 MHz) δ 15.0, 23.5, 26.9, 30.2, 30.5, 30.6 (8C), 32.8, 34.7, 38.8, 56.2, 65.5, 67.3, 71.8, 76.1, 77.0, 96.0 (2C), 128.2 (2C), 130.2 (2C), 136.2, 153.6, 155.8 (2C), 171.2. Calcd for $C_{34}H_{49}N_3O_8Cl_6$: C, 48.58; H, 5.87; N, 5.00; Cl, 25.31. Found: C, 48.83; H, 5.89; N, 4.89, Cl, 25.28. The minor diastereoisomer (4*S*,2′*S*,3′*R*)-*N*-{2′-[*N*,*N*′-bis(trichloroethyloxycarbonyl)hydrazino]-3′-hydroxyoyl}-4-benzyloxazolidin-2-one, (2′*R*,3′*S*)-**9d** was obtained in 21% yield: $[\alpha]_D^{20}=12.0$ (c=0.97, CHCl$_3$). IR (film) 3488, 3391, 2925, 2854, 1784, 1736, 1702, 1211, 1109 cm^{-1}; ^{1}H NMR (d_6-benzene, 343 K, 250 MHz) δ 0.95 (t, *J*=6.8 Hz, 3H), 1.36 (broad s, 24H), 1.49–2.09 (m, 4H), 2.53 (dd, *J*=13.6, 9.7 Hz, 1H), 3.23 (dd, *J*=13.6, 3.6 Hz, 1H), 3.44–3.73 (m, 2H), 4.26–4.32 (m, 1H), 4.33–4.51 (m, 1H), 4.55–4.75 (m, 4H), 6.37 (d, *J*=5.4 Hz, 1H), 6.99–7.21 (m, 5H), 7.57

(broad s, 1H). ^{13}C NMR (d_6-benzene, 343 K, 62.5 MHz) δ 14.7, 23.5, 27.0, 30.2, 30.3, 30.5, 30.6 (7C), 32.8, 34.6, 38.6, 56.4, 66.0, 67.3, 71.5, 76.2, 77.0, 96.0 (2C), 128.1, 129.7 (2C), 130.1 (2C), 136.4, 153.5, 155.8 (2C), 171.0.

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