

# Diastereoselective Electrochemical Carboxylation of Chiral $\alpha$ -Bromocarboxylic Acid Derivatives: An Easy Access to Unsymmetrical Alkylmalonic Ester Derivatives<sup>1,†</sup>

Marta Feroci,<sup>\*,‡</sup> Monica Orsini,<sup>§</sup> Laura Palombi,<sup>§</sup> Giovanni Sotgiu,<sup>||</sup> Marcello Colapietro,<sup>⊥</sup> and Achille Inesi<sup>\*,§</sup>

*Dip. Ingegneria Chimica, Materiali, Materie Prime e Metallurgia, Università "La Sapienza", via Castro Laurenziano, 7, I-00161 Roma, Italy, Dip. Chimica, Ingegneria Chimica e Materiali, Università degli Studi, I-67040, Monteluco di Roio, L'Aquila, Italy, Dipartimento di Ingegneria Elettronica, Università di Roma Tre, Via Vasca Navale 84, I-00146 Roma, Italy, and Dip. Chimica, Università "La Sapienza", P.le Aldo Moro, 5, I-00185 Roma, Italy*

marta.feroci@uniroma1.it; inesi@ing.univaq.it

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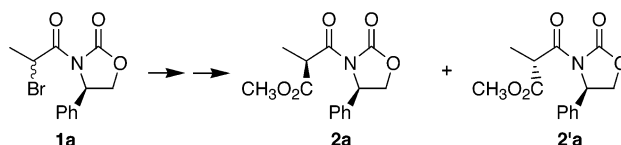
The diastereoselective electrochemical carboxylation of chiral *N*-(2-bromoacyl)oxazolidin-2-ones has been studied. This reaction was carried out by cathodic reduction of the C–Br bond, in the presence of carbon dioxide, followed by treatment with diazomethane. The yields and the diastereomeric ratio of the two epimeric alkylmalonic acid derivatives are strongly affected by various factors: solvent-supporting electrolyte system, temperature, electrode material, electrolysis conditions, oxazolidinone moiety. The higher yields (88%) were obtained starting from *N*-(2-bromopropionyl)-4*R*-phenyloxazolidin-2-one **1a**, but with poor diastereoselectivity (61:39). The two epimers were easily separated by flash chromatography. The best results were achieved using a different chiral auxiliary: Oppolzer's camphor sultam. Starting from **1j** a good yield in carboxylated product was obtained (80%) with excellent diastereoselectivity (98:2). These chiral alkylmalonic acid derivatives are valuable building blocks in the synthesis of molecules with biological activity and of chiral propane-1,3-diols derivatives.

## Introduction

Electrochemistry is now a useful tool for organic chemists, as some organic transformations take place only by electrochemical means,<sup>2</sup> and also because "electrochemistry affords a very facile and precise way to generate highly energetic intermediates via control of the electrode potential",<sup>3</sup> so it offers good alternatives to traditional "chemical" methods.

The cathodic behavior of halogenated organic compounds has been extensively studied<sup>4</sup> and normally leads to the cleavage of the carbon–halogen bond with formation of a carbanion that can successively react in various ways. One of the classical experiments to demonstrate the formation of such an anion is to trap it by reaction with carbon dioxide, giving a carboxylated product. This procedure works well in many cases (aliphatic and aromatic halides, for example), but to our knowledge, no

## SCHEME 1



electrochemical carboxylation of  $\alpha$ -haloesters or amides has been reported.

Recently, we studied the possibility of inducing, by electrochemical means, the diastereoselective carboxylation of halogenated organic compounds. Our preliminary results have been reported in a recent communication:<sup>1</sup> the cathodic reduction of *N*-(2-bromopropionyl)-4*R*-phenyloxazolidin-2-one **1a** in the presence of carbon dioxide gave rise to the formation of the corresponding unsymmetrical methylmalonic ester derivatives **2a** and **2a'** (after treatment with diazomethane) in enriched diastereomeric form (Scheme 1). The two epimers could be easily separated by flash chromatography, obtaining both pure

\* To whom correspondence should be addressed. Tel: +39-06-49766780. Fax: +39-06-49766749.

<sup>†</sup> Dedicated to Paolo Silvestroni (1917–2003), Professor of Chemistry.

<sup>‡</sup> University of Roma "La Sapienza".

<sup>§</sup> University of L'Aquila.

<sup>||</sup> University of Roma Tre.

<sup>⊥</sup> Author for X-ray analysis. University of Rome "La Sapienza", Dip. Chimica.

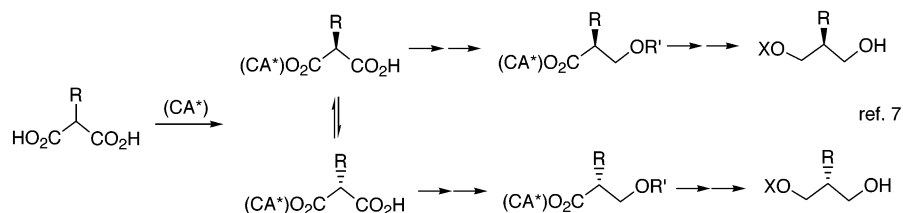
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## SCHEME 2



chiral products. These substrates are valuable synthons in asymmetric synthesis, as chiral half esters of alkylmalonic acid were used as precursors of chiral  $\alpha$ -alkyl- $\alpha$ -amino acids, useful molecules with biological activity<sup>5</sup> and in the synthesis of indole alkaloids.<sup>6</sup> Moreover, they are used as precursors of chiral propane-1,3-diol derivatives.<sup>7</sup>

The usual approach to optically active propane-1,3-diol derivatives is the enzymatic differentiation of the prochiral 2-position of a 2-substituted-1,3-diol,<sup>8</sup> while chemical approaches are rare.<sup>9</sup>

One of the chemical methods uses the condensation of a monoalkylmalonic acid and a molar equivalent of chiral alcohol (CA\*) to obtain the corresponding mixture of chiral half esters. These esters are transformed, after functionalization, into the corresponding epimeric mixture of hydroxy esters and then separated by HPLC means. After protection of the alcoholic function, the reduction of the ester to alcohol can be carried out, thus obtaining an optically active protected propane-1,3-diol (Scheme 2).<sup>7</sup> In particular, if the substituent in 2-position is a methyl group, the propandiol was used as a precursor of a potent antibiotic related to thienamycin.<sup>10</sup>

The diastereoselective synthesis of alkylmalonic ester derivatives is therefore a goal of considerable interest (the subsequent selective reduction of the amidic function in the presence of the methyl ester group of **2** and **2'**, to yield the corresponding chiral alcohol, is well described in the literature).<sup>11</sup>

Herein, we wish to report a new general methodology for this synthesis based on the diastereoselective carboxylation in the  $\alpha$ -position of chiral carboxylic acid

derivatives. The carboxylation can be achieved, as suggested by our preliminary results,<sup>1</sup> via cathodic reduction of  $\alpha$ -bromo carboxylic acid derivatives carried out in the presence of carbon dioxide.

## Results and Discussion

*N*-(2-Bromopropionyl)-4*R*-phenyloxazolidin-2-one **1a** was taken as a model compound, and its electrochemical behavior was studied using various chemical and physical parameters.

The cathodic bielectronic cleavage of the carbon–bromine bond of **1a** in MeCN–Et<sub>4</sub>NClO<sub>4</sub> (TEAP)<sup>12</sup> leads to the formation of an enolate anion with loss of bromide ion; the behavior of this enolate depends on its partner of reaction (Scheme 3). If it is in the presence of a proton donor, it is protonated, giving rise to the formation of *N*-propionyloxazolidinone **3a** (Scheme 3, eq 2; Table 1, entry 2); if it is in the presence of carbon dioxide, it is carboxylated forming the couple of epimers **2a** and **2'a** (after reaction with diazomethane) (Scheme 3, eq 3; Table 1, entries 5–7); if there is enough time between the enolate formation and its subsequent protonation, a decomposition of the enolate (probably via a ketene pathway)<sup>13</sup> is efficient, giving rise to the formation of oxazolidinone **4a** (Scheme 3, eq 1; Table 1, entries 1 and 4–7).

Our aim was to minimize both the protonation and the decomposition reactions, favoring the formation of the carboxylated product. Keeping this objective in mind, various chemical and electrochemical parameters were varied (Table 1): the use of MeCN/TEAP as solvent system seems to favor the protonation and decomposition reactions (entries 1–7). To lower the temperature does not enhance the yields in carboxylated products, probably also because of a decrease in the solubility of the supporting electrolyte (but there is a considerable enhancement in the diastereomeric ratio, see entries 5–7). Moreover, the electrolysis conditions seem to influence the outcome of the reaction and the distribution of the products (galvanostatic conditions would be preferable with respect to potentiostatic conditions in view of a possible industrial application).<sup>14</sup> The role of Et<sub>3</sub>N in this reaction is not so clear: when the reaction in MeCN–TEAP was carried out in the absence of amine, no

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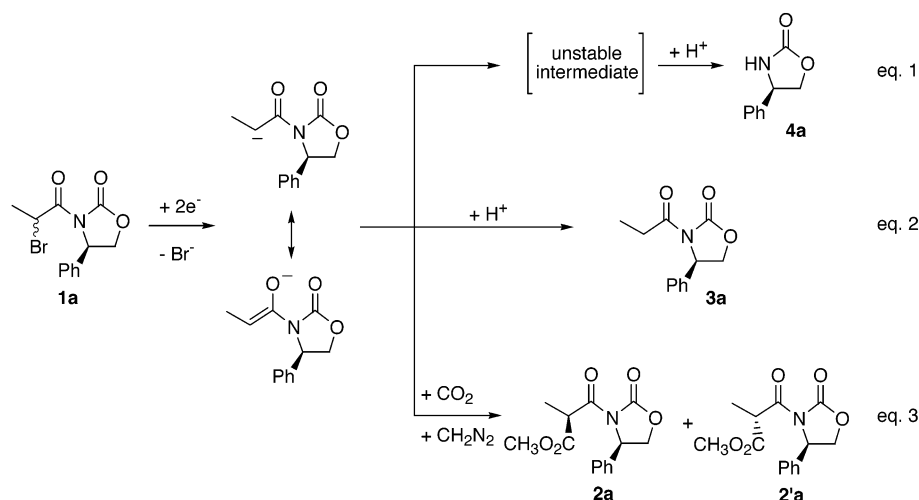
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(12) CAUTION! Although in more than 100 experiments no particular safety problem has been encountered, the use of perchlorates in organic solvent must be considered as potentially dangerous (explosive). Take adequate precautions.

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## SCHEME 3

TABLE 1. Electrolyses<sup>a</sup> of Solutions of **1a** under Different Experimental Conditions

entry	anode/cathode	electrolysis conditions	solvent/electrolyte	T (°C)	products (yields, %) <sup>b</sup>		
					<b>3a</b>	<b>4a</b>	<b>2a + 2'a</b> (dr) <sup>c</sup>
1	Mg/Pb <sup>d</sup>	potentiostatic	MeCN/Et <sub>4</sub> NClO <sub>4</sub>	rt	55	14	
2	Mg/Pb <sup>e</sup>	potentiostatic	MeCN/Et <sub>4</sub> NClO <sub>4</sub>	rt	86		
3	Mg/Pb	potentiostatic	MeCN/Et <sub>4</sub> NClO <sub>4</sub>	rt	77		
4	Mg/Pb	galvanostatic	MeCN/Et <sub>4</sub> NClO <sub>4</sub>	rt	50	11	
5	Mg/Pb <sup>f</sup>	potentiostatic	MeCN/Et <sub>4</sub> NClO <sub>4</sub>	rt	33	30	36 (57:43)
6	Mg/Pb <sup>f</sup>	potentiostatic	MeCN/Et <sub>4</sub> NClO <sub>4</sub>	-10	65	20	15 (65:35)
7	Mg/Pb <sup>f</sup>	potentiostatic	MeCN/Et <sub>4</sub> NClO <sub>4</sub>	-20	72	22	5 (83:17)
8	Mg/Pb	galvanostatic	THF/Bu <sub>4</sub> NBF <sub>4</sub>	-20	37		62 (63:37)
9	Mg/Pb <sup>f</sup>	galvanostatic	THF/Bu <sub>4</sub> NBF <sub>4</sub>	-20	32	5	40 (69:31)
10	Mg/Pb	galvanostatic	THF/Bu <sub>4</sub> NBF <sub>4</sub>	-40	22		55 (59:41)
11	Mg/Pt	galvanostatic	THF/Bu <sub>4</sub> NBF <sub>4</sub>	-20			70 (60:40)
12	Mg/Pt <sup>f</sup>	galvanostatic	THF/Bu <sub>4</sub> NBF <sub>4</sub>	-20	53	10	36 (68:32)
13	Al/Pt	galvanostatic	THF/Bu <sub>4</sub> NBF <sub>4</sub>	-20	7		78 (59:41)
14	Al/Pt <sup>f</sup>	galvanostatic	THF/Bu <sub>4</sub> NBF <sub>4</sub>	-20	22		27 (52:48)

<sup>a</sup> 2 F/mol of **1a**, undivided cells, CO<sub>2</sub> atmosphere, galvanostatic conditions:  $I = 4 \text{ mA/cm}^2$ ; potentiostatic conditions:  $E = -1.7 \text{ V}$  vs SCE. <sup>b</sup> Yields of isolated products, calculated with respect to the starting oxazolidinone **1a**. <sup>c</sup> The diastereoisomeric ratio was determined by <sup>1</sup>H NMR. <sup>d</sup> Electrolysis carried out under nitrogen atmosphere (no CO<sub>2</sub> added). <sup>e</sup> Electrolysis carried out under nitrogen atmosphere (no CO<sub>2</sub> added) in the presence of a proton donor (acetic acid). <sup>f</sup> Et<sub>3</sub>N was added to the solution prior to electrolysis.

carboxylated product could be evidenced (Table 1, entries 3 and 4), while in the presence of Et<sub>3</sub>N, (**2a** + **2'a**) were isolated in 36% yield (Table 1, entry 5). Moreover, Evans<sup>15</sup> reported that Et<sub>3</sub>N forms a kind of aggregated complex with the enolate that derives from the reduction of the C–Br bond, and so it should enhance the diastereoselectivity of the carboxylation reaction.

The use of DMF–TEAP as solvent-supporting electrolyte system led to unsatisfactory yields in carboxylated products and high yields in hydrogenated product **3a**.

To avoid the use of a solvent that acts as a proton donor, THF was selected as solvent of electrolysis, and tetrabutylammonium tetrafluoroborate was used as supporting electrolyte (it is one of the few salts that are soluble in this solvent). The yields of carboxylated products increase both in the presence and in the absence of Et<sub>3</sub>N, but the higher yields are obtained in the absence of amine (Table 1, entries 8 and 9), while the diastereomeric ratio is similar. Therefore, in THF Et<sub>3</sub>N seems to have little influence on the outcome of this carboxylation. Operating at lower temperature does not increase the yields in carboxylated products nor the diastereomeric ratio (Table 1, entry 10). Only a change in the electrode

materials leads to good yields in (**2a** + **2'a**) reaching the value of 78% using an aluminum sacrificial anode<sup>16</sup> and a platinum cathode (Table 1, entry 13). Also in this case, the diastereomeric ratio was not different from those obtained in the previous experiments.

To verify if the experimental conditions of entry 13 could be improved, the effects of temperature and of the amount of electricity supplied to the electrodes were studied (Table 2).

The yield of (**2a** + **2'a**) is strongly affected by the temperature at which the electrolysis is carried out (Table 2, entries 1–5); in particular, the choice of this parameter seems crucial for the selectivity of the electrode process. In fact, at a temperature higher of -20 °C, a considerable amount of starting bromide can be isolated from the electrolyzed mixture, while the result obtained at -40 °C is probably due both to a decrease in the supporting electrolyte solubility and to a lower conductivity of the solution (that lower the electric current yield). It may be noted a peculiar result as a consequence of a strong variation of the temperature (30 °C vs -40 °C; Table 2, entries 1 and 5): with respect to

(15) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049.

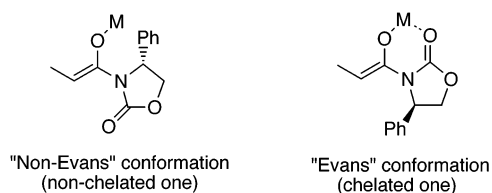
(16) The anodic process involves the oxidation of the electrode material. See: Lund, H. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; Marcel Dekker, Inc.: New York, 2001; p 245.



**TABLE 2.** Effect of Temperature and Amount of Electricity in the Electrolyses of Solutions of **1a**<sup>a</sup>

entry	F/mol of <b>1a</b>	<i>T</i> (°C)	products (yields,%) <sup>b</sup>		
			rec. <b>1a</b>	<b>3a</b>	<b>2a</b> + <b>2'a</b> (dr) <sup>c</sup>
1	2.0	30	55		34 (61:39)
2	2.0	15	47		52 (64:36)
3	2.0	0	27	9	63 (56:44)
4 <sup>d</sup>	2.0	-20	14	7	78 (59:41)
5	2.0	-40	35	10	34 (61:39)
6	0.5	-20	79		17 (56:44)
7	0.8	-20	72		26 (58:42)
8	1.0	-20	67		32 (59:41)
9 <sup>d</sup>	2.0	-20	14	7	78 (59:41)
10	3.0	-20	4	7	88 (61:39)

<sup>a</sup> Solutions of **1a** in THF/Bu<sub>4</sub>NBF<sub>4</sub>, undivided cells, Al anode and Pt cathode, CO<sub>2</sub> atmosphere, galvanostatic conditions: *I* = 4 mA/cm<sup>2</sup>. <sup>b</sup> Yields of isolated products, calculated with respect to the starting oxazolidinone **1a**. <sup>c</sup> The diastereoisomeric ratio was determined by <sup>1</sup>H NMR. <sup>d</sup> This electrolysis (the same as entry 13, Table 1) was repeated here for clarity.

**FIGURE 1.** Two possible conformations of enolate ion.

the electrolysis carried out at 30 °C, in the electrolysis at -40 °C the amount of consumed starting **1a** increases (65% vs 45%), but the percentage of reduced **1a** converted to carboxylated product decreases (76% vs 52%). Consequently the yield of (**2a** + **2'a**), with respect to starting **1a**, is occasionally the same (34%).

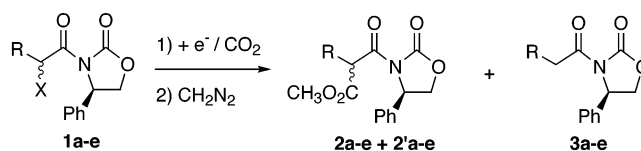
The effect of the amount of electricity supplied to the electrodes (Table 2, entries 6–10) is consistent with a bielectronic process in which the current yield is not 100%; increasing the number of faradays per mole of **1a**, the yield in carboxylated products increases, but not linearly, so the better compromise between current efficiency and chemical yield seems to be the choice of 3 F/mol of **1a** (88%; Table 2, entry 10). To have a total consumption of starting bromide, about 6 F/mol are necessary,<sup>17</sup> but in this case the current efficiency is too low and the electrolysis time quite long, rendering this synthesis not attractive from an economic point of view.

The absolute configuration of the major diastereoisomer obtained in these electrolyses was established by X-ray analysis,<sup>1</sup> and this compound was identified as **2a**, 3-(2'-S-methoxycarbonylpropionyl)-4*R*-phenyl-2-oxazolidinone.

This is probably due to the preferential "non-Evans" conformation<sup>18</sup> (that is the nonchelated one) of the enolate ion during the carboxylation (Figure 1). The metal ion derived from consumption of the sacrificial anode could

(17) The yields of (**2** + **2'**) increase on increasing the amount of electricity supplied to the electrodes, but not in a straightforward manner. Therefore, the current efficiency decreases on decreasing of the concentration of **1a**. In fact, the electrolyses are carried out under galvanostatic conditions (in all the experiments *I* = 4 mA/cm<sup>2</sup>), and consequently, the cathodic reduction of the last quantity of **1a** (4%) is associated with a particularly elevated amount of electricity supplied to the electrode (i.e., a strong decrease of the current efficiency).

(18) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-J. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.

**SCHEME 4**<sup>a</sup>

<sup>a</sup> Key: **a–e**, see Table 3.

**TABLE 3.** Effect of Different Substituents (Scheme 4) on the Electrochemical Carboxylation of **1a–e**<sup>a</sup>

entry	R	X ( <b>1</b> )	products (yields,%) <sup>b</sup>			$\delta$ (Me) <sup>d</sup>
			rec. <b>1</b>	<b>3</b>	<b>2</b> + <b>2'</b> (dr) <sup>c</sup>	
1 <sup>e</sup>	Me	Br ( <b>1a</b> )	4	7	88 (61:39)	3.71–3.67
2	Et	Br ( <b>1b</b> )		9	90 (52:48)	3.64–3.70
3	Bu	Br ( <b>1c</b> )	18	5	76 (60:40)	3.64–3.70
4	<i>i</i> -Pr	Br ( <b>1d</b> )	20	traces	79 (58:42)	3.64–3.71
5	Ph	Cl ( <b>1e</b> )		100		

<sup>a</sup> Solutions of **1a–e** in THF/Bu<sub>4</sub>NBF<sub>4</sub>, undivided cells, Al anode and Pt cathode, CO<sub>2</sub> atmosphere, *T* = -20 °C, galvanostatic conditions: *I* = 4 mA/cm<sup>2</sup>, 3 F/mol of **1a–e**. <sup>b</sup> Yields of isolated products, calculated with respect to the starting oxazolidinone **1a–e**. <sup>c</sup> The diastereoisomeric ratio was determined by <sup>1</sup>H NMR. <sup>d</sup> Chemical shifts of the hydrogen atoms of the methoxycarbonyl group (<sup>1</sup>H NMR, ppm with respect to tetramethylsilane) of the major and minor diastereoisomers, respectively. <sup>e</sup> This experiment (the same of entry 10, Table 2) was repeated here for clarity.

potentially chelate both oxygen atoms, but is probably present in too low concentration relative to the non-chelating electrolyte cation R<sub>4</sub>N<sup>+</sup>. It is also possible that in a solvent such as THF (with low dielectric constant) the metal cation is not free, but ion-paired with the bromide ion released during the electrolysis.

The diastereomeric ratio was not encouraging, but as both carboxylated diastereoisomers are very easy to isolate in pure form (simple flash chromatography of the electrolysis solution permits the resolution of this diastereomeric mixture), this methodology permits an easy access to this methylmalonic ester derivatives in pure chiral form.





As many alkylmalonic acid derivatives are precursors of biologically active molecules, this reaction was carried out (using the same experimental conditions as entry 10 in Table 2) with substrates in which the group in the position  $\alpha$  to the bromine atom was other than methyl (Scheme 4).

The results of these electrolyses are reported in Table 3.

It can be seen that this electrochemical synthesis works well when an alkyl group is geminal to the bromine atom, albeit with similarly modest diastereomeric ratios (76–90% yields in carboxylated products; Table 3, entries 1–4). However, if a phenyl group is present, no carboxylated product can be detected and only the protonated molecule can be isolated (Table 3, entry 5). This fact can be explained with the higher stability of the enolate ion (produced by the bielectronic cleavage of the C–Cl bond) due to the presence of the phenyl group. However, the hypothesis of an one-electron reduction of **1e** and the formation of **3** via the radical cannot be excluded.

Having obtained high yields in carboxylated products, we tried to improve the diastereomeric ratio, varying the substituents in the 4-position of oxazolidin-2-one (in fact, it is known that substituents in this position of the chiral

**TABLE 4. Electrochemical Carboxylation of 1a,f–h<sup>a</sup>**

R–Br <b>1a,f–h</b>		1) + e <sup>−</sup> / CO <sub>2</sub> 2) CH <sub>2</sub> N <sub>2</sub>	R–H <b>3a,f–h</b>	+	R–CO <sub>2</sub> CH <sub>3</sub> <b>2a,f–h + 2'a,f–h</b>			
entry	R (1)	rec. <b>1</b>	products (yields,%) <sup>b</sup>					
			<b>3</b>	<b>2+2'</b>	(d.r.) <sup>c</sup>		$\delta(\text{Me})^d$	
1 <sup>e</sup>		4	7	88	(61:39)		3.71-3.67	
	<b>1a</b>							
2		10	traces	77	(61:39)		3.71-3.68	
	<b>1f</b>							
3		26	traces	62	(56:44)		3.69-3.69 <sup>f</sup>	
	<b>1g</b>							
4		14	4	80	(74:26)		3.72-3.57	
	<b>1h</b>							

<sup>a</sup> Solutions of **1a,f–h** in THF/Bu<sub>4</sub>NBF<sub>4</sub>, undivided cells, Al anode and Pt cathode, CO<sub>2</sub> atmosphere, *T* = −20 °C, galvanostatic conditions: *I* = 4 mA/cm<sup>2</sup>, 3 F/mol of **1a,f–h**. <sup>b</sup> Yields of isolated products, calculated with respect to the starting oxazolidinone **1a,f–h**. <sup>c</sup> The diastereoisomeric ratio was determined by <sup>1</sup>H NMR. No correlation between NMR signals reported in the last column and structures **2** and **2'** can be inferred, except for compounds **2a** and **2'a** (confirmed by X-ray analysis). Thus, the dr reports only the ratio between the major and the minor diastereoisomers. <sup>d</sup> Chemical shifts of the hydrogen atoms of the methoxycarbonyl group (<sup>1</sup>H NMR, ppm with respect to tetramethylsilane) of the major and minor diastereoisomers, respectively. <sup>e</sup> This experiment (the same of entry 10, Table 2) was repeated here for clarity. <sup>f</sup> The diastereoisomeric ratio was determined by <sup>13</sup>C NMR.

**TABLE 5. Effect of Temperature on the Diastereomeric Ratio of 2h + 2'h**

<i>T</i> (°C)	20	0	−20	−40
dr <sup>a</sup>	71:29	70:30	74:26	72:28

<sup>a</sup> The diastereoisomeric ratio was determined by <sup>1</sup>H NMR.

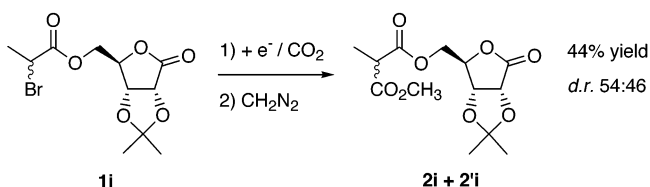
auxiliary can greatly affect the outcome of the asymmetric reaction). These results are reported in Table 4.

A higher diastereomeric ratio (ca. 3:1) was obtained using (4*R*,5*S*)-indano[1,2-*d*]oxazolidin-2-one as chiral oxazolidinone (Table 4, entry 4), and this ratio was not affected by the reaction temperature, as reported in Table 5.

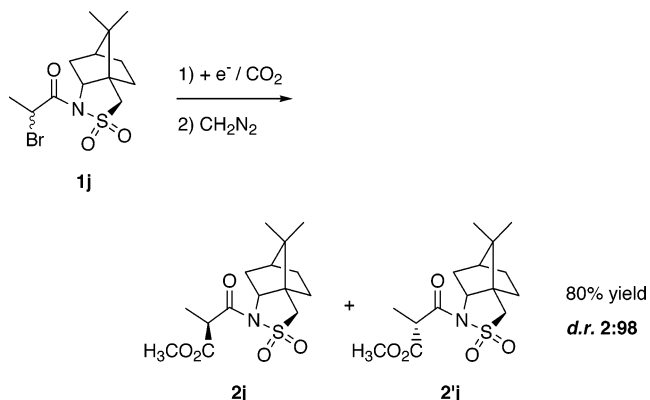
Our last attempt to improve the diastereomeric ratio of the two methylmalonic acid derivatives was to change the kind of chiral auxiliary, at first taking into account 2,3-*O*-isopropylidene-D-ribonic  $\gamma$ -lactone. This electrolysis gave very poor results both in the yields in carboxylated products and in their diastereomeric ratio (Scheme 5).

On the other hand, when Oppolzer's camphor sultam was used as chiral auxiliary the best result was obtained: a good yield (80%) and a very satisfactory diastereomeric ratio of 98:2 (Scheme 6).

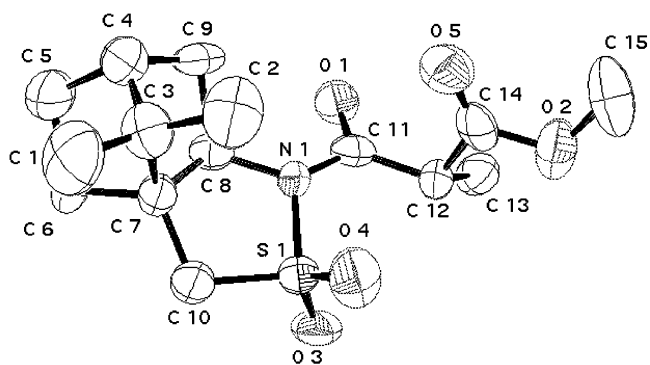
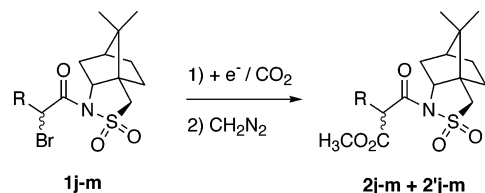
The absolute configuration of the major diastereoisomer has been established by X-ray analysis, and this compound has been identified as the *R*-isomer (Figure 2).

**SCHEME 5<sup>a</sup>**

<sup>a</sup> Experimental conditions: see Table 4. Recovered starting material: 37%.

**SCHEME 6<sup>a</sup>**

<sup>a</sup> Experimental conditions: see Table 4. Recovered starting material: 19%.

**FIGURE 2.** ORTEP drawing of compound **2j** (major diastereoisomer).**SCHEME 7<sup>a</sup>**

<sup>a</sup> Key: **j–m**, see Table 6.

This high diastereoselectivity, due to the presence of Oppolzer's camphor sultam as chiral auxiliary, was confirmed using different acyl groups (Scheme 7 and Table 6):

## Conclusions

Unsymmetrical alkylmalonic ester derivatives (valuable precursors of chiral propane-1,3-diol derivatives, of

**TABLE 6.** Effect of Different Substituents (Scheme 7) on the Electrochemical Carboxylation of **1j–m**<sup>a</sup>

entry	R	<b>1</b>	rec. <b>1</b>	products (yields, %) <sup>b</sup>	$\delta(\text{Me})^d$
				<b>2 + 2'</b> (dr) <sup>c</sup>	
1 <sup>e</sup>	Me	<b>1j</b>	19	80 (2:98)	3.71–3.66
2	Et	<b>1k</b>	21	77 (2:98)	3.71–3.67
3	Bu	<b>1l</b>	25	71 (3:97)	3.71–3.66
4	<i>i</i> -Pr	<b>1m</b>	23	70 (4:96)	3.71–3.67

<sup>a</sup> Solutions of **1j–m** in THF/ $\text{Bu}_4\text{NBF}_4$ , undivided cells, Al anode and Pt cathode,  $\text{CO}_2$  atmosphere,  $T = -20^\circ\text{C}$ , galvanostatic conditions:  $I = 4 \text{ mA/cm}^2$ , 3 F/mol of **1j–m**. <sup>b</sup> Yields of isolated products, calculated with respect to the starting oxazolidinone **1j–m**. <sup>c</sup> The diastereoisomeric ratio was determined by  $^1\text{H}$  NMR. <sup>d</sup> Chemical shifts of the hydrogen atoms of the methoxycarbonyl group ( $^1\text{H}$  NMR, ppm with respect to tetramethylsilane) of the two diastereoisomers reported in the dr. <sup>e</sup> This experiment (the same of Scheme 6) was repeated here for clarity.

chiral  $\alpha$ -alkyl- $\alpha$ -amino acids and of indole alkaloids) have been obtained, under mild conditions, in good to high yields by electrochemical reduction (under  $\text{CO}_2$  atmosphere) of  $\alpha$ -bromocarboxylic acid derivatives. The two epimers can be easily separated by flash chromatography.

The absolute configuration, obtained by X-ray analysis, of the major diastereoisomer of 3-(2-methoxycarbonylpropionyl)-4*R*-phenyl-2-oxazolidinone has been related to the “non-chelated conformation” of the enolate that undergoes carboxylation.

The influence of the electrolysis conditions and of the various chiral auxiliaries on the yields and on the diastereoisomeric ratio has been studied. The use of Oppolzer's camphor sultam as chiral auxiliary allowed the achievement of good yields in carboxylated product (80%) and above all a very high diastereoisomeric ratio (98:2). The major diastereoisomer was identified as the (2*R*)-isomer.

## Experimental Section

**General Procedure.** A solution of 3-(2-bromopropionyl)-4*R*-phenyl-2-oxazolidinone **1a** (1.0 mmol) in 30 mL of THF–0.2 M  $\text{Bu}_4\text{NBF}_4$  was electrolyzed (undivided cells, Pt or Pb cathode, Al or Mg anode, at  $-20^\circ\text{C}$ ) under galvanostatic conditions ( $I = 4 \text{ mA cm}^{-2}$ ) in the presence of carbon dioxide ( $p = 1 \text{ atm}$ ). After the consumption of 2 F/mol of **1a**, the current flow was stopped, the solvent was evaporated under reduced pressure, and the residue was poured into water. This aqueous phase was extracted with diethyl ether ( $3 \times 30 \text{ mL}$ ), and this organic solution was worked up as usual, giving the starting material **1a**, (*R*)-(-)-4-phenyl-3-propionyl-2-oxazolidinone **3a** and (*R*)-(-)-4-phenyl-2-oxazolidinone **4a**, if any. The aqueous solution was then acidified (pH 3) with dilute HCl and extracted again with ether. This second ethereal phase was cooled at  $0^\circ\text{C}$  and treated with ethereal  $\text{CH}_2\text{N}_2$ .<sup>19</sup> (CAUTION! Diazomethane is toxic and prone to cause development of specific sensitivity; in addition, it is potentially explosive). The usual workup gave the mixture of **2a** and **2b**, whose ratio was calculated by  $^1\text{H}$  NMR. The two pure isomers were obtained after flash column chromatography (*n*-hexanes–ethyl acetate 8:2 as eluent).

**Starting Materials and Electrolyses Products** (the spectral data of known compounds have been compared with those reported in the literature):

**3-(2-Bromopropionyl)-4*R*-phenyl-2-oxazolidinone 1a (Both Isomers).**<sup>20</sup>

**3-(2-Methoxycarbonylpropionyl)-4*R*-phenyl-2-oxazolidinone 2a + 2'a (Both Isomers).**<sup>1</sup>

**4*R*-Phenyl-3-propionyl-2-oxazolidinone 3a.**<sup>21</sup>

**4*R*-Phenyl-2-oxazolidinone 4a:** commercial.

**3-(2-Bromobutanoyl)-4*R*-phenyl-2-oxazolidinone 1b (Both Isomers).**<sup>1</sup>

**3-(2-Methoxycarbonylbutanoyl)-4*R*-phenyl-2-oxazolidinone 2b + 2'b (Both Isomers).**<sup>1</sup>

**3-Butanoyl-4*R*-phenyl-2-oxazolidinone 3b.**<sup>22</sup>

**3-(2-Bromohexanoyl)-4*R*-phenyl-2-oxazolidinone 1c (less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 7.38–7.24 (m, 5H), 5.62 (t, 1H,  $J = 7.2 \text{ Hz}$ ), 5.42 (dd, 1H,  $J = 8.8, 3.4 \text{ Hz}$ ), 4.73 (t, 1H,  $J = 8.8 \text{ Hz}$ ), 4.29 (dd, 1H,  $J = 8.8, 3.4 \text{ Hz}$ ), 1.99–1.92 (m, 2H), 1.62–1.29 (m, 4H), 0.80 (t, 3H,  $J = 6.7 \text{ Hz}$ );  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ): 168.6, 152.8, 138.7, 129.2, 128.9, 125.9, 70.0, 58.1, 44.1, 33.9, 29.1, 21.9, 13.7; GC–MS  $m/z$  ( $\text{M}^+$  absent), 285 (10), 283 (11), 260 ( $\text{M}^+ - \text{Br}$ , 16), 162 (17), 104 (100);  $[\alpha]^{20}_{\text{D}} = -96.8$  ( $c = 0.78$ ,  $\text{AcOEt}$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{18}\text{BrNO}_3$ : C, 52.96; H, 5.33; N, 4.12. Found: C, 53.11; H, 5.35; N, 4.17.

**3-(2-Bromohexanoyl)-4*R*-phenyl-2-oxazolidinone 1c (more polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 7.38–7.31 (m, 5H), 5.62 (t, 1H,  $J = 7.3 \text{ Hz}$ ), 5.43 (dd, 1H,  $J = 8.9, 4.8 \text{ Hz}$ ), 4.70 (t, 1H,  $J = 8.9 \text{ Hz}$ ), 4.24 (dd, 1H,  $J = 8.9, 4.8 \text{ Hz}$ ), 2.04–1.94 (m, 2H), 1.43–1.26 (m, 4H), 0.87 (t, 3H,  $J = 7.0 \text{ Hz}$ );  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 168.5, 152.7, 137.7, 129.2, 128.9, 125.8, 69.9, 57.8, 43.9, 33.2, 29.4, 22.1, 13.8; GC–MS  $m/z$  ( $\text{M}^+$  absent), 285 (10), 283 (11), 260 ( $\text{M}^+ - \text{Br}$ , 16), 162 (17), 104 (100);  $[\alpha]^{20}_{\text{D}} = -67.1$  ( $c = 0.80$ ,  $\text{AcOEt}$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{18}\text{BrNO}_3$ : C, 52.96; H, 5.33; N, 4.12. Found: C, 53.06; H, 5.37; N, 4.14.

**3-(2-Methoxycarbonylhexanoyl)-4*R*-phenyl-2-oxazolidinone 2c or 2'c (less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 7.37–7.24 (m, 5H), 5.47 (dd, 1H,  $J = 8.8, 3.9 \text{ Hz}$ ), 4.70 (t, 1H,  $J = 8.8 \text{ Hz}$ ), 4.56 (t, 1H,  $J = 7.0 \text{ Hz}$ ), 4.26 (dd, 1H,  $J = 8.8, 3.9 \text{ Hz}$ ), 3.70 (s, 3H), 1.86–1.82 (m, 2H), 1.23–1.16 (m, 4H), 0.78 (t, 3H,  $J = 6.6 \text{ Hz}$ );  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 170.0, 168.7, 153.6, 138.8, 129.2, 128.8, 125.9, 70.0, 57.8, 52.4, 50.6, 29.4, 28.3, 22.3, 13.7; GC–MS  $m/z$  288 ( $\text{M}^+ - \text{OCH}_3$ , 5), 263 (43), 104 (88), 69 (89), 55 (100);  $[\alpha]^{20}_{\text{D}} = -72.0$  ( $c = 1.01$ ,  $\text{AcOEt}$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_5$ : C, 63.94; H, 6.63; N, 4.39. Found: C, 64.07; H, 6.67; N, 4.41.

**3-(2-Methoxycarbonylhexanoyl)-4*R*-phenyl-2-oxazolidinone 2c or 2'c (more polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 7.38–7.24 (m, 5H), 5.44 (dd, 1H,  $J = 8.8, 3.8 \text{ Hz}$ ), 4.70 (t, 1H,  $J = 8.8 \text{ Hz}$ ), 4.47 (dd, 1H,  $J = 8.4 \text{ Hz}$ ,  $J = 5.5 \text{ Hz}$ ), 4.25 (dd, 1H,  $J = 8.8 \text{ Hz}$ ,  $J = 3.8 \text{ Hz}$ ), 3.64 (s, 3H), 1.94–1.86 (m, 2H), 1.32–1.24 (m, 4H), 0.85 (t, 3H,  $J = 6.6 \text{ Hz}$ );  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 169.9, 168.2, 153.6, 138.4, 129.2, 129.0, 128.7, 125.8, 70.2, 57.9, 52.2, 50.9, 29.7, 27.9, 22.5, 13.7; GC–MS  $m/z$  288 ( $\text{M}^+ - \text{OCH}_3$ , 5), 263 (43), 104 (88), 69 (89), 55 (100);  $[\alpha]^{20}_{\text{D}} = -88.0$  ( $c = 0.78$ ,  $\text{AcOEt}$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_5$ : C, 63.94; H, 6.63; N, 4.39. Found: C, 64.11; H, 6.71; N, 4.38.

**3-Hexanoyl-4*R*-phenyl-2-oxazolidinone 3c:** GC–MS  $m/z$  261 ( $\text{M}^+$ , 1), 218 (12), 205 (61), 162 (15), 118 (60), 104 (61), 91 (31), 43 (100).

**3-(2-Bromo-3-methylbutanoyl)-4*R*-phenyl-2-oxazolidinone 1d (Both Isomers).**<sup>1</sup>

**3-(2-Methoxycarbonyl-3-methylbutanoyl)-4*R*-phenyl-2-oxazolidinone 2d + 2'd (Both Isomers).**<sup>1</sup>

**3-(3-Methylbutanoyl)-4*R*-phenyl-2-oxazolidinone 3d.**<sup>23</sup>

**3-(2-Chloro-2-phenylacetyl)-4*R*-phenyl-2-oxazolidinone 1e (Both Isomers).**<sup>1</sup>

**3-(2-Phenylacetyl)-4*R*-phenyl-2-oxazolidinone 3e.**<sup>1</sup>

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**3-(2-Bromopropionyl)-4S-benzyl-2-oxazolidinone 1f.**<sup>20</sup>

**3-(2-Methoxycarbonylpropionyl)-4S-benzyl-2-oxazolidinone 2f + 2'f (Mixture of Two Isomers).** More abundant isomer: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 7.33–7.14 (m, 5H), 4.75–4.62 (m, 1H), 4.50 (q, 1H,  $J = 7.2$  Hz), 4.27–4.02 (m, 2H), 3.71 (s, 3H), 3.38–3.21 (m, 1H), 2.81–2.70 (m, 1H), 1.45 (d, 3H,  $J = 7.2$  Hz); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 170.8, 169.3, 153.2, 135.2, 129.3, 128.8, 127.2, 66.2, 55.3, 52.4, 45.4, 37.2, 13.1; GC–MS  $m/z$  291 ( $M^+$ , 4), 260 ( $M^+ - OCH_3$ , 5), 115 (100), 91 (34), 59 (44). Less abundant isomer: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 7.33–7.14 (m, 5H), 4.75–4.62 (m, 1H), 4.54 (q, 1H,  $J = 7.2$  Hz), 4.27–4.02 (m, 2H), 3.68 (s, 3H), 3.38–3.21 (m, 1H), 2.81–2.70 (m, 1H), 1.46 (d, 3H,  $J = 7.2$  Hz); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 170.7, 169.6, 153.3, 134.9, 129.4, 128.8, 127.3, 66.4, 55.1, 52.4, 45.4, 37.7, 13.2; GC–MS  $m/z$  291 ( $M^+$ , 4), 260 ( $M^+ - OCH_3$ , 5), 115 (100), 91 (34), 59 (44).

**4S-Benzyl-3-propionyl-2-oxazolidinone 3f:** commercial.

**3-(2-Bromopropionyl)-4S-isopropyl-2-oxazolidinone 1g (Both Isomers).**<sup>20</sup>

**3-(2-Methoxycarbonylpropionyl)-4S-isopropyl-2-oxazolidinone 2g + 2'g (Mixture of Two Isomers).** More abundant isomer: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.59–4.39 (m, 2H), 4.34–4.10 (m, 2H), 3.69 (s, 3H), 2.52–2.30 (m, 1H), 1.42 (d, 3H,  $J = 7.2$  Hz), 0.93 (s, 3H), 0.89 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 170.9, 169.2, 154.0, 63.6, 58.6, 52.4, 45.5, 28.2, 17.8, 14.5, 13.1; GC–MS  $m/z$  ( $M^+$  absent) 212 ( $M^+ - OCH_3$ , 7), 200 ( $M^+ - iPr$ , 4), 115 (100), 87 (21), 59 (32). Less abundant isomer: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.59–4.39 (m, 2H), 4.34–4.10 (m, 2H), 3.69 (s, 3H), 2.52–2.30 (m, 1H), 1.42 (d, 3H,  $J = 7.2$  Hz), 0.93 (s, 3H), 0.89 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 170.9, 169.2, 154.0, 63.6, 58.6, 52.4, 45.5, 28.4, 17.8, 14.7, 13.4; GC–MS  $m/z$  ( $M^+$  absent) 212 ( $M^+ - OCH_3$ , 6), 200 ( $M^+ - iPr$ , 4), 115 (100), 87 (16), 59 (28).

**4S-Isopropyl-3-propionyl-2-oxazolidinone 3g:** commercial.

**3-(2-Bromopropionyl)-(4R,5S)-indano[1,2-d]oxazolidin-2-one 1h (isolated only one isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 7.62–7.59 (m, 1H), 7.38–7.22 (m, 3H), 5.92 (d, 1H,  $J = 6.8$  Hz), 5.68 (q, 1H,  $J = 6.7$  Hz), 5.33 (dt, 1H,  $J = 6.8$  Hz,  $J = 3.5$  Hz), 3.38 (d, 2H,  $J = 3.3$  Hz), 1.84 (d, 3H,  $J = 6.7$  Hz); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 170.1, 152.1, 139.5, 138.6, 130.1, 128.3, 127.2, 125.3, 78.5, 63.7, 38.5, 37.8, 20.8; GC–MS  $m/z$  311 ( $M^+ + 2$ , 16%), 309 ( $M^+$ , 17%), 230 (62%), 115 (100%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –206.5 ( $c = 0.77$ , AcOEt). Anal. Calcd. for C<sub>13</sub>H<sub>12</sub>BrNO<sub>3</sub>: C, 50.34; H, 3.90; N, 4.52. Found: C, 50.51; H, 3.94; N, 4.61.

**3-(2-Methoxycarbonylpropionyl)-(4R,5S)-indano[1,2-d]oxazolidin-2-one 2h or 2'h (more polar isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 7.62–7.59 (m, 1H), 7.37–7.27 (m, 3H), 5.97 (d, 1H,  $J = 6.8$  Hz), 5.29 (dt, 1H,  $J = 6.8$ , 3.4 Hz), 4.52 (q, 1H,  $J = 7.2$  Hz), 3.57 (s, 3H), 3.37 (d, 2H,  $J = 3.4$  Hz), 1.48 (d, 3H,  $J = 7.2$  Hz); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 170.6, 170.0, 152.8, 139.2, 138.6, 129.9, 128.1, 127.2, 125.1, 78.6, 63.1, 52.3, 45.3, 37.8, 13.2; GC–MS  $m/z$  ( $M^+$  absent) 258 ( $M^+ - OCH_3$ , 7), 245 ( $M^+ - CO_2$ , 17), 174 (5), 130 (100), 115 (65); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –85.1 ( $c = 0.47$ , AcOEt). Anal. Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>5</sub>: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.41; H, 5.27; N, 4.90.

**3-(2-Methoxycarbonylpropionyl)-(4R,5S)-indano[1,2-d]oxazolidin-2-one 2h or 2'h (less polar isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 7.60–7.57 (m, 1H), 7.37–7.24 (m, 3H), 5.97 (d, 1H,  $J = 6.9$  Hz), 5.33 (dt, 1H,  $J = 6.9$ , 3.1 Hz), 4.54 (q, 1H,  $J = 7.2$  Hz), 3.72 (s, 3H), 3.38 (d, 2H,  $J = 3.1$  Hz), 1.45 (d, 3H,  $J = 7.2$  Hz); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>): 170.9, 170.1, 153.0, 139.4, 138.9, 130.0, 128.23, 127.1, 125.2, 78.3, 63.2, 52.5, 45.3, 38.0, 13.3; GC–MS  $m/z$  ( $M^+$  absent) 258 ( $M^+ - OCH_3$ , 7), 245 ( $M^+ - CO_2$ , 17), 174 (5), 130 (100), 115 (65); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –200.0 ( $c = 0.87$ , AcOEt). Anal. Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>5</sub>: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.39; H, 5.31; N, 4.87.

**3-Propionyl-(4R,5S)-indano[1,2-d]oxazolidin-2-one 3h.**<sup>24</sup>

**2,3-O-Isopropylidene- $\gamma$ -D-ribonolactone 2-bromopropionate 1i (more polar isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.89 (d, AB, 1H,  $J_{AB} = 5.6$  Hz,  $\Delta\nu = 38.1$  Hz), 4.69 (app d, AB, 1H,  $J_{AB} = 5.6$  Hz,  $\Delta\nu = 38.1$  Hz), 4.75 (dd, 1H,  $J = 2.5$ , 2.5 Hz),

4.47 (dd, AB, 1H,  $J_{AB} = 12.5$  Hz,  $J = 2.6$  Hz,  $\Delta\nu = 44.9$  Hz), 4.32 (q, 1H,  $J = 6.8$  Hz), 4.24 (dd, AB, 1H,  $J_{AB} = 12.5$  Hz,  $J = 2.6$  Hz,  $\Delta\nu = 44.9$  Hz), 1.74 (d, 3H,  $J = 6.8$  Hz), 1.41 (s, 3H), 1.33 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 173.2, 169.0, 113.7, 79.3, 77.5, 75.1, 64.6, 39.0, 26.6, 25.4, 21.4; GC–MS  $m/z$  ( $M^+$  absent) 309 ( $M^+ + 2 - CH_3$ , 21), 307 ( $M^+ - CH_3$ , 23), 109 (13), 107 (14), 43 (100); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –20.9 ( $c = 0.52$ , AcOEt). Anal. Calcd for C<sub>11</sub>H<sub>15</sub>BrO<sub>6</sub>: C, 40.89; H, 4.68. Found: C, 40.93; H, 4.70.

**2,3-O-Isopropylidene- $\gamma$ -D-ribonolactone 2-bromopropionate 1i (less polar isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.91 (d, AB, 1H,  $J_{AB} = 5.6$  Hz,  $\Delta\nu = 43.6$  Hz), 4.69 (app d, AB, 1H,  $J_{AB} = 5.6$  Hz,  $\Delta\nu = 43.6$  Hz), 4.77 (dd, 1H,  $J = 2.2$ , 2.2 Hz), 4.37 (d, 2H,  $J = 2.2$  Hz), 4.33 (q, 1H,  $J = 6.8$  Hz), 1.78 (d, 3H,  $J = 6.8$  Hz), 1.44 (s, 3H), 1.36 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 173.3, 169.2, 113.8, 79.4, 77.6, 75.2, 64.8, 38.8, 26.6, 25.5, 21.2; GC–MS  $m/z$  ( $M^+$  absent) 309 ( $M^+ + 2 - CH_3$ , 54), 307 ( $M^+ - CH_3$ , 63), 109 (13), 107 (14), 43 (100); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –25.0 ( $c = 0.83$ , AcOEt). Anal. Calcd for C<sub>11</sub>H<sub>15</sub>BrO<sub>6</sub>: C, 40.89; H, 4.68. Found: C, 4.90; H, 4.69.

**2,3-O-Isopropylidene- $\gamma$ -D-ribonolactone 2-Methoxycarbonylpropionate 2i + 2'i (Mixture of Two Isomers).** More abundant isomer: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.80–4.21 (m, 5H), 3.72 (s, 3H), 3.43 (q, 1H,  $J = 7.2$  Hz), 1.45 (s, 3H), 1.38 (d, 3H,  $J = 0.2$  Hz), 1.36 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 173.4, 169.7, 168.8, 113.8, 79.5, 75.1, 64.3, 52.9, 45.9, 29.6, 26.7, 25.6, 13.6; GC–MS  $m/z$  ( $M^+$  absent) 287 ( $M^+ - CH_3$ , 23), 307 ( $M^+ - CH_3$ , 63), 213 (6), 115 (76), 59 (75), 43 (100). Less abundant isomer: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.80–4.21 (m, 5H), 3.71 (s, 3H), 3.43 (q, 1H,  $J = 7.2$  Hz), 1.45 (s, 3H), 1.40 (d, 3H,  $J = 0.2$  Hz), 1.36 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 173.3, 170.0, 169.0, 113.8, 79.4, 75.1, 64.3, 52.8, 45.7, 29.6, 26.7, 25.5, 13.4; GC–MS  $m/z$  ( $M^+$  absent) 287 ( $M^+ - CH_3$ , 23), 307 ( $M^+ - CH_3$ , 63), 213 (6), 115 (76), 59 (75), 43 (100).

**N-[(5R)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-bromopropionamide 1j (Both Isomers).**<sup>25</sup>

**N-[(5R)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonylpropionamide 2j' (more abundant, less polar isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.05 (q, 1H,  $J = 7.1$  Hz), 3.85 (dd, 1H,  $J = 7.5$ , 5.1 Hz), 3.66 (s, 3H), 3.47 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 12.09$  Hz), 3.41 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 12.09$  Hz), 2.12–1.79 (m, 5H), 1.40 (d, 3H,  $J = 7.1$  Hz), 1.38–1.25 (m, 2H), 1.35 (s, 3H), 0.93 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>) 170.2, 168.0, 65.1, 52.9, 52.4, 48.5, 47.8, 45.9, 44.5, 37.8, 32.7, 26.4, 20.2, 19.9, 13.2; GC–MS  $m/z$  ( $M^+$  absent) 298 ( $M^+ - OCH_3$ , 10), 214 (14), 115 (100), 87 (40), 59 (95); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –77.9 ( $c = 0.68$ , AcOEt). Anal. Calcd for C<sub>15</sub>H<sub>23</sub>NO<sub>5</sub>S: C, 54.69; H, 7.04; N, 4.25. Found: C, 54.73; H, 7.10; N, 4.20.

This isomer was identified as the (2*R*) compound, and this assignment is supported by an X-ray crystallographic structure determination.

**N-[(5R)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonylpropionamide 2j (less abundant, more polar isomer in mixture with less polar isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.07 (q, 1H,  $J = 7.1$  Hz), 3.92 (t, 1H,  $J = 6.4$  Hz), 3.71 (s, 3H), 3.50 (d, AB, 1H,  $J = 13.9$  Hz,  $\Delta\nu = 8.57$  Hz), 3.46 (d, AB, 1H,  $J = 13.9$  Hz,  $\Delta\nu = 8.57$  Hz), 2.12–1.79 (m, 5H), 1.44 (d, 3H,  $J = 7.1$  Hz), 1.38–1.25 (m, 2H), 1.21 (s, 3H), 0.94 (s, 3H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>): 169.8, 169.3, 65.3, 52.9, 52.5, 48.5, 47.8, 46.2, 44.6, 38.2, 32.8, 26.4, 20.8, 19.8, 14.8; GC–MS  $m/z$  ( $M^+$  absent) 298 ( $M^+ - OCH_3$ , 18), 214 (19), 115 (80), 87 (40), 59 (100).

**N-[(5R)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-bromobutyramide 1k (less polar isomer):** <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 4.74 (t, 1H,  $J = 7.2$  Hz), 3.91 (dd, 1H,  $J = 6.9$ , 5.6 Hz), 3.50 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 15.12$  Hz), 3.43 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 15.12$  Hz), 2.23–1.88 (m, 6H), 1.45–1.23 (m, 3H), 1.17 (s, 3H), 1.00 (t, 3H,  $J =$

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7.2 Hz), 0.96 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 168.3, 64.9, 53.1, 48.7, 47.9, 46.5, 44.5, 37.6, 32.7, 27.3, 26.5, 20.6, 19.9, 11.9; GC-MS  $m/z$  ( $\text{M}^+$  absent) 337 (3), 335 (3), 284 ( $\text{M}^+ - \text{Br}$ , 10), 220 (47), 135 (82), 134 (100);  $[\alpha]^{20}_{\text{D}} = -64.4$  ( $c = 0.26$ , AcOEt). Anal. Calcd for  $\text{C}_{14}\text{H}_{22}\text{BrNO}_5\text{S}$ : C, 46.16; H, 6.09; N, 3.84. Found: C, 46.63; H, 6.21; N, 3.92.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-bromobutyramide 1k (more polar isomer, in mixture with less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 4.83 (t, 1H,  $J = 7.0$  Hz), 3.91 (t, 1H,  $J = 6.4$  Hz), 3.52 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 6.80$  Hz), 3.45 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 6.80$  Hz), 2.23–1.88 (m, 6H), 1.45–1.23 (m, 3H), 1.11 (s, 3H), 1.00 (t, 3H,  $J = 7.2$  Hz), 0.96 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 167.8, 65.5, 52.8, 48.6, 47.7, 47.6, 44.4, 38.2, 32.6, 29.7, 26.3, 20.6, 19.8, 11.6; GC-MS  $m/z$  ( $\text{M}^+$  absent) 337 (3), 335 (3), 284 ( $\text{M}^+ - \text{Br}$ , 10), 220 (47), 135 (82), 134 (100).

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonylbutyramide 2k or 2'k (more abundant, less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 3.97–3.86 (m, 2H), 3.66 (s, 3H), 3.51 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 11.29$  Hz), 3.39 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 11.29$  Hz), 2.20–1.80 (m, 6H), 1.44–1.19 (m, 3H), 1.13 (s, 3H), 0.97 (t, 3H,  $J = 7.3$  Hz), 0.94 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 169.5, 167.2, 65.1, 53.0, 52.3, 48.4, 47.7, 44.5, 37.8, 32.7, 26.4, 22.0, 20.1, 19.9, 11.9; GC-MS  $m/z$  ( $\text{M}^+$  absent) 312 ( $\text{M}^+ - \text{OCH}_3$ , 1), 214 (2), 129 (49), 59 (100);  $[\alpha]^{20}_{\text{D}} = -77.4$  ( $c = 0.67$ , AcOEt). Anal. Calcd for  $\text{C}_{16}\text{H}_{25}\text{NO}_5\text{S}$ : C, 55.96; H, 7.34; N, 4.08. Found: C, 56.03; H, 7.51; N, 4.16.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonylbutyramide 2k or 2'k (Less Abundant, More Polar Isomer).** In all our experiments, it has never been possible to obtain a chromatographic fraction of this isomer sufficiently pure to describe its NMR spectra. Only the signal of the methyl group of the carboxylate moiety can be given with precision: 3.71 ppm; GC-MS  $m/z$  ( $\text{M}^+$  absent) 312 ( $\text{M}^+ - \text{OCH}_3$ , 1), 214 (2), 129 (50), 59 (100).

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-bromohexanamide 1l (less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 4.80 (t, 1H,  $J = 7.2$  Hz), 3.91 (dd, 1H,  $J = 6.9$ , 5.6 Hz), 3.52 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 15.34$  Hz), 3.39 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 15.34$  Hz), 2.16–1.88 (m, 6H), 1.45–1.22 (m, 7H), 1.17 (s, 3H), 0.96 (s, 3H), 0.90 (t, 3H,  $J = 6.8$  Hz);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 168.3, 64.9, 53.1, 48.7, 47.9, 44.8, 44.5, 37.6, 33.5, 32.7, 29.3, 26.5, 22.1, 20.6, 19.9, 13.7; GC-MS  $m/z$  ( $\text{M}^+$  absent) 337 (4), 335 (3), 312 ( $\text{M}^+ - \text{Br}$ , 12), 248 (16), 135 (100);  $[\alpha]^{20}_{\text{D}} = -44.3$  ( $c = 0.41$ , AcOEt). Anal. Calcd for  $\text{C}_{16}\text{H}_{26}\text{BrNO}_5\text{S}$ : C, 48.98; H, 6.68; N, 3.57. Found: C, 49.16; H, 6.41; N, 3.82.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-bromohexanamide 1l (more polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 4.86 (t, 1H,  $J = 7.1$  Hz), 3.90 (t, 1H,  $J = 6.3$  Hz), 3.48 (d, AB, 1H,  $J = 14.9$  Hz,  $\Delta\nu = \text{app. } 0.00$  Hz), 3.48 (d, AB, 1H,  $J = 14.9$  Hz,  $\Delta\nu = \text{app. } 0.00$  Hz), 2.13–1.85 (m, 6H), 1.45–1.22 (m, 7H), 1.10 (s, 3H), 0.94 (s, 3H), 0.85 (t, 3H,  $J = 6.7$  Hz);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 167.1, 65.6, 52.8, 48.6, 47.8, 45.9, 44.6, 38.2, 36.0, 32.8, 29.2, 26.3, 21.8, 20.7, 19.8, 13.7; GC-MS  $m/z$  ( $\text{M}^+$  absent) 337 (4), 335 (3), 312 ( $\text{M}^+ - \text{Br}$ , 12), 248 (16), 135 (100);  $[\alpha]^{20}_{\text{D}} = -74.4$  ( $c = 0.34$ , AcOEt). Anal. Calcd for  $\text{C}_{16}\text{H}_{26}\text{BrNO}_5\text{S}$ : C, 48.98; H, 6.68; N, 3.57. Found: C, 49.03; H, 6.71; N, 3.68.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonylhexanamide 2l or 2'1 (more abundant, less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 3.98 (dd, 1H,  $J = 8.6$ , 5.4 Hz), 3.88 (dd, 1H,  $J = 7.6$ , 5.0 Hz), 3.66 (s, 3H), 3.47 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 11.31$  Hz), 3.42 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 11.31$  Hz), 2.19–1.79 (m, 7H), 1.43–1.19 (m, 6H), 1.12 (s, 3H), 0.94 (s, 3H), 0.86 (t, 3H,  $J = 6.9$  Hz);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 169.7, 167.2, 65.1, 53.0, 52.3, 51.6, 48.4, 47.7, 44.5, 37.8, 32.7, 29.4, 28.3, 26.4, 22.4, 20.1, 19.8, 13.7; GC-MS  $m/z$  ( $\text{M}^+$  absent) 340 ( $\text{M}^+ - \text{OCH}_3$ , 2), 214 (5), 157 (66), 69 (100);  $[\alpha]^{20}_{\text{D}} = -70.3$  ( $c = 0.77$ , AcOEt).

Anal. Calcd for  $\text{C}_{18}\text{H}_{29}\text{NO}_5\text{S}$ : C, 58.20; H, 7.87; N, 3.77. Found: C, 58.43; H, 7.91; N, 3.79.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonylhexanamide 2l or 2'1 (Less Abundant, More Polar Isomer).** In all our experiments, it has never been possible to obtain a chromatographic fraction of this isomer sufficiently pure to describe its NMR spectra. Only the signal of the methyl group of the carboxylate moiety can be given with precision: 3.71 ppm; GC-MS  $m/z$  ( $\text{M}^+$  absent) 340 ( $\text{M}^+ - \text{OCH}_3$ , 1), 214 (5), 157 (67), 69 (100).

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-bromo-3-methylbutyramide 1m (less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 4.54 (d, 1H,  $J = 9.4$  Hz), 3.91 (dd, 1H,  $J = 7.2$ , 5.4 Hz), 3.51 (d, AB, 1H,  $J = 13.7$  Hz,  $\Delta\nu = 15.35$  Hz), 3.40 (d, AB, 1H,  $J = 13.7$  Hz,  $\Delta\nu = 15.35$  Hz), 2.41–2.26 (m, 1H), 2.07–1.87 (m, 4H), 1.44–1.22 (m, 3H), 1.16 (s, 3H), 1.13 (d, 3H,  $J = 6.6$  Hz), 0.99 (d, 3H,  $J = 6.6$  Hz), 0.94 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 168.0, 64.9, 53.1, 52.8, 48.6, 47.8, 44.5, 37.5, 32.7, 31.4, 26.4, 20.6, 20.5, 19.8; GC-MS  $m/z$  ( $\text{M}^+$  absent) 337 (12), 335 (13), 298 ( $\text{M}^+ - \text{Br}$ , 10), 234 (28), 165 (7), 163 (8), 135 (100);  $[\alpha]^{20}_{\text{D}} = -65.6$  ( $c = 0.32$ , AcOEt). Anal. Calcd for  $\text{C}_{15}\text{H}_{24}\text{BrNO}_5\text{S}$ : C, 47.62; H, 6.39; N, 3.70. Found: C, 47.77; H, 6.49; N, 3.76.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-bromo-3-methylbutyramide 1m (more polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 4.66 (d, 1H,  $J = 7.7$  Hz), 3.92 (t, 1H,  $J = 6.3$  Hz), 3.51 (d, AB, 1H,  $J = 13.9$  Hz,  $\Delta\nu = 6.63$  Hz), 3.46 (d, AB, 1H,  $J = 13.9$  Hz,  $\Delta\nu = 6.63$  Hz), 2.28 (app sept, 1H,  $J = 6.7$  Hz), 2.10–1.86 (m, 4H), 1.58–1.27 (m, 3H), 1.11 (s, 3H), 1.09 (d, 3H,  $J = 6.7$  Hz), 1.02 (d, 3H,  $J = 6.7$  Hz), 0.96 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 167.9, 65.7, 54.1, 52.9, 48.5, 47.7, 44.6, 38.3, 33.6, 32.9, 26.3, 20.7, 19.9, 19.8, 19.6; GC-MS  $m/z$  ( $\text{M}^+$  absent) 337 (12), 335 (13), 298 ( $\text{M}^+ - \text{Br}$ , 10), 234 (28), 165 (7), 163 (8), 135 (100);  $[\alpha]^{20}_{\text{D}} = -71.9$  ( $c = 0.31$ , AcOEt). Anal. Calcd for  $\text{C}_{15}\text{H}_{24}\text{BrNO}_5\text{S}$ : C, 47.62; H, 6.39; N, 3.70. Found: C, 47.73; H, 6.51; N, 3.74.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonyl-3-methylbutyramide 2m or 2'm (more abundant, less polar isomer):**  $^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 3.88 (dd, 1H,  $J = 7.3$ , 5.3 Hz), 3.81 (d, 1H,  $J = 7.6$  Hz), 3.67 (s, 3H), 3.49 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 10.57$  Hz), 3.39 (d, AB, 1H,  $J = 13.8$  Hz,  $\Delta\nu = 10.57$  Hz), 2.51–2.41 (m, 1H), 2.16–1.79 (m, 4H), 1.43–1.19 (m, 3H), 1.09 (s, 3H), 1.01 (t, 6H,  $J = 6.2$  Hz), 0.93 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 168.8, 166.7, 65.2, 58.4, 53.1, 52.1, 48.4, 47.8, 44.6, 37.9, 32.8, 28.8, 26.5, 20.9, 20.2, 20.0, 19.9; GC-MS  $m/z$  ( $\text{M}^+$  absent) 326 ( $\text{M}^+ - \text{OCH}_3$ , 7), 143 (100), 115 (17), 59 (65), 43 (25);  $[\alpha]^{20}_{\text{D}} = -66.2$  ( $c = 0.27$ , AcOEt). Anal. Calcd for  $\text{C}_{17}\text{H}_{27}\text{NO}_5\text{S}$ : C, 57.12; H, 7.61; N, 3.92. Found: C, 57.83; H, 7.84; N, 4.02.

**N-[(5*R*)-10,10-Dimethyl-3,3-dioxo-3-thia-4-azatricyclo-[5.2.1.0<sup>1,5</sup>]dec-4-yl]-2-methoxycarbonyl-3-methylbutyramide 2m or 2'm (Less Abundant, More Polar Isomer in Mixture with Less Polar Isomer).** In all our experiments, it has never been possible to obtain a chromatographic fraction of this isomer sufficiently pure to describe its NMR spectra. Only the signal of the methyl group of the carboxylate moiety can be given with precision: 3.71 ppm; GC-MS  $m/z$  ( $\text{M}^+$  absent) 326 ( $\text{M}^+ - \text{OCH}_3$ , 5), 143 (100), 115 (16), 59 (65), 43 (24).

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**Supporting Information Available:** General remarks and proton-decoupled  $^{13}\text{C}$  NMR spectra of **1c**, **2c**, **2f**, **g**, **1h**, **2h**, **1i**, **2i**, **2j**, **1k**, **2k**, **1l**, **2l**, **1m**, and **2m**. Details of X-ray analysis of compound **2j**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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