First Highly Regio- and Diastereoselective [3+2] Cycloaddition of Chiral Nonracemic Fischer Carbene Complexes with Azomethine Ylides: An Enantioselective Synthesis of (+)-Rolipram

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Abstract: A new procedure for the synthesis of 1,3,4-trisubstituted and 1,4-disubstituted pyrrolidin-2-one derivatives in an enantioselective fashion is reported. The 1,3-dipolar cycloaddition of (±)-menthol and (−)-8-phenylmenthol derived Fischer alkoxy alkenyl carbene complexes with in situ generated functionalized azomethine ylides gives the corresponding cycloadducts as chelated tetracarbonyl Fischer carbene complexes. Only one regioisomer is detected in all cases, and the diastereoselectivity of the reaction is very high when (−)-8-phenylmenthol derived carbenes are employed. Oxidation and further transformation of the cycloadducts provide an easy access to pyrrolidin-2-ones. The anti-inflammatory and antidepressant drug (+)-Rolipram is readily prepared in four steps in a 20% overall yield by taking advantage of this newly developed methodology.

Keywords: azomethine ylides · carbenes · cycloaddition · pyrrolidinones · Rolipram

Introduction

Five- and six-membered rings are ubiquitous in both naturally occurring compounds and synthetic products. The most powerful tool to access six-membered rings is widely recognized to be the Diels–Alder reaction, while 1,3-dipolar cycloadditions have proved to be extremely versatile for the preparation of five-membered rings. We have been interested in the role of Fischer carbene complexes[1] to create six- and five-membered rings by means of [4+2] and [3+2] cycloadditions.[2] While the former have been widely developed,[3] few examples of the latter can be found in the chemical literature.[4] In these 1,3-dipolar cycloadditions, the presence of the metal pentacarbonyl moiety results in an increase of the reaction rate, as well as in an improvement in the regio- and diastereoselectivity of the processes when carbenes are employed instead of their ester analogues. This allows one to prepare enantiopure cycloadducts when starting from (−)-8-phenylmenthol derived carbenes.[5]

Pyrrolidin-2-ones possess varied biological and pharmaceutical activity and are also valuable and effective intermediates for the synthesis of pyrrolidine alkaloids, γ-amino acids, and other biologically interesting nitrogen-containing products.[6] The preparation of pyrrolidin-2-ones is mainly based on two approaches: i) transformation of pyroglutamic acid derivatives[7] and ii) Michael addition of glycine derived enolates to activated olefins followed by cyclization,[8] although other routes, including 1,3-dipolar cycloadditions, have also been reported.[9]

Among the drugs bearing a pyrrolidin-2-one ring, Rolipram **1** is a potent and selective inhibitor of cyclic-AMP specific phosphodiesterase (cAMP PDE) designated PDE IV, and it is known to bind stereoselectively and with very high affinity to binding sites in brain tissue. PDE IV appears also to be the predominant functional enzyme in a variety of human inflammatory cells. As a consequence Rolipram, which was initially developed as a therapeutically interesting reagent for the treatment of central nervous system (CNS) disorders (mainly as an antidepressant),[10] has presented great potential (as well as other selective PDE IV inhibitors) as an anti-

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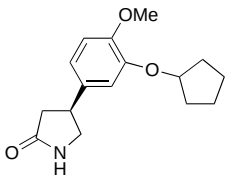
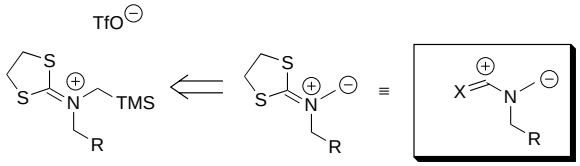


1 (+)-Rolipram

inflammatory agent, of particular value in the treatment of diseases such as asthma.[11] In fact, although both enantiomers are active, the levorotatory isomer, for which several syntheses have been recently reported,[12] has proved to be the most active one.

The recently described functionalized azomethine ylide precursor **2a**[13] attracted our attention as it seemed to be a suitable starting material to react with Fischer alkenyl carbene complexes. In fact, treatment of iminium salt **2a** with CsF generates azomethine ylide **3a** that behaves as a synthetic equivalent of carbonyl-fused and thiocarbonyl-fused dipoles **4a** and **5a** (Scheme 1) and cycloadds in a 1,3-dipolar fashion to alkenes, ketones, and thioketones; the addition allows the preparation of interesting γ-lactam alkaloids,[14] 1,3-oxazolidine,[15] and thiazolidine-2-thiones,[15] respectively.[16]



2 a R = H **b** R = Ph **3** **4** X = O **5** X = S

Scheme 1. Iminium salts (**2**) as precursors of azomethine ylides (**3**) that behave as synthetic equivalents of carbonyl-fused and thiocarbonyl-fused dipoles.

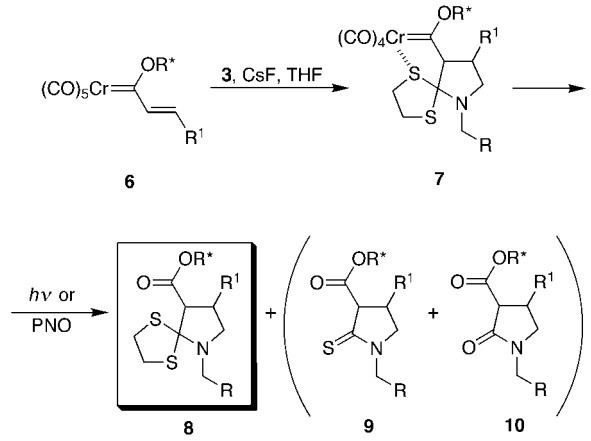
Abstract in Spanish: *En este artículo se describe un nuevo procedimiento para la preparación de derivados 1,3,4-trisustituidos y 1,4-disustituidos de pirrolidin-2-ona de forma enantioselectiva. La cicloadición 1,3-dipolar de complejos alcoxialquenilcarbeno de Fischer derivados de (±)-mentol y (−)-8-fenilmentol con iluros de azometino funcionalizados, generados in situ, origina los correspondientes cicloaductos como tetracarbonil complejos carbeno de Fischer quelados. En todos los casos se detecta solamente un regioisómero de los dos posibles; además, la diastereoselectividad de la reacción es muy elevada cuando se utilizan complejos carbeno derivados de (−)-8-fenilmentol. La oxidación y posterior transformación de los cicloaductos supone una ruta muy sencilla para acceder a pirrolidin-2-onas. Como una aplicación de la nueva metodología desarrollada se llevó a cabo la síntesis del fármaco (+)-Rolipram, que presenta actividad anti-inflamatoria y antidepresiva, en cuatro pasos y con un rendimiento global del 20 %.*

We disclose here a novel synthesis of pyrrolidin-2-ones with **2** as dipole precursors in [3+2] dipolar cycloadditions with chiral nonracemic alkoxy alkenyl Fischer carbenes and the application of the developed methodology to an enantioselective synthesis of (+)-Rolipram.

Results and Discussion

The cycloaddition reactions were initially performed by using (±)-menthol derived carbene **6a** as a model system at different temperatures. Treatment of (±)-menthol derived carbene **6a** with **2a** in the presence of CsF at room temperature yielded cycloadduct **7a** as a single regioisomer, although a mixture of two diastereomers with moderate diastereoselectivity could be detected (Scheme 2). The reaction was immediate when carried out at room temperature (see Table 1, entry 1) and it only took 30 minutes to be completed at −30 °C with a slight improvement in the diastereoselectivity (Table 1, entry 2), but it did not proceed at temperatures lower than −50 °C. The reaction was extended to other menthol derived Fischer alkenyl carbene complexes **6b–d** and iminium salts **2a** and **2b**; in all these cases, 1:1 mixtures of diastereomers were obtained at −50 °C (Table 1, entries 3–5). However, when the reaction was performed using (−)-8-phenylmenthol derived carbenes **6e–h** a great improvement in the diastereoselectivity was achieved, and only one diastereomer was detected by ^{1}H NMR spectroscopy (300 MHz) (Table 1, entries 6–12).

Carbenes **7** bear only four carbonyl ligands as supported by the observation in the ^{13}C NMR and FT-IR spectra of a tetracarbonyl ligand pattern. This fact indicates that they are chelated tetracarbonyl alkoxy Fischer carbenes stabilized by coordination of S to the metal center.[17] This is one of the few cases reported so far of this situation, although several examples in which other heteroatoms (N, O),[5, 17a, 18] olefins,[3k, 19] or alkynes[20] stabilize the metal have been described. This result is particularly interesting as it allows us to assign the proposed regiochemistry to carbenes **7**; the other

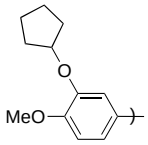
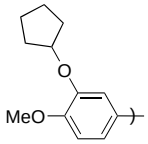
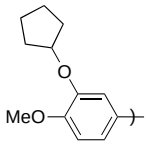


6 **7** **8** **9** **10**

Scheme 2. Reaction of in situ generated azomethine ylides (**3**) with carbene complexes (**6**).

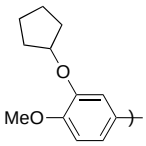
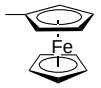
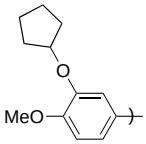
0947-6539/01/0716-3534 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 16

Table 1. Carbene cycloadducts **7** obtained by cycloaddition of alkenyl carbenes **6** with azomethine ylides **3** derived from iminium salts **2a** and **2b**.

	6	R*OH	R^1	R	7	*dr*[a]	Yield [%][b]
1	**a**	(±)-menthol	Ph	H	**a**	3:1[c]	28
2	**a**	(±)-menthol	Ph	H	**a**	4:1[d]	54
3	**b**	(±)-menthol		Ph	**b**	1:1	67
4	**c**	(±)-menthol	Ph	Ph	**c**	1:1	45
5	**d**	(±)-menthol	2-furyl	Ph	**d**	1:1	69
6	**e**	(−)-8-phenylmenthol	Ph	H	**e**	>95:5	29
7	**f**	(−)-8-phenylmenthol	2-furyl	H	**f**	>95:5	57
8	**g**	(−)-8-phenylmenthol		H	**g**	>95:5	60
9	**h**	(−)-8-phenylmenthol		H	**h**	>95:5	66
10	**e**	(−)-8-phenylmenthol	Ph	Ph	**i**	>95:5	60
11	**f**	(−)-8-phenylmenthol	2-furyl	Ph	**j**	>95:5	68
12	**g**	(−)-8-phenylmenthol		Ph	**k**	>95:5	58

[a] Diastereomeric ratio (*dr*) determined by ^{1}H NMR spectroscopy (300 MHz). [b] Isolated yields based on alkenyl carbenes **6;** all reactions were carried out at −50 °C unless otherwise stated. [c] Reaction performed at room temperature. [d] Reaction performed at −30 °C.

Table 2. Esters **8** resulting from oxidation of carbene adducts **7** or by sequential cycloaddition–oxidation from carbenes **6**.

	s.m.[a]	R*OH	R^1	R	8	Yield [%][b] (**8**/**9**/**10**)
1	**7a**	(±)-menthol	Ph	H	**a**	28[c] (28/-/-)
2	**7a**	(±)-menthol	Ph	H	**a**	26[c,d] (26/-/-)
3	**7c**	(±)-menthol	Ph	Ph	**b**	78[c] (45/33/-)
4	**6c**	(±)-menthol	Ph	Ph	**b**	38[c,e] (38/-/-)
5	**7d**	(±)-menthol	2-furyl	Ph	**c**	52[c] (20/32/-)
6	**6d**	(±)-menthol	2-furyl	Ph	**c**	32[c,e] (32/-/-)
7	**7e**	(−)-8-phenyl-menthol	Ph	H	**d**	quantitative (>99/-/-)
8	**7f**	(−)-8-phenyl-menthol	2-furyl	H	**e**	25[c] (25/-/-)
9	**7g**	(−)-8-phenyl-menthol		H	**f**	93 (55/23/15)
10	**7h**	(−)-8-phenyl-menthol		H	**g**	77 (38/19/20)
11	**6e**	(−)-8-phenyl-menthol	Ph	Ph	**h**	31[c,e] (31/-/-)
12	**6f**	(−)-8-phenyl-menthol	2-furyl	Ph	**i**	27[c,e] (27/-/-)
13	**7k**	(−)-8-phenyl-menthol		Ph	**j**	61 (37/8/16)

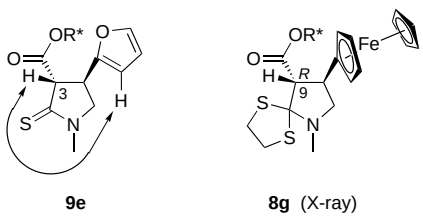
[a] Starting material. [b] Isolated and combined yields for the sunlight promoted oxidation step, based on carbene adducts **7** unless otherwise stated; in brackets, isolated yields of each compound. [c] Variable amounts of **9** and/or **10** were also detected, although not isolated. [d] Oxidation performed with PNO. [e] Isolated yields for a sequential cycloaddition–oxidation procedure based on alkenyl carbenes **6**.

regioisomer must be a pentacarbonyl derivative, as S coordination to chromium would not be feasible in this case.

Carbenes **7** could be readily oxidized to the corresponding esters **8** by treatment with pyridine *N*-oxide (PNO) or, better, just by sunlight exposure. However, the isolated yield of esters **8** was low to moderate in most cases, as variable amounts of thiopyrrolidinones **9** and pyrrolidinones **10** were obtained (Table 2); the combined yield was quite high (entries 3, 7, 9, and 10, Table 2). Other oxidants commonly employed in carbene chemistry (such as cerium ammonium nitrate, DMSO) gave less satisfactory results.

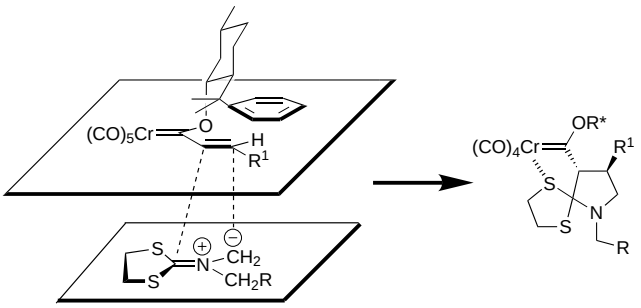
The relative stereochemistry of the cycloadducts was proposed to be *trans* as a result of the observation of crosspeaks between H-3 and the hydrogen in position 3 in the furyl group in NOESY experiments performed on thiolactam **9e** (Scheme 3). This was as expected if the facts that 1,3-dipolar cycloadditions are suprafacial, and the stereochemistry of the alkene is maintained are taken into account. The absolute configuration of carbene complexes **7** was assigned to be *R* for C-9 on the basis of the X-ray structure of dithiolane derivative **8g**[21] (Scheme 3). This should be the result of a dipole approach to the olefin from the bottom face because of an effective blocking of the upper face by the phenyl group of the (−)-8-phenylmenthol chiral auxiliary due to a π-*stacking* interaction between that phenyl group and the alkene double bond,[5] as depicted in Scheme 4.

We then checked the [3+2] cycloaddition reactions of dipole **2** with the analogue esters, such as (1*R*,2*S*,3*R*)-8-phenylmenthyl cinnamate and (±)-menthyl cinnamate, in order to confirm the advantages of our carbene chemistry. Those reactions did not proceed either at low or at room temperature; in fact the mixture had to be refluxed in THF for several days and was worked up before the starting esters were totally consumed. The ^{1}H NMR spectrum of the crude residue showed the presence of compounds **8**, **9**, and **10** as a complex mixture of regio- and diastereomers, the ratio of which could not be determined (Scheme 5). This result was

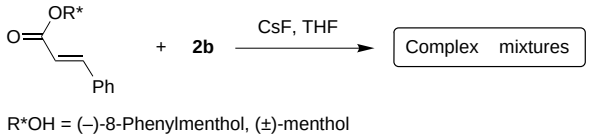


9e **8g** (X-ray)

Scheme 3. Structural assignments: NOESY crosspeaks for compound **9e** and absolute configuration for compound **8g** determined by X-ray analysis.

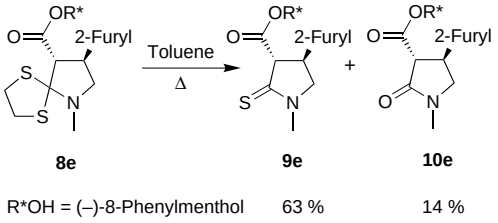


Scheme 4. Mechanistic hypothesis: Postulated reactive conformation of **6**, in which the chiral auxiliary phenyl group shields the (*Re*,*Re*)-face of the double bond, inducing selective attack from the (*Si*,*Si*)-face.



Scheme 5. Reaction of in situ generated azomethine ylides (**3**) with cinnamates.

not surprising as we had previously observed that thiirane extrusion and dithiolane hydrolysis could be achieved when heating **8e** in refluxing toluene to afford pyrrolidinone derivatives **9e** and **10e** as a mixture in 63 % and 14 % isolated yield, respectively (Scheme 6).



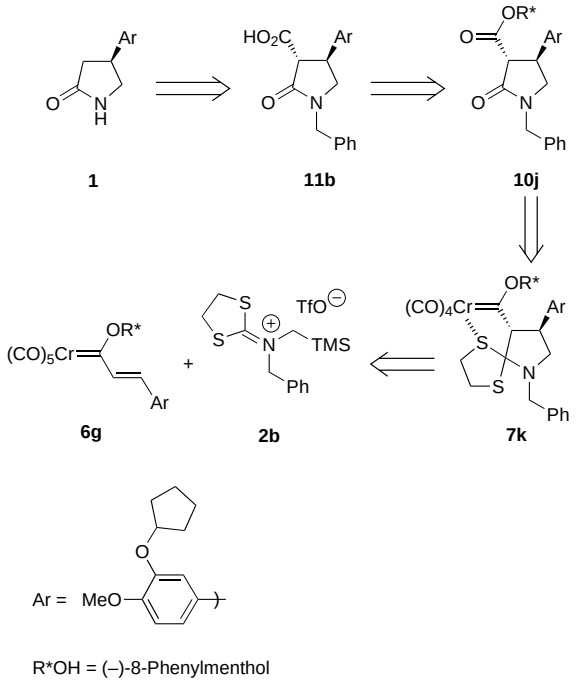
Scheme 6. Thermal decomposition of **8e** in refluxing toluene.

As an application of the methodology described above for the synthesis of pharmaceutically interesting compounds, (+)-Rolipram **1** was chosen as a target. The retrosynthetic route to **1** is depicted in Scheme 7. As proposed therein, (+)-Rolipram **1** should be easily prepared by a decarboxylation – hydrogenolysis sequence from *N*-benzyl pyrrolidinone carboxylic acid **11b**, which, in turn, should be accessed by hydrolysis of **10j**. Pyrrolidin-2-one **10j** can be obtained by transformation of the cycloadduct **7k** that results from the reaction between Fischer carbene **6g** and azomethine ylide **3b**, as described earlier (Table 1, entry 12 and Table 2, entry 13).

As the oxidation of cycloadducts **7** led to a mixture of products, several attempts to deprotect the carbonyl group were unsuccessfully carried out on cycloadducts **7** and on esters **8**. We then decided to perform the hydrolysis of the ester functionality prior to the carbonyl group deprotection. To our surprise, when the crude residue from sunlight oxidation of cycloadducts **7** was submitted to basic hydrolysis (LiOH in 1,4-dioxane/H_2O) *N*-benzylpyrrolidin-2-ones **12**, which resulted from an ester hydrolysis – decarboxylation – carbonyl deprotection sequence, were obtained together with variable amounts of *N*-benzylpyrrolidin-2-one carboxylic acids **11** (Scheme 8). These compounds could be easily separated by acid – base extraction, and it is noteworthy that (−)-8-phenylmenthol, employed as a chiral auxiliary during the cycloaddition process, was recovered in high yield and purity after chromatographic purification. On the other hand, treatment of **11** with copper(I) oxide in refluxing pyridine allowed decarboxylation, which led to **12** in good yields.

The synthetic sequence from carbenes **6** to *N*-benzylpyrrolidin-2-ones **12** that involves five steps (cycloaddition – carbene oxidation – ester hydrolysis – carbonyl deprotection – decarboxylation) resulted in an expedient and easy-to-work transformation; it can be performed avoiding the isolation of intermediates **7** – **10** and with no more than two rapid filtrations through Celite to remove cesium and chromium salts. The reaction allows rapid access to *N*-benzylpyrrolidin-2-ones **12**. *N*-Benzyl pyrrolidin-2-ones **12** were analyzed by HPLC using a chiral column in order to determine the enantiomeric ratio, which was found to be 92:8 for **12a** (Table 3, entry 1), but this procedure was unsuccessful for **12b**.

The final debenzylation step was accomplished by treatment with lithium in liquid ammonia to give Rolipram **1** in 95 % yield, while other classical hydrogenolysis methods (for example, H_2, Pd/C; H_2, $Pd(OH)_2$/C; cyclohexene, $Pd(OH)_2$/C; formic acid) failed. At this point, the sign of the specific rotation $\{[\alpha]_D^{26} = +24.7$ ($c = 0.23$ in MeOH)$\}$ indicated that we had prepared the dextrorotatory enantiomer, and this confirmed our model for the cycloaddition step. However, the value of the specific rotation was smaller than the one reported in the literature for the (−)-isomer $\{[\alpha]_D = -31$ ($c =$ 0.5 in MeOH)$\}$;[12d] a similar result had been previously observed for the synthesis of Meyers and Snyder who



Scheme 7. Retrosynthetic analysis of (+)-Rolipram (**1**).

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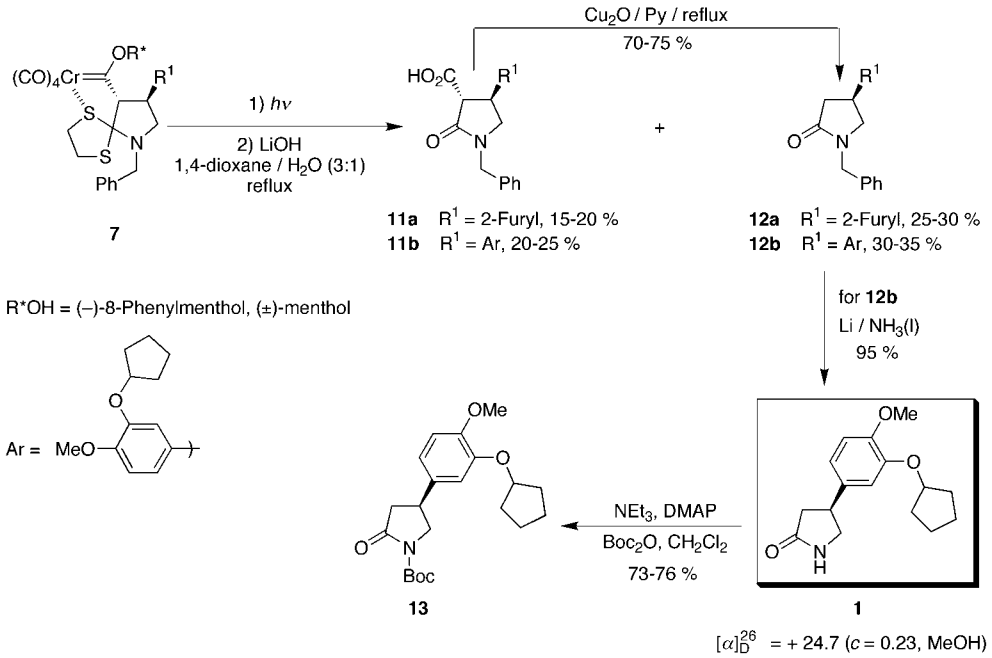


Scheme 8. Synthesis of (+)-Rolipram (**1**).

Table 3. Determination of the enantiomeric ratio by chiral HPLC analysis.

	Column	Eluent	Flow Rate [mL min^{-1}]	Retention Time [min] *R* isomer	Retention Time [min] *S* isomer	*er*
12a	Chiralcel-OJ	HexH/IPA[a] 50:1	1.0	64.3	80.6	92:8 (*R*/*S*)
13	Chiralcel-OD-H	HexH/IPA 9:1	0.8	19.3	23.9	91:9 (*S*/*R*)

[a] HexH = Hexane; IPA = Isopropyl alcohol.

reported a specific rotation of $[\alpha]_D = -19.5$ ($c = 1.15$ in MeOH)[12d] for a sample which proved to have *ee* > 99%. To determine exactly the enantiomeric purity of our compound, (+)-Rolipram **1** was transformed into its Boc-protected derivative **13** (Scheme 8). Chiral HPLC analysis of **13** indicated an enantiomeric ratio of 91:9 (Table 3, entry 2). This unexpected result is probably the consequence of the undetected presence of the other diastereomer after the cycloaddition reaction.[22]

Conclusion

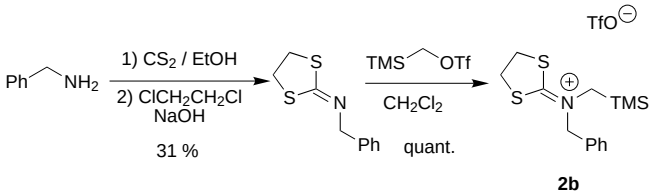
In summary, we have established a new protocol to access 3,4-disubstituted pyrrolidinone derivatives by a [3+2] cycloaddition reaction; *the employment of (–)-8-phenylmenthol derived alkenyl Fischer carbenes allows us to obtain the cycloadducts as a single regioisomer in a highly diastereoselective fashion*. The usefulness of this methodology for the synthesis of pharmaceutically interesting compounds that contain a pyrrolidinone ring was proved by accomplishing the synthesis of (+)-Rolipram in 20% overall yield.

Experimental Section

General: All reactions involving air-sensitive compounds were carried out under a N_2 atmosphere (99.99%). All glassware was oven-dried (120°C), evacuated, and purged with nitrogen. All common reagents and solvents were obtained from commercial suppliers and used without any further purification unless otherwise indicated. CsF was dried by heating at 120°C under vacuum (0.01 mmHg) for several hours (3–10 h) immediately prior to use. Fischer carbene complexes **6** were prepared following described procedures,[5] except for **6h**, which was obtained following a slightly modified method; **6b** and **6g** have been synthesized for the first time, and their spectroscopic data are reported below. The compound 3-cyclopentyloxy-4-methoxybenzaldehyde, required for the synthesis of carbenes **6b** and **6g**, was prepared following literature procedures.[12b] Iminium salt **2a** was prepared as reported.[13] Solvents were dried by standard methods. Hexane, ethyl acetate, and triethylamine were distilled before use. TLC was performed on aluminum-backed plates coated with silica gel 60 with F_{254} indicator; the chromatograms were visualized under ultraviolet light and/or by staining with a Ce/Mo reagent, or anisaldehyde or phosphomolibdic acid solutions and subsequent heating. R_f values are reported on silica gel. Flash column chromatography was carried out on silica gel 60 (230–240 mesh). For the determination of the enantiomeric ratio by HPLC, a Shimadzu LC-10 and a Waters LC Module I Plus chromatograph were used, both of them equipped with V-UV Diode-Array detectors; Chiralcel OJ and OD-H were employed as chiral columns. Routine NMR measurements were recorded on Bruker AC-200, AC-300, or DPX-300 spectrometers. ^{1}H NMR: splitting pattern abbreviations are: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet, ABq (AB quartet). ^{13}C NMR: multiplicities were determined by DEPT 90 and DEPT 135 experiments, abbreviations are: q, CH_3; t, CH_2; d, CH; s, quaternary carbons. In the cases where a mixture of diastereomers was observed, the abbreviation "min" refers to the signals assigned to the minor diastereomer, and the abbreviation "maj" to the signals belonging to the major one; in the cases where nothing is specified, either it hasn't been possible to assign the signal to any of the diastereomers, or it belongs to both of them. NOESY experiments were carried out on a Bruker AMX-400 spectrometer. Standard pulse sequences were employed for the DEPT experiments. FT-IR measurements were

performed with a Mattson 3000 FT-IR spectrometer. High-resolution mass spectra (HRMS) were obtained with a Finnigan Mat95 Mass Spectrometer; low-resolution mass spectra were obtained with a Hewlett-Packard 5880 A Spectrometer. In both cases, electron impact techniques (70 eV) were employed. Melting points were determined on a Büchi – Tottoli apparatus and are uncorrected. For optical rotations, a Perkin-Elmer 241 polarimeter was employed; values were determined using a sodium lamp, and the concentration was reported in g/100 mL. Elemental analyses were carried out with a Perkin-Elmer 240 B microanalyzer.

Synthesis of *N*-benzyl,1,3-dithiolanilidene,trimethylsilyl ammonium trifluoromethanesulfonate 2b: It was prepared following a two-step procedure similar to the one employed for the synthesis of **2a**[13] (Scheme 9). In the first step the yield was low (31 %), but cheap reagents were employed; in the second step, which required the more expensive trimethylsilylmethyl trifluoromethanesulfonate the yield was quantitative.



Scheme 9. Preparation of iminium salt (**2b**).

***N*-Benzyl-1,3-dithiolane-2-imine**: Thus, in this first step the compound was prepared as follows. Benzylamine (200 mmol, 21.84 mL) was added dropwise to a solution of CS_2 (200 mmol, 12.03 mL) in EtOH (200 mL) at 0 °C. A white suspension was formed and, once the addition of benzylamine was completed, the reaction mixture was stirred for 30 min. A solution of NaOH (400 mmol, 2 equiv, 16.0 g) in H_2O (10 mL) was added at 0 °C followed by the dropwise addition of 1,2-dichloroethane (500 mmol, 39.4 mL) at the same temperature. The white solid disappeared, and the reaction mixture was heated at 60 °C for 3 h. The solution turned yellow, and the reaction mixture was allowed to cool down to room temperature. Solvents were evaporated under vacuum to give a yellow solid residue, that was partitioned between AcOEt (50 mL) and HCl (2 N, 50 mL). The layers were separated, and the aqueous acidic layer was extracted twice more with AcOEt (2 × 30 mL). The organic layers were discarded. The aqueous layer was neutralized with NaOH (3 N) till pH > 10 and extracted with AcOEt (3 × 40 mL). The combined organic layer was dried over Na_2SO_4 and filtered, and the solvents were removed at low pressure. The oily residue was purified by column chromatography on silica gel using hexane/AcOEt (3:1) as eluent, to give the desired compound, which presented the following properties. Brown oil; yield: 31 % (12.98 g).

$R_f = 0.46$ (hexane/AcOEt, 3:1); FT-IR (neat): $\tilde{\nu} = 1593\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.42 - 7.28$ (m, 5H), 4.57 (s, 2H), 3.63 (m, 2H), 3.45 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 168.9$ (s), 138.7 (s), 128.2 (d), 127.6 (d), 126.7 (d), 62.7 (t), 37.7 (t), 34.5 (t); MS (70 eV, EI): *m*/*z* (%): 209 (42) $[M]^+$, 181 (18), 91 (100), 83 (18); HRMS for $C_{10}H_{11}NS_2$: calcd 209.0333; found 209.0337; elemental analysis calcd (%) for $C_{10}H_{11}NS_2$ (209.32): C 57.38, H 5.30, N 6.69; found C 57.22, H 5.18, N 6.59.

In the second step, trimethylsilylmethyl trifluoromethanesulfonate (33.8 mmol, 6.76 mL) was added by syringe to a solution of *N*-benzyl-1,3-dithiolane-2-imine (33.8 mmol, 7.08 g) in dry CH_2Cl_2 at 0 °C and stirred for 24 h at room temperature. Solvents were evaporated under vacuum to give a quantitative yield of a brownish oil, which solidified on standing and was used without further purification. A small amount was recrystallized in hexane/$CHCl_3$ (95:5) to be fully characterized. White solid; yield: quantitative (15.06 g); m.p. 103 – 105 °C.

FT-IR (neat): $\tilde{\nu} = 1562$, 1261 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.48 - 7.36$ (m, 5H), 5.09 (s, 2H), 4.05 (s, 4H), 3.70 (s, 2H), 0.17 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 192.9$ (s), 132.0 (s), 129.2 (d), 129.0 (d), 128.0 (d), 64.3 (t), 54.0 (t), 41.7 (t), 41.3 (t), −1.3 (q); elemental analysis calcd (%) for $C_{15}H_{22}F_3NO_3S_3Si$ (445.61): C 40.43, H 4.98, N 3.14; found C 40.27, H 4.85, N 3.11.

Pentacarbonyl[1-((1*R,3*R**,4*S**)-menthyloxy)-*trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-2-propenylidene]chromium(0) (6b)**: Red oil; yield: 94 % (2.71 g); $R_f = 0.18$ (hexane/CH_2Cl_2: 3:1); FT-IR (neat): $\tilde{\nu} = 2052$, 1977, 1928 (broad band), 1586 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.92 - 7.70$ (br s, 1H), 7.32 – 6.85 (m, 4H), 5.19 – 4.75 (m, 2H), 3.91 (s, 3H), 2.10 – 0.70 (m, 26H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 224.2$ (s), 217.0 (s), 152.9 (s), 147.9 (s), 127.1 (s), 124.1 (d), 114.0 (d), 111.6 (d), 80.5 (d), 67.8 (t), 55.9 (q), 48.1 (d), 33.9 (t), 32.7 (t), 31.0 (d), 26.4 (d), 25.4 (t), 24.0 (t), 21.8 (q), 21.4 (q), 16.9 (q); -the signals for the carbene carbon (around $\delta = 323$) and the menthyl CH−O carbon (around $\delta = 91$) were not observed-; elemental analysis calcd (%) for $C_{30}H_{36}CrO_8$ (576.61): C 62.49, H 6.29; found C 62.25, H 6.20.

Pentacarbonyl[1-((1*R*,3*R*,4*S*)-8-phenylmenthyloxy)-*trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-2-propenylidene]chromium(0) (6g): Red oil; yield: 80 % (2.61 g); $R_f = 0.57$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} =$ 2051, 1975, 1932 (broad band), 1587 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.66$ (br s, 1H), 7.42 – 6.83 (m, 8H), 6.10 (br s, 1H), 5.26 (br s, 1H), 4.87 (br s, 1H), 3.92 (s, 3H), 2.60 (br s, 1H), 2.40 – 0.70 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 324.4$ (s), 223.9 (s), 217.1 (s), 152.6 (s), 151.0 (s), 147.7 (s), 139.4 (d), 128.9 (d), 127.9 (d), 127.0 (s), 125.3 (d), 124.9 (d), 124.4 (d), 114.5 (d), 111.4 (d), 91.3 (d), 80.5 (d), 55.9 (q), 52.5 (d), 43.5 (t), 39.5 (s), 34.5 (t), 32.7 (t), 31.1 (d), 28.0 (q), 26.5 (t), 25.1 (q), 24.1 (t), 21.6 (q); elemental analysis calcd (%) for $C_{36}H_{40}CrO_8$ (652.70): C 66.25, H 6.18; found C 66.03, H 6.15.

Pentacarbonyl[1-((1*R*,3*R*,4*S*)-8-phenylmenthyloxy)-*trans*-3-ferrocenyl-2-propenylidene]chromium(0) (6h): BuLi (4.37 mmol, 2.73 mL, 1.6 M in hexanes) was added dropwise to a solution of pentacarbonyl[1-((1*R*,3*R*,4*S*)-8-phenylmenthyloxy)ethenylidene]chromium(0)[5] (3.64 mmol, 1.64 g) in dry Et_2O (40 mL) at −80 °C. After 1 h, a solution of ferrocenecarbaldehyde (7.28 mmol, 1.56 g) and $BF_3 \cdot OEt_2$ (7.28 mmol, 0.92 mL) in dry Et_2O (40 mL) was added dropwise at −80 °C, and the reaction mixture was stirred and allowed to reach room temperature overnight. Silica gel (5 g) was added, and solvents were evaporated under vacuum. The residue was purified by column chromatography on silica gel under nitrogen using hexane/CH_2Cl_2 (95:5) as eluent. Purple foam; yield: 65 % (1.53 g).

$R_f = 0.39$ (hexane/CH_2Cl_2, 95:5); FT-IR (neat): $\tilde{\nu} = 2050$, 1974, 1728 (broad band), 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.58 - 7.10$ (m, 6H), 6.51 (br s, 1H), 5.20 (br s, 1H), 4.58 (m, 4H), 4.15 (m, 5H), 2.65 – 0.72 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 320.2$ (s), 223.9 (s), 217.2 (s), 150.9 (s), 139.6 (d), 133.9 (d), 128.0 (d), 125.4 (d), 125.2 (d), 91.1 (d), 78.1 (s), 72.2 (d), 70.5 (d), 70.3 (d), 70.1 (d), 69.1 (d), 52.5 (d), 43.5 (t), 39.9 (s), 34.5 (t), 31.1 (d), 27.5 (q), 26.8 (t), 26.0 (q), 21.7 (q); elemental analysis calcd (%) for $C_{34}H_{34}CrFeO_6$ (646.48): C 63.17, H 5.30; found C 62.98, H 5.29.

Cycloaddition of dithiolane stabilized azomethine ylides 2 with Fischer alkoxy alkenyl carbenes 6: A solution of the corresponding Fischer alkoxy alkenyl carbene **6** (1 mmol) and the corresponding iminium salt **2** (1.5 equiv, 1.5 mmol) in dry THF (10 mL) was added dropwise to a white suspension of anhydrous CsF (5 equiv, 5 mmol, 760 mg) in dry THF (5 mL) under an inert atmosphere at −50 °C. The resulting suspension was stirred at −50 °C till TLC analysis showed complete consumption of the starting material (7 – 10 h). Silica gel (0.5 g) was then added to the reaction mixture, and solvents were evaporated under vacuum. The residue was purified by column chromatography on silica gel under a nitrogen atmosphere using hexane/AcOEt (100:1 to 9:1) mixtures as eluents. Cycloadducts **7** were isolated as orange oils and as a mixture of diastereomers for (±)-menthol derived carbenes or as only one diastereomer for (−)-8-phenylmenthol derived carbenes.

Tetracarbonyl{[6-methyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-yl]-[(1*R,3*R**,4*S**)-menthyloxy]methyliden}chromium(0) (7a)**: Orange oil; mixture (4:1) of diastereomers; yield: 54 % (314 mg); $R_f = 0.79$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 2059$, 2010, 1909 (broad band), 1864 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.41 - 6.77$ (m, 10H), 5.39 (m, 1H, min), 5.08 (m, 1H, maj), 4.16 – 2.70 (m, 16H), 2.59 (s, 3H, maj), 2.52 (s, 3H, min), 2.39 – 0.66 (m, 36H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta =$ 353.2 (s), 230.7 (s), 228.9 (s), 218.3 (s), 217.2 (s), 142.8 (s, min), 141.9 (s, maj), 128.4 (d, min), 128.3 (d, maj), 127.8 (d, maj), 127.2 (d, min), 126.7 (d), 105.5 (s, min), 104.4 (s, maj), 92.7 (d, min), 91.4 (d, maj), 88.4 (d, maj), 87.3 (d, min), 63.3 (t, min), 62.8 (t, maj), 48.3 (t, maj), 48.1 (t, min), 47.4 (d, maj), 47.1

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(d, min), 46.7 (d, maj), 45.9 (d, min), 41.5 (t, maj), 40.9 (t, min), 37.5 (t, maj), 37.4 (t, min), 34.1 (q), 33.9 (t, maj), 33.6 (t, min), 31.0 (d, min), 30.7 (d, maj), 26.3 (d, maj), 25.2 (d, min), 23.5 (t, maj), 22.3 (t, min), 22.0 (q, maj), 21.9 (q, min), 21.0 (q, min), 20.5 (q, maj), 16.5 (q, maj), 15.4 (q, min); elemental analysis calcd (%) for $C_{28}H_{35}CrNO_5S_2$ (581.70): C 57.81, H 6.06, N 2.41; found C 57.60, H 6.00, N 2.42.

Tetracarbonyl{[6-benzyl-8-(3-cyclopentyloxy-4-methoxyphenyl)-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R,3*R**,4*S**)-menthyloxy]methyliden}chromium(0) (7b)**: Orange oil; mixture (1:1) of diastereomers; yield: 67% (517 mg); $R_f = 0.39$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 2059$, 2011, 1909 (broad band), 1514 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.45-7.10$ (m, 10H), 6.88–6.60 (m, 6H), 5.62 (m, 1H), 5.18 (m, 1H), 4.82 (m, 2H), 4.29–3.60 (m, 12H), 3.58–2.87 (m, 8H), 2.73–0.70 (m, 58H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 354.7$ (s), 353.2 (s), 230.4 (s), 228.8 (s), 228.5 (s), 219.8 (s), 218.2 (s), 217.1 (s), 216.8 (s), 148.6 (s), 147.5 (s), 147.3 (s), 137.5 (s), 137.4 (s), 135.1 (s), 134.1 (s), 128.7 (d), 128.3 (d), 128.1 (d), 127.0 (d), 126.6 (d), 119.6 (d), 114.1 (d), 113.9 (d), 111.5 (d), 111.0 (d), 105.1 (s), 103.9 (s), 92.7 (d), 91.2 (d), 88.7 (d), 87.6 (d), 80.0 (d), 60.1 (t), 59.7 (t), 55.7 (q), 55.5 (q), 52.1 (t), 47.6 (t), 47.3 (t), 47.0 (d), 46.7 (d), 46.5 (d), 45.7 (d), 41.4 (t), 40.8 (t), 37.2 (t), 37.0 (t), 33.5 (t), 32.5 (t), 31.0 (d), 30.5 (d), 26.4 (d), 25.1 (d), 23.8 (t), 21.8 (q), 21.6 (q), 21.4 (t), 21.3 (t), 20.8 (q), 20.4 (q), 16.6 (q), 15.2 (q); elemental analysis calcd (%) for $C_{40}H_{49}CrNO_7S_2$ (771.95): C 62.24, H 6.40, N 1.81; found C 62.36, H 6.29, N 1.77.

Tetracarbonyl{[6-benzyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R,3*R**,4*S**)menthyloxy]methyliden}chromium(0) (7c)**: Orange oil; mixture (1:1) of diastereomers; yield: 45% (296 mg); $R_f = 0.45$ (hexane); FT-IR (neat): $\tilde{\nu} = 2011$, 1909 (broad band), 1863 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.40-6.95$ (m, 20H), 5.46 (m, 1H), 5.15 (m, 1H), 4.42–3.62 (m, 6H), 3.58–3.37 (m, 4H), 3.32–2.80 (m, 6H), 2.69–2.20 (m, 4H), 2.00–0.59 (m, 36H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 355.0$ (s), 353.4 (s), 230.7 (s), 229.1 (s), 228.8 (s), 219.8 (s), 218.3 (s), 217.1 (s), 216.8 (s), 142.5 (s), 141.6 (s), 137.7 (s), 137.6 (s), 128.45 (d), 128.37 (d), 128.30 (d), 127.8 (d), 127.3 (d), 127.2 (d), 126.7 (d), 105.0 (s), 103.8 (s), 92.9 (d), 91.4 (d), 88.8 (d), 87.6 (d), 60.4 (t), 59.8 (t), 52.2 (t), 48.2 (t), 47.9 (t), 47.5 (d), 47.2 (d), 46.9 (d), 46.1 (d), 41.6 (t), 41.0 (t), 37.6 (t), 37.4 (t), 33.9 (t), 33.7 (t), 31.2 (d), 30.7 (d), 26.5 (d), 25.3 (d), 23.6 (t), 22.3 (t), 22.0 (q), 21.0 (q), 20.6 (q), 16.6 (q), 15.4 (q); elemental analysis calcd (%) for $C_{34}H_{39}CrNO_5S_2$ (657.80): C 62.08, H 5.98, N 2.13; found C 61.99, H 5.95, N 2.08.

Tetracarbonyl{[6-benzyl-8-(2-furyl)-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R,3*R**,4*S**)menthyloxy]methyliden}chromium(0) (7d)**: Orange oil; mixture (1:1) of diastereomers; yield: 69% (447 mg); $R_f = 0.45$ (hexane); FT-IR (neat): $\tilde{\nu} = 2060$, 2011, 1906 (broad band), 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.75-6.95$ (m, 12H), 6.40 (m, 2H), 6.06 (m, 2H), 5.47 (m, 1H), 5.20 (m, 1H), 4.28 (d, $^3J(H,H) = 13.4$ Hz, 1H), 4.15–3.61 (m, 6H), 3.57–2.98 (m, 9H), 2.71 (m, 2H), 2.37 (m, 2H), 2.00–0.68 (m, 36H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 353.6$ (s), 352.6 (s), 230.7 (s), 229.0 (s), 228.7 (s), 219.3 (s), 217.9 (s), 217.0 (s), 216.6 (s), 154.6 (s), 153.5 (s), 141.45 (d), 141.40 (d), 137.6 (d), 137.5 (d), 128.3 (d), 128.2 (d), 127.2 (d), 110.1 (d), 106.4 (d), 105.6 (d), 103.8 (d), 102.8 (d), 92.9 (d), 91.5 (d), 85.5 (d), 84.9 (d), 56.9 (t), 56.3 (t), 52.0 (t), 48.5 (t), 48.2 (t), 47.6 (d), 47.3 (d), 41.4 (t), 41.0 (t), 39.8 (d), 38.9 (d), 37.8 (t), 37.6 (t), 33.9 (t), 33.7 (t), 31.2 (d), 30.7 (d), 26.4 (d), 25.3 (d), 23.6 (t), 22.5 (t), 22.0 (q), 21.0 (q), 20.8 (q), 16.6 (q), 15.4 (q); elemental analysis calcd (%) for $C_{32}H_{37}CrNO_6S_2$ (647.76): C 59.34, H 5.76, N 2.16; found C 59.15, H 5.69, N 2.14.

Tetracarbonyl{[(8*S*,9*R*)-6-methyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R*,3*R*,4*S*)-8-phenylmenthyloxy]methyliden}chromium(0) (7e): Orange oil; yield: 29% (191 mg); $R_f = 0.56$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 2005$, 1943, 1886 (broad band), 1842 cm^{-1}; $[\alpha]_D^{26} = +409.0$ ($c = 0.35$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.42-6.90$ (m, 10H), 5.32 (m, 1H), 3.64 (m, 1H), 3.44 (t, $^3J(H,H) = 5.8$ Hz, 2H), 3.14–2.98 (m, 2H), 2.78 (ABq, $^3J(H,H) = 6.1$ Hz, 2H), 2.54 (s, 3H), 2.33 (m, 1H), 2.00–0.72 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 353.9$ (s), 230.7 (s), 228.9 (s), 219.2 (s), 217.3 (s), 151.0 (s), 142.1 (s), 128.3 (d), 128.2 (d), 128.1 (d), 126.7 (d), 125.1 (d), 124.8 (d), 104.9 (s), 91.4 (d), 86.4 (d), 62.6 (t), 50.9 (d), 47.5 (t), 46.8 (d), 42.7 (t), 39.4 (s), 37.4 (t), 34.34 (q), 34.28 (t), 30.8 (d), 27.1 (q), 26.3 (t), 25.1 (q), 21.9 (q); elemental analysis calcd (%) for $C_{34}H_{39}CrNO_5S_2$ (657.80): C 62.08, H 5.98, N 2.13; found C 61.89, H 5.99, N 2.12.

Tetracarbonyl{[(8*R*,9*R*)-8-(2-furyl)-6-methyl-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R*,3*R*,4*S*)-8-phenylmenthyloxy]methyliden}chromium(0) (7f): Orange oil; yield: 57% (369 mg); $R_f = 0.37$ (hexane/AcOEt, 9:1); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.45-7.12$ (m, 6H), 6.41 (dd, $^3J(H,H) = 3.0$ and 1.8 Hz, 1H), 6.00 (d, $^3J(H,H) = 3.0$ Hz, 1H), 5.38 (m, 1H), 3.58 (m, 1H), 3.40 (t, $^3J(H,H) = 5.4$ Hz, 2H), 3.11–2.84 (m, 4H), 2.51 (s, 3H), 2.35 (m, 1H), 2.22–0.75 (m, 17H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 353.0$ (s), 230.5 (s), 228.8 (s), 218.9 (s), 217.1 (s), 153.8 (s), 150.9 (s), 141.4 (d), 128.3 (d), 125.6 (d), 125.0 (d), 110.1 (d), 106.6 (d), 103.8 (s), 91.4 (d), 83.5 (d), 59.2 (t), 54.0 (d), 51.0 (d), 47.7 (t), 42.5 (t), 37.6 (t), 34.7 (t), 34.2 (q), 30.7 (d), 27.0 (q), 26.3 (t), 25.3 (q), 21.9 (q); elemental analysis calcd (%) for $C_{32}H_{37}CrNO_6S_2$ (647.76): C 59.34, H 5.76, N 2.16; found C 59.30, H 5.70, N 2.15.

Tetracarbonyl{[(8*S*,9*R*)-8-(3-cyclopentyloxy-4-methoxyphenyl)-6-methyl-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R*,3*R*,4*S*)-8-phenylmenthyloxy]methyliden}chromium(0) (7g): Orange oil; yield: 60% (463 mg); $R_f = 0.28$ (hexane/AcOEt, 100:1); FT-IR (neat): $\tilde{\nu} = 2010$, 1905 (broad band), 1860 cm^{-1}; $[\alpha]_D^{26} = +351.4$ ($c = 0.25$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.29-6.95$ (m, 5H), 6.85 (m, 1H), 6.66 (m, 2H), 5.34 (m, 1H), 4.80 (m, 1H), 3.93 (s, 3H), 3.65 (m, 1H), 3.43 (t, $^3J(H,H) = 5.6$ Hz, 2H), 3.07 (m, 2H), 2.72 (m, 2H), 2.53 (s, 3H), 2.34 (m, 3H), 2.08–0.80 (m, 23H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 354.1$ (s), 230.6 (s), 228.9 (s), 219.2 (s), 217.3 (s), 150.9 (s), 148.8 (s), 147.5 (s), 135.0 (s), 128.0 (d), 125.1 (d), 124.9 (d), 120.1 (d), 114.8 (d), 111.8 (d), 104.8 (s), 91.3 (d), 87.3 (d), 80.4 (d), 63.0 (t), 56.2 (q), 51.1 (d), 47.6 (t), 46.7 (d), 42.7 (t), 39.7 (s), 37.4 (t), 34.4 (q), 34.3 (t), 33.0 (t), 32.9 (t), 30.8 (d), 29.6 (q), 26.3 (t), 26.0 (q), 24.1 (t), 21.9 (q); elemental analysis calcd (%) for $C_{40}H_{49}CrNO_7S_2$ (771.95): C 62.24, H 6.40, N 1.81; found C 62.01, H 6.31, N 1.77.

Tetracarbonyl{[(8*S*,9*R*)-8-ferrocenyl-6-methyl-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R*,3*R*,4*S*)-8-phenylmenthyloxy]methyliden}chromium(0) (7h): Orange oil; yield: 66% (505 mg); $R_f = 0.49$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 2009$, 1908 (broad band), 1858 cm^{-1}; $[\alpha]_D^{31} = +471.1$ ($c = 0.45$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.40-6.98$ (m, 5H), 5.35 (m, 1H), 4.28–3.92 (m, 8H), 3.56 (m, 1H), 3.38 (t, $^3J(H,H) = 5.5$ Hz, 2H), 3.18–2.95 (m, 2H), 2.61–2.18 (m, 3H), 2.56 (s, 3H), 1.95–0.72 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 354.5$ (s), 230.6 (s), 228.7 (s), 219.3 (s), 217.2 (s), 150.9 (s), 128.1 (d), 125.2 (d), 124.8 (d), 105.1 (s), 91.5 (d), 90.3 (s), 87.1 (d), 69.5 (d), 68.3 (d), 68.1 (d), 66.8 (d), 65.7 (d), 61.2 (t), 51.1 (d), 47.0 (t), 42.7 (t), 40.7 (d), 39.7 (s), 37.3 (t), 34.5 (q), 34.3 (t), 30.8 (d), 26.8 (q), 26.4 (t), 25.8 (q), 21.9 (q); elemental analysis calcd (%) for $C_{38}H_{43}CrFeNO_5S_2$ (765.72): C 59.61, H 5.66, N 1.83; found C 59.52, H 5.60, N 1.83.

Tetracarbonyl{[(8*S*,9*R*)-6-benzyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R*,3*R*,4*S*)-8-phenylmenthyloxy]methyliden}chromium(0) (7i): Orange oil; yield: 60% (440 mg); $R_f = 0.62$ (hexane/AcOEt, 20:1); FT-IR (neat): $\tilde{\nu} = 2010$, 1909 (broad band), 1859 cm^{-1}; $[\alpha]_D^{33} = +432.2$ ($c = 0.32$ in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.57-6.92$ (m, 15H), 5.43 (m, 1H), 4.06 (m, 2H), 3.75 (m, 1H), 3.53 (m, 2H), 3.28–3.03 (m, 3H), 2.83 (m, 1H), 2.62 (t, $^3J(H,H) = 7.5$ Hz, 1H), 2.44 (m, 1H), 2.05–0.72 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 354.0$ (s), 230.6 (s), 228.8 (s), 219.0 (s), 217.2 (s), 150.9 (s), 141.7 (s), 137.7 (s), 128.5 (d), 128.3 (d), 128.0 (d), 127.2 (d), 126.7 (d), 125.2 (d), 124.9 (d), 104.0 (s), 91.4 (d), 87.4 (d), 59.7 (t), 52.5 (t), 51.0 (d), 47.6 (t), 47.1 (d), 42.8 (t), 39.6 (s), 37.5 (t), 34.3 (t), 30.7 (d), 26.4 (q), 26.3 (t), 25.9 (q), 21.9 (q); elemental analysis calcd (%) for $C_{40}H_{43}CrNO_5S_2$ (733.90): C 65.46, H 5.91, N 1.91; found C 65.22, H 5.86, N 1.90.

Tetracarbonyl{[(8*S*,9*R*)-6-benzyl-8-(2-furyl)-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R*,3*R*,4*S*)-8-phenylmenthyloxy]methyliden}chromium(0) (7j): Orange oil; yield: 68% (492 mg); $R_f = 0.61$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 2011$, 1908 (broad band), 1861 cm^{-1}; $[\alpha]_D^{26} = +469.3$ ($c = 0.51$ in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.49-6.94$ (m, 11H), 6.38 (m, 1H), 5.98 (m, 1H), 5.38 (m, 1H), 4.14 (m, 1H), 3.83–3.52 (m, 2H), 3.43 (m, 2H), 3.20 (m, 1H), 3.09–2.75 (m, 3H), 2.61 (m, 1H), 2.35 (m, 1H), 2.11–0.68 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 353.3$ (s), 230.5 (s), 228.8 (s), 218.7 (s), 217.0 (s), 153.6 (s), 150.9 (s), 141.4 (d), 137.7 (s), 128.4 (d), 128.3 (d), 127.9 (d), 127.2 (d), 125.6 (d), 125.3 (d), 110.2 (d), 106.7 (d), 102.9 (s), 91.5 (d), 84.7 (d), 56.3 (t), 52.3 (t), 51.1 (d), 47.9 (t), 42.7 (t), 40.0 (d), 39.8 (s), 37.8 (t), 34.3 (t), 30.7 (d), 26.5 (t), 26.4 (q), 26.0 (q), 21.9 (q); elemental analysis calcd (%) for $C_{38}H_{41}CrNO_6S_2$ (723.86): C 63.05, H 5.71, N 1.94; found C 62.89, H 5.71, N 1.93.

Tetracarbonyl{[(8*S*,9*R*)-6-benzyl-8-(3-cyclopentyloxy-4-methoxyphenyl)-1,4-dithia-6-azaspiro[4,4]nonan-9-yl][(1*R*,3*R*,4*S*)-8-phenylmenthyloxy]-

methyliden}chromium(0) (7k): Orange oil; yield: 58% (492 mg); $R_f = 0.50$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 2058$, 2010, 1980 cm^{-1} (broad band); $[\alpha]_D^{30} = +398.3$ ($c = 0.35$ in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.50-6.99$ (m, 10H), 6.93 (d, $^3J(H,H) = 6.8$ Hz, 1H), 6.74–6.67 (s + d, $^3J(H,H) = 8.3$ Hz, 2H), 5.46 (m, 1H), 4.82 (m, 1H), 4.06 (m, 2H), 3.98 (s, 3H), 3.73 (m, 1H), 3.53 (m, 2H), 3.25–3.00 (m, 3H), 2.76–2.62 (m, 2H), 2.50 (m, 1H), 2.01–0.70 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 354.1$ (s), 230.5 (s), 228.7 (s), 218.9 (s), 217.1 (s), 150.7 (s), 148.7 (s), 147.6 (s), 137.7 (s), 134.8 (s), 128.5 (d), 128.2 (d), 127.9 (d), 127.2 (d), 125.0 (d), 124.9 (d), 120.0 (d), 114.5 (d), 111.6 (d), 104.1 (s), 91.2 (d), 88.1 (d), 80.2 (d), 59.8 (t), 56.1 (q), 52.6 (t), 51.0 (d), 47.5 (t), 46.7 (d), 42.7 (t), 39.6 (s), 37.1 (t), 34.2 (t), 32.9 (t), 32.8 (t), 30.6 (d), 26.3 (t), 26.2 (q), 25.9 (q), 24.0 (t), 23.9 (t), 21.8 (q); elemental analysis calcd (%) for $C_{46}H_{53}CrNO_7S_2$ (848.04): C 65.15, H 6.30, N 1.65; found C 65.01, H 6.25, N 1.66.

Oxidation of the cycloadducts 7: A solution of chromium carbene cycloadducts **7** (1 mmol) in hexane/AcOEt (3:1, 100 mL) was exposed to sunlight till the solution turned almost colorless (two to five hours on a sunny day). The reaction mixture was filtered through Celite, and solvents were evaporated under vacuum. The residue was purified by column chromatography on silica gel using hexane/AcOEt mixtures (50:1 to 1:1) as sequential eluents to isolate compounds **8**, **9**, and **10** in the yields reported in Table 2.

(1*R,3*R**,4*S**)-Menthyl (8*S**,9*R**)-6-methyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8a)**: Yellow oil; mixture (4:1) of diastereomers; yield: 28% (121 mg); $R_f = 0.37$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 1727$ cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.38-7.16$ (m, 10H), 4.75 (m, 2H), 3.76 (m, 4H), 3.40–3.10 (m, 10H), 3.00–2.85 (m, 2H), 2.51 (s, 6H), 2.03 (m, 2H), 1.79–0.62 (m, 34H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 170.1$ (s, min), 170.0 (s, maj), 141.9 (s, maj), 141.8 (s, min), 128.4 (d), 127.4 (d), 127.3 (d), 126.6 (d), 99.5 (s, maj), 99.3 (s, min), 74.9 (d, maj), 74.8 (d, min), 68.3 (d, min), 67.8 (d, maj), 60.6 (t, maj), 59.9 (t, min), 46.9 (d), 43.7 (d, maj), 43.5 (d, min), 40.71 (t, maj), 40.66 (t, min), 40.0 (t), 39.4 (t, min), 39.3 (t, maj), 34.2 (t, min), 34.1 (t, maj), 33.8 (q), 31.3 (d), 26.0 (q, min), 25.2 (q, maj), 23.3 (t, min), 22.7 (t, maj), 22.0 (d), 20.9 (q, maj), 20.6 (q, min), 16.0 (q, min), 15.6 (q, maj); MS (70 eV, EI): m/z (%): 433 (<5) $[M]^+$, 373 (9), 236 (100), 218 (51), 190 (63); HRMS for $C_{24}H_{35}NO_2S_2$: calcd 433.2109; found 433.2130; elemental analysis calcd (%) for $C_{24}H_{35}NO_2S_2$ (433.67): C 66.47, H 8.13, N 3.23; found C 66.52, H 8.01, N 3.20.

(1*R,3*R**,4*S**)-Menthyl (8*S**,9*R**)-6-benzyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8b)**: Yellow oil; mixture (1:1) of diastereomers; yield: 45% (229 mg); $R_f = 0.60$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1726$ cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.45-7.05$ (m, 20H), 4.79 (m, 2H), 4.26–3.55 (m, 8H), 3.41–3.12 (m, 8H), 3.03 (m, 2H), 2.73 (m, 2H), 2.16–0.51 (m, 36H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 169.7$ (s), 141.8 (s), 141.7 (s), 138.8 (s), 128.4 (d), 128.3 (d), 128.1 (d), 127.3 (d), 127.2 (d), 126.8 (d), 126.5 (d), 99.2 (s), 99.0 (s), 74.8 (d), 68.3 (d), 67.6 (d), 57.5 (t), 56.9 (t), 51.7 (t), 46.9 (d), 46.7 (d), 43.5 (d), 43.3 (d), 40.7 (t), 40.6 (t), 39.9 (t), 39.3 (t), 39.2 (t), 34.2 (t), 34.1 (t), 31.3 (d), 25.9 (d), 25.1 (d), 23.2 (t), 22.6 (t), 22.0 (q), 20.9 (q), 20.6 (q), 16.0 (q), 15.5 (q); MS (70 eV, EI): m/z (%): 509 (<5) $[M]^+$, 449 (10), 311 (100), 266 (49), 91 (83); HRMS for $C_{30}H_{39}NO_2S_2$: calcd 509.2422; found 509.2453; elemental analysis calcd (%) for $C_{30}H_{39}NO_2S_2$ (509.76): C 70.69, H 7.71, N 2.75; found C 70.55, H 7.67, N 2.77.

(1*R,3*R**,4*S**)-Menthyl (8*S**,9*R**)-6-benzyl-8-(2-furyl)-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8c)**: Yellow oil; mixture (1:1) of diastereomers; yield: 20% (100 mg); $R_f = 0.40$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 1729$ cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.49-7.15$ (m, 12H), 6.23 (m, 2H), 6.02 (m, 2H), 4.81 (m, 2H), 4.09–3.73 (m, 8H), 3.41–3.11 (m, 8H), 3.04 (m, 2H), 2.74 (m, 2H), 2.19–0.61 (m, 36H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 169.7$ (s), 169.5 (s), 154.2 (s), 154.1 (s), 141.4 (d), 141.3 (d), 138.6 (s), 128.4 (d), 128.2 (d), 126.8 (d), 109.9 (d), 105.1 (d), 98.6 (s), 98.4 (s), 75.1 (d), 75.0 (d), 65.1 (d), 64.8 (d), 54.3 (t), 53.9 (t), 51.5 (t), 51.4 (t), 46.95 (d), 46.89 (d), 40.6 (t), 39.9 (t), 39.8 (t), 39.5 (t), 39.3 (t), 37.35 (d), 37.26 (d), 34.2 (t), 34.1 (t), 31.3 (d), 26.0 (d), 25.2 (d), 23.3 (t), 22.7 (t), 22.0 (q), 20.9 (q), 20.6 (q), 16.2 (q), 15.6 (q); elemental analysis calcd (%) for $C_{28}H_{37}NO_3S_2$ (499.73): C 67.30, H 7.46, N 2.80; found C 67.18, H 7.45, N 2.77.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (8*S*,9*R*)-6-methyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8d): Yellow oil; yield: quantitative (509 mg); $R_f = 0.54$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1728$ cm^{-1}; $[\alpha]_D^{25} = -25.6$ ($c = 1.08$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.45-7.09$ (m, 10H), 4.93 (m, 1H), 3.60 (m, 2H), 3.38–3.17 (m, 5H), 2.83 (m, 1H), 2.50 (s, 3H), 2.07–0.82 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 171.2$ (s), 150.7 (s), 141.8 (s), 128.5 (d), 127.8 (d), 127.6 (d), 126.7 (d), 125.6 (d), 125.1 (d), 99.3 (s), 75.7 (d), 66.9 (d), 60.9 (t), 50.2 (d), 44.7 (d), 41.6 (t), 40.3 (s), 40.0 (t), 39.3 (t), 34.3 (t), 33.8 (q), 31.2 (d), 29.7 (q), 27.1 (t), 23.0 (q), 21.7 (q); MS (70 eV, EI): m/z (%): 449 (<5) $[M - C_2H_4S]^+$, 236 (85), 191 (67), 119 (100), 91 (78); HRMS for $C_{28}H_{35}NO_2S$ $[M - C_2H_4S]^+$: calcd 449.2389; found 449.2378; elemental analysis calcd (%) for $C_{30}H_{39}NO_2S_2$ (509.76): C 70.69, H 7.71, N 2.75; found C 70.50, H 7.64, N 2.74.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (8*R*,9*R*)-8-(2-furyl)-6-methyl-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8e): Yellow oil; yield: 25% (125 mg); $R_f = 0.29$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 1722$ cm^{-1}; $[\alpha]_D^{23} = -31.2$ ($c = 0.86$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.39-7.12$ (m, 6H), 6.30 (dd, $^3J(H,H) = 2.2$ and 3.1 Hz, 1H), 6.09 (d, $^3J(H,H) = 3.1$ Hz, 1H), 4.95 (m, 1H), 3.70 (m, 2H), 3.39–3.18 (m, 5H), 2.86 (m, 1H), 2.48 (s, 3H), 2.18–0.84 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.6$ (s), 154.5 (s), 150.6 (s), 141.5 (d), 127.8 (d), 125.6 (d), 125.1 (d), 110.1 (d), 105.4 (d), 98.8 (s), 76.2 (d), 64.2 (d), 57.9 (t), 50.3 (d), 41.5 (t), 40.3 (s), 39.9 (t), 39.3 (t), 37.7 (d), 34.3 (t), 33.7 (q), 31.2 (d), 30.0 (q), 27.2 (t), 23.0 (q), 21.7 (q); elemental analysis calcd (%) for $C_{28}H_{37}NO_3S_2$ (499.73): C 67.30, H 7.46, N 2.80; found C 67.12, H 7.40, N 2.79.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (8*S*,9*R*)-8-(3-cyclopentyloxy-4-methoxyphenyl)-6-methyl-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8f): Yellow oil; yield: 55% (343 mg); $R_f = 0.59$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1726$ cm^{-1}; $[\alpha]_D^{31} = +22.4$ ($c = 0.84$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.38-7.10$ (m, 6H), 6.82 (m, 2H), 4.93 (m, 1H), 4.80 (m, 1H), 3.85 (s, 3H), 3.54 (m, 1H), 3.39–3.14 (m, 5H), 2.79 (m, 1H), 2.51 (s, 3H), 2.29 (m, 1H), 2.02–0.61 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 171.5$ (s), 150.6 (s), 148.7 (s), 147.6 (s), 134.1 (s), 127.7 (d), 125.5 (d), 125.0 (d), 119.6 (d), 114.2 (d), 111.8 (d), 99.2 (s), 80.2 (d), 75.6 (d), 67.4 (d), 61.0 (t), 56.0 (q), 50.2 (d), 44.6 (d), 41.6 (t), 40.3 (s), 39.8 (t), 39.2 (t), 34.3 (t), 33.8 (q), 32.7 (t), 31.1 (d), 29.7 (q), 27.1 (t), 24.0 (t), 22.9 (q), 21.7 (q); MS (70 eV, EI): m/z (%): 563 (<5) $[M - C_2H_4S]^+$, 349 (92), 236 (100), 119 (80), 91 (21); HRMS for $C_{34}H_{45}NO_4S$ $[M - C_2H_4S]^+$: calcd 563.3069; found 563.3090; elemental analysis calcd (%) for $C_{36}H_{49}NO_4S_2$ (623.91): C 69.31, H 7.92, N 2.25; found C 69.26, H 7.83, N 2.21.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (8*S*,9*R*)-8-ferrocenyl-6-methyl-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8g): Yellow solid; yield: 38% (235 mg); m.p. 120–122 °C; $R_f = 0.27$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 1724$ cm^{-1}; $[\alpha]_D^{30} = -62.9$ ($c = 1.09$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.40-7.12$ (m, 5H), 4.90 (m, 1H), 4.18–4.03 (m, 9H), 3.43–3.16 (m, 7H), 2.74 (m, 1H), 2.50 (s, 3H), 2.20–0.86 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 150.9$ (s), 127.9 (d), 125.7 (d), 125.1 (d), 99.1 (s), 89.3 (s), 76.4 (d), 68.4 (d), 67.6 (d), 67.5 (d), 66.1 (d), 59.8 (t), 50.5 (d), 41.4 (t), 40.4 (t), 39.7 (t), 39.3 (d), 34.4 (t), 33.9 (q), 31.3 (d), 30.0 (q), 27.3 (t), 23.2 (q), 21.8 (q), the quaternary carbon from the chiral auxiliary (around $\delta = 40$) and the ester carbonyl carbon (around $\delta = 170$) were not observed; MS (70 eV, EI): m/z (%): 557 (16) $[M - C_2H_4S]^+$, 299 (24), 143 (30), 119 (100), 91 (62); HRMS for $C_{32}H_{39}FeNO_2S$ $[M - C_2H_4S]^+$: calcd 557.2052; found 557.2054; elemental analysis calcd (%) for $C_{34}H_{43}FeNO_2S_2$ (617.69): C 66.11, H 7.02, N 2.27; found C 65.99, H 6.99, N 2.29.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (8*S*,9*R*)-6-benzyl-8-phenyl-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8h): Yellow oil; yield: 31% (182 mg); $R_f = 0.37$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 1730$ cm^{-1}; $[\alpha]_D^{22} = -19.7$ ($c = 0.35$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.42-7.07$ (m, 15H), 4.97 (m, 1H), 4.07–3.90 (ABq, $^2J(H,H) = 13.3$ Hz, 2H), 3.73 (d, $^3J(H,H) = 8.7$ Hz, 1H), 3.56 (m, 1H), 3.44–3.32 (m, 4H), 3.08 (dd, $^3J(H,H) = 8.7$ and 9.5 Hz, 1H), 2.70 (dd, $^3J(H,H) = 7.9$ and 9.2 Hz, 1H), 2.07–0.68 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.9$ (s), 150.6 (s), 142.0 (s), 138.8 (s), 128.5 (d), 128.4 (d), 128.2 (d), 127.8 (d), 127.6 (d), 126.8 (d), 126.7 (d), 125.6 (d), 125.1 (d), 99.3 (s), 75.7 (d), 67.0 (d), 58.0 (t), 51.6 (t), 50.2 (d), 44.5 (d), 41.8 (t), 40.3 (s), 40.0 (t), 39.2 (t), 34.3 (t), 31.3 (d), 29.9 (q), 27.2 (t), 22.8 (q), 21.7 (q); MS (70 eV, EI): m/z (%): 525 (11) $[M - C_2H_4S]^+$, 311 (100), 266 (57), 119 (38), 91 (83); HRMS for $C_{34}H_{39}NO_2S$ $[M - C_2H_4S]^+$: calcd 525.2702; found 525.2699; elemental analysis calcd (%) for $C_{36}H_{43}NO_2S_2$ (585.86): C 73.81, H 7.40, N 2.39; found C 72.98, H 7.30, N 2.42.

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(1*R*,3*R*,4*S*)-8-Phenylmenthyl (8*S*,9*R*)-6-benzyl-8-(2-furyl)-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8i): Yellow oil; yield: 27% (155 mg); $R_f = 0.38$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 1726\ cm^{-1}$; $[\alpha]_D^{25} = -49.1$ ($c = 0.81$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.41-7.12$ (m, 11H), 6.27 (dd, $^3J(H,H) = 1.8$ and 3.2 Hz, 1H), 6.06 (d, $^3J(H,H) = 3.2$ Hz, 1H), 4.96 (m, 1H), 4.12 (d, $^2J(H,H) = 13.3$ Hz, 1H), 3.79 (d + m, $^2J(H,H) = 13.3$ Hz, 2H), 3.64 (m, 1H), 3.43–3.22 (m, 4H), 3.05 (dd, $^3J(H,H) = 8.5$ and 9.1 Hz, 1H), 2.69 (dd, $^3J(H,H) = 8.0$ and 9.1 Hz, 1H), 2.46–0.73 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.4$ (s), 154.5 (s), 150.7 (s), 141.5 (d), 138.8 (s), 128.5 (d), 128.2 (d), 127.9 (d), 126.9 (d), 125.7 (d), 125.2 (d), 110.1 (d), 105.5 (d), 98.9 (s), 76.3 (d), 64.6 (d), 54.9 (t), 51.5 (t), 50.3 (d), 41.6 (t), 40.4 (s), 39.9 (t), 39.3 (t), 37.6 (d), 34.4 (t), 31.4 (d), 29.9 (q), 27.3 (t), 23.1 (q), 21.8 (q); MS (70 eV, EI): *m/z* (%): 515 (13) $[M - C_2H_4S]^+$, 301 (100), 256 (70), 91 (73); HRMS for $C_{32}H_{37}NO_3S$ $[M - C_2H_4S]^+$: calcd 515.2494; found 515.2504; elemental analysis calcd (%) for $C_{34}H_{41}NO_3S_2$ (575.82): C 70.92, H 7.18, N 2.43; found C 70.90, H 7.28, N 2.45.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (8*S*,9*R*)-6-benzyl-8-(3-cyclopentyloxy-4-methoxyphenyl)-1,4-dithia-6-azaspiro[4,4]nonan-9-carboxylate (8j): Yellow oil; yield: 37% (259 mg); $R_f = 0.31$ (hexane/AcOEt, 9:1); FT-IR (neat): $\tilde{\nu} = 1727\ cm^{-1}$; $[\alpha]_D^{33} = -18.7$ ($c = 1.82$ in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.42-7.14$ (m, 11H), 6.82–6.78 (d + s, $^3J(H,H) = 8.3$ Hz, 2H), 4.98 (m, 1H), 4.75 (m, 1H), 4.07 (d, $^2J(H,H) = 13.1$ Hz, 1H), 3.90 (d, $^2J(H,H) = 13.1$ Hz, 1H), 3.82 (s, 3H), 3.67 (d, $^3J(H,H) = 8.3$ Hz, 1H), 3.50–3.32 (m, 5H), 3.08 (t, $^3J(H,H) = 9.1$ Hz, 1H), 2.69 (dd, $^3J(H,H) = 8.1$ and 9.0 Hz, 1H), 2.06–0.85 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 171.2$ (s), 150.5 (s), 148.6 (s), 147.6 (s), 138.8 (s), 134.6 (s), 128.4 (d), 128.1 (d), 127.7 (d), 126.8 (d), 125.5 (d), 125.0 (d), 119.6 (d), 114.1 (d), 111.7 (d), 99.2 (s), 80.1 (d), 75.6 (d), 67.6 (d), 58.2 (t), 55.9 (q), 51.5 (t), 50.2 (d), 44.2 (d), 41.7 (t), 40.3 (s), 39.8 (t), 39.1 (t), 34.2 (t), 32.7 (t), 31.2 (d), 30.0 (q), 27.1 (t), 24.0 (t), 22.7 (q), 21.7 (q); MS (70 eV, EI): *m/z* (%): 639 (<5) $[M - C_2H_4S]^+$, 194 (20), 119 (100), 91 (56); HRMS for $C_{40}H_{49}NO_4S$ $[M - C_2H_4S]^+$: calcd 639.3382; found 639.3376; elemental analysis calcd (%) for $C_{42}H_{53}NO_4S_2$ (700.01): C 72.07, H 7.63, N 2.00; found C 71.90, H 7.71, N 1.97.

(1*R,3*R**,4*S**)-Menthyl (3*R**,4*S**)-1-benzyl-4-phenylpyrrolidin-2-thione-3-carboxylate (9b)**: Mixture (1:1) of diastereomers; yellow oil; yield: 33% (148 mg); $R_f = 0.43$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1728$, 1261 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.40-7.11$ (m, 20H), 5.23–4.89 (m, 4H), 4.78 (m, 2H), 4.10–3.99 (m, 4H), 3.95–3.80 (m, 2H), 3.68–3.59 (m, 2H), 2.17–0.63 (m, 36H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 196.3$ (s), 169.4 (s), 169.1 (s), 139.8 (s), 139.1 (s), 134.7 (s), 134.5 (s), 128.95 (d), 128.90 (d), 128.8 (d), 128.7 (d), 128.2 (d), 128.1 (d), 127.6 (d), 126.7 (d), 126.6 (d), 75.8 (d), 75.7 (d), 68.1 (d), 67.8 (d), 59.6 (t), 59.0 (t), 51.6 (t), 51.5 (t), 46.83 (d), 46.77 (d), 43.6 (d), 43.2 (d), 40.6 (t), 40.3 (t), 34.1 (t), 31.4 (d), 31.3 (d), 25.9 (d), 25.7 (d), 23.2 (t), 22.9 (t), 21.9 (q), 20.8 (q), 20.5 (q), 16.0 (q), 15.8 (q); MS (70 eV, EI): *m/z* (%): 449 (<5) $[M]^+$, 311 (28), 149 (43), 119 (68), 91 (70), 84 (100); HRMS for $C_{28}H_{35}NO_2S$: calcd 449.2389; found 449.2378; elemental analysis calcd (%) for $C_{28}H_{35}NO_2S$ (449.65): C 74.79, H 7.85, N 3.12; found C 75.02, H 7.75, N 3.11.

(1*R,3*R**,4*S**)-Menthyl (3*R**,4*S**)-1-benzyl-4-(2-furyl)pyrrolidin-2-thione-3-carboxylate (9c)**: Mixture (1:1) of diastereomers; yellow oil; yield: 32% (141 mg); $R_f = 0.41$ (hexane/AcOEt, 3:1); FT-IR (neat): $\tilde{\nu} = 1725$, 1262 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.51-7.20$ (m, 12H), 6.27 (m, 2H), 6.06 (m, 2H), 5.15–4.72 (m, 6H), 4.29–3.85 (m, 6H), 3.80–3.52 (m, 2H), 2.19–0.70 (m, 36H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 195.8$ (s), 168.9 (s), 168.6 (s), 151.9 (s), 151.5 (s), 142.2 (d), 134.3 (s), 128.7 (d), 128.0 (d), 125.6 (d), 110.2 (d), 106.3 (d), 106.1 (d), 75.8 (d), 65.5 (d), 65.1 (d), 56.7 (t), 56.2 (t), 51.4 (t), 51.3 (t), 46.7 (d), 40.4 (t), 40.2 (t), 37.2 (d), 37.0 (d), 34.0 (t), 31.2 (d), 25.9 (d), 25.6 (d), 23.2 (t), 22.8 (t), 21.9 (q), 20.7 (q), 20.5 (q), 16.1 (q), 15.8 (q); MS (70 eV, EI): *m/z* (%): 439 (10) $[M]^+$, 302 (68), 256 (100), 91 (92); HRMS for $C_{26}H_{33}NO_3S$: calcd 439.2181; found 439.2187; elemental analysis calcd (%) for $C_{26}H_{33}NO_3S$ (439.61): C 71.04, H 7.57, N 3.19; found C 71.25, H 7.62, N 3.16.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*S*)-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-methylpyrrolidin-2-thione-3-carboxylate (9f): Yellow oil; yield: 23% (130 mg); $R_f = 0.30$ (hexane/AcOEt, 3:1); FT-IR (neat): $\tilde{\nu} = 1727$, 1262 cm^{-1}; $[\alpha]_D^{31} = +69.2$ ($c = 0.52$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.40-7.11$ (m, 5H), 6.81 (d, $^3J(H,H) = 8.2$ Hz, 1H), 6.66–6.61 (d + s, $^3J(H,H) = 8.2$ Hz, 2H), 4.90–4.76 (m, 2H), 3.97–3.37 (m, 4H), 3.85 (s, 3H), 3.30 (s, 3H), 1.96–0.83 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 196.0$ (s), 169.4 (s), 151.2 (s), 149.3 (s), 147.8 (s), 132.0 (s), 127.8 (d), 125.7 (d), 124.9 (d), 118.7 (d), 113.4 (d), 112.0 (d), 80.4 (d), 76.8 (d), 67.4 (d), 62.6 (t), 56.0 (q), 50.1 (d), 43.0 (d), 40.9 (t), 40.0 (s), 35.3 (q), 34.4 (t), 32.8 (t), 31.2 (d), 27.5 (q), 26.9 (t), 25.9 (q), 24.0 (t), 21.6 (q); MS (70 eV, EI): *m/z* (%): 563 (18) $[M]^+$, 350 (45), 236 (90), 119 (100); HRMS for $C_{34}H_{45}NO_4S$: calcd 536.3069; found 536.3071; elemental analysis calcd (%) for $C_{34}H_{45}NO_4S$ (563.79): C 72.43, H 8.05, N 2.48; found C 72.25, H 7.97, N 2.47.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*S*)-4-ferrocenyl-1-methylpyrrolidin-2-thione-3-carboxylate (9g): Yellow oil; yield: 19% (106 mg); $R_f = 0.16$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1727$, 1261 cm^{-1}; $[\alpha]_D^{28} = +3.17$ ($c = 0.31$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.41-7.16$ (m, 5H), 4.87 (m, 1H), 4.17 (m, 7H), 4.02–3.95 (m, 2H), 3.82 (d, $^3J(H,H) = 4.8$ Hz, 1H), 3.54 (m, 1H), 3.28 (s, 3H), 3.11 (m, 2H), 2.34 (m, 1H), 2.06 (m, 3H), 1.75–0.80 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 195.8$ (s), 169.7 (s), 151.2 (s), 128.0 (d), 125.8 (d), 125.0 (d), 89.2 (s), 76.8 (d), 68.6 (d), 68.1 (d), 67.9 (d), 66.5 (d), 62.9 (t), 50.3 (d), 41.1 (t), 40.0 (s), 37.4 (d), 35.4 (q), 34.5 (t), 31.3 (d), 27.4 (q), 27.0 (t), 26.3 (q), 21.7 (q); MS (70 eV, EI): *m/z* (%): 557 (66) $[M]^+$, 299 (100), 119 (42); HRMS for $C_{32}H_{39}FeNO_2S$: calcd 557.2052; found 557.2072; elemental analysis calcd (%) for $C_{32}H_{39}FeNO_2S$ (557.57): C 68.93, H 7.05, N 2.51; found C 68.70, H 7.00, N 2.54.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*S*)-1-benzyl-4(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-thione-3-carboxylate (9j): Yellow oil; yield: 8% (51 mg); $R_f = 0.45$ (hexane/AcOEt, 3:1); FT-IR (neat): $\tilde{\nu} = 1726$, 1263 cm^{-1}; $[\alpha]_D^{33} = +30.9$ ($c = 0.79$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.40-7.09$ (m, 10H), 6.76 (m, 1H), 6.56 (m, 2H), 5.17 (d, $^2J(H,H) = 14.3$ Hz, 1H), 4.88–4.42 (d + m, $^2J(H,H) = 14.3$ Hz, 3H), 3.84–3.73 (m, 2H), 3.81 (s, 3H), 3.54 (m, 2H), 2.29–0.74 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 196.4$ (s), 169.3 (s), 151.3 (s), 149.2 (s), 147.8 (s), 134.6 (s), 132.5 (s), 128.8 (d), 128.3 (d), 127.9 (d), 125.7 (d), 125.0 (d), 118.6 (d), 113.2 (d), 111.9 (d), 80.4 (d), 76.8 (d), 67.9 (d), 60.0 (t), 56.0 (q), 51.5 (t), 50.1 (d), 42.5 (d), 41.0 (t), 40.0 (s), 34.5 (t), 32.8 (t), 31.2 (d), 27.2 (q), 26.9 (t), 26.3 (q), 24.0 (t), 21.7 (q); MS (70 eV, EI): *m/z* (%): 639 (10) $[M]^+$, 214 (30), 119 (100), 91 (78); HRMS for $C_{40}H_{49}NO_4S$: calcd 639.3382; found 639.3384; elemental analysis calcd (%) for $C_{40}H_{49}NO_4S$ (639.89): C 75.08, H 7.72, N 2.19; found C 74.82, H 7.68, N 2.22.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*S*)-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-methylpyrrolidin-2-one-3-carboxylate (10f): Yellow oil; yield: 15% (82 mg); $R_f = 0.10$ (hexane/AcOEt, 3:1); FT-IR (neat): $\tilde{\nu} = 1737$, 1698 cm^{-1}; $[\alpha]_D^{31} = +33.3$ ($c = 0.42$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.39-7.10$ (m, 5H), 6.82 (d, $^3J(H,H) = 8.0$ Hz, 1H), 6.69–6.64 (d + s, $^3J(H,H) = 8.0$ Hz, 2H), 4.87–4.76 (m, 2H), 3.85 (s, 3H), 3.71–3.53 (m, 2H), 3.39–3.12 (m, 2H), 2.94 (s, 3H), 2.40–2.15 (m, 1H), 2.09–0.70 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 169.7$ (s), 169.3 (s), 151.1 (s), 149.2 (s), 147.7 (s), 132.3 (s), 127.8 (d), 125.7 (d), 124.9 (d), 118.7 (d), 113.7 (d), 112.0 (d), 80.4 (d), 76.6 (d), 56.1 (d), 56.0 (q), 54.8 (t), 50.3 (d), 41.7 (d), 41.2 (t), 40.0 (s), 34.4 (t), 32.8 (t), 31.2 (q), 29.8 (d), 27.7 (q), 26.9 (t), 25.3 (q), 24.0 (t), 21.6 (q); MS (70 eV, EI): *m/z* (%): 547 (<5) $[M]^+$, 546 (20), 289 (21), 265 (48), 220 (69), 119 (100); HRMS for $C_{34}H_{45}NO_5$: calcd 547.3298; found 547.3305; elemental analysis calcd (%) for $C_{34}H_{45}NO_5$ (547.73): C 74.56, H 8.28, N 2.56; found C 74.30, H 8.15, N 2.60.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*S*)-4-ferrocenyl-1-methylpyrrolidin-2-one-3-carboxylate (10g): Yellow oil; yield: 20% (108 mg); $R_f = 0.11$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1728$, 1698 cm^{-1}; $[\alpha]_D^{28} = +25.6$ ($c = 0.39$ in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.46-7.17$ (m, 5H), 4.91 (m, 1H), 4.18 (br s, 9H), 4.03–3.98 (m, 2H), 3.35–3.23 (m, 2H), 2.96 (s, 3H), 2.06 (m, 2H), 1.65–0.80 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.1$ (s), 169.5 (s), 151.3 (s), 127.9 (d), 125.7 (d), 125.0 (d), 89.3 (s), 76.7 (d), 68.4 (d), 68.1 (d), 67.9 (d), 66.5 (d), 66.3 (d), 56.4 (d), 54.6 (t), 50.4 (d), 41.3 (t), 39.9 (s), 35.9 (q), 34.4 (t), 31.2 (d), 29.8 (d), 27.2 (q), 26.9 (t), 25.8 (q), 21.7 (q); MS (70 eV, EI): *m/z* (%): 541 (59) $[M]^+$, 283 (100), 119 (52), 91 (20); HRMS for $C_{32}H_{39}FeNO_3$: calcd 541.2279; found 541.2290; elemental analysis calcd (%) for $C_{32}H_{39}FeNO_3$ (541.51): C 70.98, H 7.26, N 2.59; found C 70.79, H 7.27, N 2.57.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*S*)-1-benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-one-3-carboxylate (10j): Yellow oil; yield: 16% (100 mg); $R_f = 0.32$ (hexane/AcOEt, 3:1); FT-IR (neat): $\tilde{\nu} = 1730$, 1697 cm^{-1}; $[\alpha]_D^{33} = +35.4$ ($c = 0.92$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$,

25 °C, TMS): $\delta = 7.40-7.10$ (m, 10H), 6.78 (d, ^3J(H,H) = 7.9 Hz, 1H), 6.62–6.58 (d + s, ^3J(H,H) = 7.9 Hz, 2H), 4.86 (m, 1H), 4.70 (m, 1H), 4.54 (ABq, ^2J(H,H) = 14.8 Hz, 2H), 3.83 (s, 3H), 3.57–3.41 (m, 2H), 3.24–3.18 (m, 2H), 1.97–0.82 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 169.6$ (s), 169.3 (s), 151.2 (s), 149.1 (s), 147.6 (s), 135.8 (s), 132.5 (s), 128.7 (d), 128.1 (d), 127.8 (d), 127.7 (d), 125.6 (d), 124.9 (d), 118.6 (d), 113.6 (d), 111.9 (d), 80.4 (d), 76.6 (d), 56.2 (d), 56.0 (q), 52.1 (t), 50.2 (d), 46.7 (t), 41.4 (d), 41.2 (t), 39.9 (s), 34.4 (t), 32.7 (t), 31.2 (d), 27.2 (q), 26.8 (t), 25.8 (q), 24.0 (t), 21.6 (q); MS (70 eV, EI): *m/z* (%): 623 (7) $[M]^+$, 297 (58), 119 (82), 91 (100); HRMS for $C_{40}H_{49}NO_5$: calcd 623.3611; found 623.3608; elemental analysis calcd (%) for $C_{40}H_{49}NO_5$ (623.83): C 77.01, H 7.92, N 2.25; found C 76.78, H 7.95, N 2.21.

Preparation of 9e and 10e by thiirane extrusion and dithiolane hydrolysis: A solution of **8e** (1 mmol, 500 mg) was heated to reflux in toluene (10 mL) for 48 hours. Solvents were evaporated under vacuum, and the residue was purified by chromatography on silica gel with hexane/AcOEt (100:1 to 5:1) as sequential eluents to give compounds **9e** and **10e** in 63% and 14% yield, respectively.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*R*)-4-(2-furyl)-1-methylpyrrolidin-2-thione-3-carboxylate (9e): Yellow oil; yield: 63% (277 mg); $R_f = 0.14$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1728$, 1261 cm^{-1}; $[\alpha]_D^{33} = +16.1$ ($c = 1.15$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.37-7.12$ (m, 6H), 6.30 (d, ^3J(H,H) = 2.1 Hz, 1H), 6.06 (d, ^3J(H,H) = 3.0 Hz, 1H), 4.86 (m, 1H), 3.92 (dd, ^3J(H,H) = 8.6 and 10.7 Hz, 1H), 3.78–3.68 (m, 2H), 3.45 (m, 1H), 3.28 (s, 3H), 2.06–0.78 (m, 17H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 195.3$ (s), 168.6 (s), 152.1 (s), 151.3 (s), 142.2 (d), 127.9 (d), 125.6 (d), 125.0 (d), 110.2 (d), 106.2 (d), 76.9 (d), 64.9 (d), 59.6 (t), 50.0 (d), 40.9 (t), 39.9 (s), 36.6 (d), 35.3 (q), 34.5 (t), 31.2 (d), 27.0 (q), 26.9 (t), 26.5 (q), 21.7 (q); MS (70 eV, EI): *m/z* (%): 439 (5) $[M]^+$, 226 (100), 180 (41), 119 (40), 91 (20); HRMS for $C_{26}H_{33}NO_3S$: calcd 439.2181; found 439.2160; elemental analysis calcd (%) for $C_{26}H_{33}NO_3S$ (439.61): C 71.04, H 7.57, N 3.19; found C 71.08, H 7.51, N 3.22.

(1*R*,3*R*,4*S*)-8-Phenylmenthyl (3*R*,4*R*)-4-(2-furyl)-1-methylpyrrolidin-2-one-3-carboxylate (10e): Yellow oil; yield: 14% (59 mg); $R_f = 0.10$ (hexane/AcOEt, 5:1); FT-IR (neat): $\tilde{\nu} = 1731$, 1698 cm^{-1}; $[\alpha]_D^{33} = +17.4$ ($c = 1.05$ in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.40-7.05$ (m, 6H), 6.32 (dd, ^3J(H,H) = 2.0 and 3.3 Hz, 1H), 6.06 (d, ^3J(H,H) = 3.3 Hz, 1H), 4.86 (m, 1H), 3.71–3.53 (m, 2H), 3.48–3.25 (m, 2H), 2.91 (s, 3H), 2.36–2.24 (m, 1H), 2.06–0.71 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 168.9$ (s), 168.7 (s), 152.7 (s), 151.1 (s), 142.1 (d), 127.9 (d), 125.6 (d), 125.0 (d), 110.2 (d), 105.9 (d), 76.8 (d), 53.7 (d), 51.9 (t), 50.2 (d), 41.1 (t), 40.0 (s), 35.4 (q), 34.4 (t), 31.2 (d), 29.8 (d), 27.5 (q), 26.9 (t), 25.6 (q), 21.7 (q); MS (70 eV, EI): *m/z* (%): 423 (< 5) $[M]^+$, 210 (75), 119 (100), 91 (41); HRMS for $C_{26}H_{33}NO_4$: calcd 423.2410; found 423.2427; elemental analysis calcd (%) for $C_{26}H_{33}NO_4$ (423.55): C 73.73, H 7.85, N 3.31; found C 73.80, H 7.79, N 3.28.

Synthesis of *N*-benzylpyrrolidin-2-ones (12): A solution of the corresponding cycloadduct **7** (1 mmol) in hexane/AcOEt (3:1, 100 mL) was exposed to sunlight till it turned almost colorless. The reaction mixture was then filtered through Celite, and solvents were evaporated under vacuum. The crude residue was dissolved in a 1,4-dioxane/water (3:1, 32 mL) mixture; $LiOH \cdot H_2O$ (10 equiv, 0.42 g, 10 mmol) was added, and the reaction mixture was heated to reflux for 48 h. After cooling down to room temperature, solvents were evaporated, and the residue was partitioned between water (20 mL) and AcOEt (20 mL); the organic layer was separated, and the aqueous layer was extracted twice more with AcOEt (2×15 mL). The combined organic layer was dried over Na_2SO_4 and filtered, and the solvents were evaporated under vacuum. The residue was purified by column chromatography using hexane/AcOEt (20:1 to 1:2) as sequential eluents to give *N*-benzylpyrrolidin-2-ones **12** in the yields described in the text; the chiral auxiliary was recovered almost quantitatively after the chromatographic separation. The aqueous layer was acidified with HCl (2N), and AcOEt (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted again with AcOEt (2×15 mL) and discarded. The combined organic layer was treated with Na_2SO_4 and filtered, and solvents were removed under vacuum. The residue was purified by column chromatography using sequential elution with hexane/AcOEt (9:1 to 2:1) and hexane/AcOEt/HCOOH (20:12:1) to give compounds **11**.

(3*R*,4*R*)-1-Benzyl-4-(2-furyl)-pyrrolidin-2-one-3-carboxylic acid (11a): Yield 15–20% (43–57 mg) from **7j**; $R_f = 0.30$ (hexane/AcOEt/HCOOH, 20:12:1); FT-IR (neat): $\tilde{\nu} = 3429$ (broad band), 1728, 1678 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.32$ (br s, 1H), 7.39–7.11 (m, 6H), 6.25 (m, 1H), 6.11 (m, 1H), 4.52 (s, 2H), 4.07 (m, 1H), 3.79 (d, $J = 8.2$ Hz, 1H), 3.62 (m, 1H), 3.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.8$ (s), 169.7 (s), 151.8 (s), 142.1 (d), 134.7 (s), 128.8 (d), 128.0 (d), 127.9 (d), 110.3 (d), 106.6 (d), 52.6 (d), 49.4 (t), 47.0 (t), 34.5 (d); MS (70 eV, EI): *m/z* (%): 285 (17) $[M]^+$, 241 (54), 91 (100); HRMS for $C_{16}H_{15}NO_4$: calcd 285.1001; found 285.1005; elemental analysis calcd (%) for $C_{16}H_{15}NO_4$ (285.30): C 67.36, H 5.30, N 4.91; found C 67.49, H 5.35, N 4.88.

(3*R*,4*S*)-1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one-3-carboxylic acid (11b): Yield 20–25% (82–102 mg) from **7k**; $R_f = 0.42$ (hexane/AcOEt/HCOOH, 20:12:1); FT-IR (neat): $\tilde{\nu} = 3503$ (broad band), 1732, 1689 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.22$ (br s, 1H), 7.39–6.92 (m, 5H), 6.84–6.46 (m, 3H), 4.82–4.25 (m, 3H), 4.09–3.12 (m, 4H), 3.83 (s, 3H), 1.95–1.40 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 171.1$ (s), 170.2 (s), 149.0 (s), 147.6 (s), 135.0 (s), 132.4 (s), 128.6 (d), 127.7 (d), 118.6 (d), 113.6 (d), 111.9 (d), 80.2 (d), 55.8 (q), 55.5 (d), 52.1 (t), 46.9 (t), 40.2 (d), 34.5 (t), 23.8 (t); MS (70 eV, EI): *m/z* (%): 365 (46) $[M - CO_2]^+$, 297 (100), 150 (88), 91 (40); HRMS for $C_{23}H_{27}NO_3$ $[M - CO_2]^+$: calcd 365.1991; found 365.1992; elemental analysis calcd (%) for $C_{24}H_{27}NO_5$ (409.48): C 70.40, H 6.65, N 3.42; found C 70.48, H 6.59, N 3.38.

(*R*)-1-Benzyl-4-(2-furyl)-pyrrolidin-2-one (12a): Colorless oil; yield: 30% (72 mg) from **7j** [**(±)-12a** was obtained in 25% yield (60 mg) from **7d**]; $R_f = 0.10$ (hexane/AcOEt, 3:1); FT-IR (neat): $\tilde{\nu} = 1671$ cm^{-1}; $[\alpha]_D^{29} = -18.5$ ($c = 0.88$ in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.49-7.08$ (m, 6H), 6.28 (m, 1H), 6.05 (m, 1H), 4.49 (s, 2H), 3.67–3.50 (m, 2H), 3.44–3.21 (m, 1H), 2.94–2.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 173.1$ (s), 154.5 (s), 141.7 (d), 135.9 (s), 128.5 (d), 127.9 (d), 127.5 (d), 110.0 (d), 105.1 (d), 50.9 (t), 46.3 (t), 36.2 (t), 30.8 (d); MS (70 eV, EI): *m/z* (%): 241 (19) $[M]^+$, 149 (38), 91 (42), 85 (62), 83 (100); HRMS for $C_{15}H_{15}NO_2$: calcd 241.1103; found 241.1096; elemental analysis calcd (%) for $C_{15}H_{15}NO_2$ (241.29): C 74.67, H 6.27, N 5.81; found C 74.81, H 6.22, N 5.79.

(*S*)-1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one (12b): Yellow oil; yield: 30–35% (110–128 mg) from **7k** [**(±)-12b** was obtained in 28% yield (102 mg) from **7b**]; $R_f = 0.26$ (hexane/AcOEt, 1:1); FT-IR (neat): $\tilde{\nu} = 1687$ cm^{-1}; $[\alpha]_D^{26} = -26.14$ ($c = 1.32$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.27-7.20$ (m, 5H), 6.72 (d, ^3J(H,H) = 8.0 Hz, 1H), 6.64–6.62 (d + s, ^3J(H,H) = 8.0 Hz, 1H), 4.64 (m, 1H), 4.51–4.38 (ABq, ^2J(H,H) = 14.5 Hz, 2H), 3.74 (s, 3H), 3.56 (m, 1H), 3.41 (m, 1H), 3.20 (m, 1H), 2.81 (dd, ^3J(H,H) = 9.0 and ^2J(H,H) = 17.0 Hz, 1H), 2.53 (dd, ^3J(H,H) = 8.0 and ^2J(H,H) = 17.0 Hz, 1H), 1.80 (m, 6H), 1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 173.5$ (s), 148.7 (s), 147.4 (s), 135.9 (s), 134.5 (s), 128.3 (d), 127.8 (d), 127.3 (d), 118.3 (d), 113.3 (d), 111.8 (d), 80.1 (d), 55.7 (q), 53.7 (t), 46.2 (t), 38.8 (t), 36.2 (d), 32.4 (t), 23.7 (t); MS (70 eV, EI): *m/z* (%): 365 (20) $[M]^+$, 297 (80), 150 (63), 91 (52), 85 (60), 83 (100); HRMS for $C_{23}H_{27}NO_3$: calcd 365.1991; found 365.1993; elemental analysis calcd (%) for $C_{23}H_{27}NO_3$ (365.47): C 75.59, H 7.45, N 3.83; found C 75.43, H 7.44, N 3.80.

Decarboxylation of compounds 11: Copper(I) oxide (0.1 equiv, 0.05 mmol, 7 mg) was added to a solution of the corresponding carboxylic acid **11** (0.5 mmol) in pyridine (10 mL), and the mixture was refluxed under a continuous flow of nitrogen till TLC monitoring showed complete disappearance of the starting material. The reaction mixture was filtered through Celite and extracted with water and diethyl ether (3×15 mL). The combined organic layer was dried over Na_2SO_4 and filtered, and solvents were evaporated. Finally the crude residue was purified by column chromatography on silica gel using hexane/AcOEt (20:1 to 4:1) as eluents to give *N*-benzylpyrrolidin-2-ones **12** in 70–75% yield.

Synthesis of (+)-Rolipram 1: *N*-benzylpyrrolidin-2-one **12b** (0.5 mmol) was dissolved in the minimum amount of dry THF under an inert atmosphere and cooled to −78 °C; NH_3 was then bubbled through the flask till approximately 25 mL were collected, and the reaction flask was allowed to warm to −40 °C. Excess lithium (bars) was added, and the resulting deep blue solution was stirred for 10 min. Solid NH_4Cl was added to quench the reaction; NH_3 was evaporated by allowing the reaction mixture to warm till room temperature, and the residue was extracted with water and CH_2Cl_2 (3×15 mL). The organic layer was dried with Na_2SO_4, filtered, and

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evaporated, and the residue was purified by flash chromatography using hexane/AcOEt (1:5) and AcOEt as sequential eluents to give (+)-Rolipram **1**. White solid; yield: 95 % (131 mg).

$R_f = 0.16$ (hexane/AcOEt, 1:5); FT-IR (neat): $\tilde{\nu} = 1686\ cm^{-1}$; $[\alpha]_D^{26} = +24.7$ ($c = 0.23$ in MeOH) {ref. [12d] $[\alpha]_D = -31$ ($c = 0.5$ in MeOH) for the levorotatory isomer}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 6.90-6.70$ (m, 3H), 6.60 (br s, 1H), 4.77 (m, 1H), 3.84 (s, 3H), 3.83–3.59 (m, 2H), 3.39 (m, 1H), 2.72 (dd, $^3J(H,H) = 8.4$ and $^2J(H,H) = 16.9$ Hz, 1H), 2.48 (dd, $^3J(H,H) = 8.7$ and $^2J(H,H) = 16.9$ Hz, 1H), 1.90–1.85 (m, 6H), 1.62 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 177.8$ (s), 149.1 (s), 147.8 (s), 134.4 (s), 118.7 (d), 113.7 (d), 112.1 (d), 80.5 (d), 56.0 (q), 49.7 (t), 39.9 (d), 38.1 (t), 32.7 (t), 23.9 (t); MS (70 eV, EI): *m/z* (%): 275 (12) $[M]^+$, 207 (78), 150 (100), 57 (66); HRMS for $C_{16}H_{21}NO_3$: calcd 275.1521; found 275.1515.

The reaction performed with a racemic sample of **12b** gave (±)-Rolipram in 95 % yield (131 mg).

***tert*-Butyl (*S*)-4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one-1-carboxylate (13)**: Triethylamine (0.1 mmol, 14 mL), DMAP (0.1 mmol, 12 mg), and $t(Boc)_2O$ (0.2 mmol, 44 mg) were added successively to a solution of (+)-Rolipram **1** (0.1 mmol, 27.5 mg) in dry dichloromethane (5 mL) under nitrogen at room temperature, and the resulting solution was stirred till disappearance of **12** was detected by TLC. Solvents were then evaporated, and the obtained residue was purified by flash chromatography on silica gel using hexane/AcOEt (20:1 to 1:1 mixtures) to give **13**, which has the following data: yellow oil, yield: 76 % (29 mg) [73 % yield (27 mg) for the racemic compound from **(±)-1**).

$R_f = 0.50$ (hexane/AcOEt, 1:1); FT-IR (neat): $\tilde{\nu} = 1784$, 1751, 1713, 1516 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 6.86-6.74$ (m, 3H), 4.77 (m, 1H), 4.13 (dd, $^3J(H,H) = 7.8$ and 10.6 Hz, 1H), 3.84 (s, 3H), 3.65 (dd, $^3J(H,H) = 7.5$ and 10.5 Hz, 1H), 3.46 (m, 1H), 2.88 (dd, $^3J(H,H) = 8.5$ and $^2J(H,H) = 17.3$ Hz, 1H), 2.67 (dd, $^3J(H,H) = 9.7$ and $^2J(H,H) = 17.3$ Hz, 1H), 2.00–1.71 (m, 4H), 1.68–1.43 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 173.1$ (s), 149.9 (s), 149.3 (s), 147.9 (s), 132.8 (s), 118.7 (d), 113.6 (d), 112.1 (d), 83.0 (s), 80.5 (d), 56.1 (q), 53.3 (t), 40.5 (t), 36.0 (d), 32.7 (t), 27.9 (q), 23.9 (t); MS (70 eV, EI): *m/z* (%): 375 (< 5) $[M]^+$, 207 (95), 150 (100); HRMS for $C_{21}H_{29}NO_5$: calcd 375.2046; found 375.2057.

Acknowledgements

We acknowledge the financial support received from DGICYT (PB92-1005). F.F.-M. is indebted to the Ministerio de Educación y Ciencia (Spain) for a predoctoral fellowship. A.S. thanks the Universidad de Oviedo for an undergraduate fellowship.

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[22] Several assays were performed in an attempt to rule out one of the two options: the undetected presence of the other diastereomer after the cycloaddition reaction or a partial racemization of the cycloadduct during the basic hydrolysis step. Thus, a sample of **12a** with an *er* = 92:8 was treated with LiOH under the same hydrolysis conditions described before. After three days, an *er* = 91:9 was observed using chiral HPLC analysis; this turned into an *er* = 85:15 after fifteen days of reaction. Also, the whole sequence that leads to (+)-Rolipram **1** was repeated, but this time the crude mixture after the cycloaddition step was purified by column chromatography, and three sequential fractions in approximately 1:1:1 ratio were taken. Solvents were evaporated, and NMR experiments (^{1}H NMR: 300 MHz; ^{13}C NMR: 75 MHz) did not detect the presence of the other diastereomer in any of the fractions. The three fractions were then transformed into (+)-Rolipram **1** {$[\alpha]_D^{20} = +26.7$ ($c = 0.55$ in MeOH), $[\alpha]_D^{20} = +19.3$ ($c = 0.72$ in MeOH), and $[\alpha]_D^{20} = +21.5$ ($c = 0.97$ in MeOH) for the first, second, and third fraction, respectively} and into the BOC-protected compound **13** to be purified by chiral HPLC analysis. The *er* values observed in these analyses were 97:3 for the first fraction, 95:5 for the second fraction, and 90:10 for the third fraction. From these results, the presence of the NMR-undetected diastereomer after the cycloaddition step is evident.

Received: November 16, 2000 [F2874]

  0947-6539/01/0716-3544 $ 17.50+.50/0