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A two-step four-component queuing cascade involving a Heck coupling, π-allylpalladium trapping and Diels–Alder reaction☆

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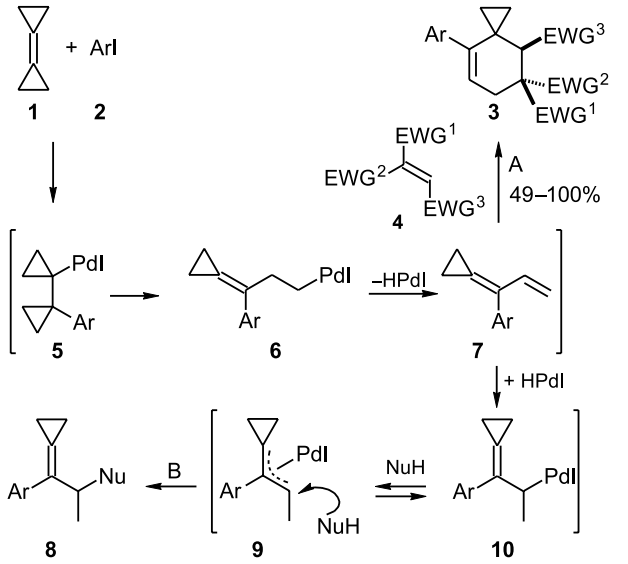
Abstract—Palladium-catalyzed cross-coupling of bicyclopropylidene (**1**) with iodoethene (**11**) in the presence of a secondary amine **12** provides allylidenecyclopropanes **13** which undergo immediate Diels–Alder reactions upon addition of dienophiles **14**–**18** to provide 8-(1′-aminoethyl)-substituted spiro[2.5]oct-7-ene derivatives **23a**–**26a** in 29–66% yield. The same one-pot, two-step queuing cascade can be carried out with other iodoalkenes including cyclic ones and with cyclic dienophiles such as *N*-arylmaleinamides **19**–**22** and *N*-phenyltriazolinedione **37** to furnish highly substituted spiro[2.5]oct-4-enes and spirocyclopropanated heterobicycles **47a**–**49a**, **41a**–**46a** (17–50%). Spirocyclopropanated heterobicycles such as **55**, **56** (25 and 38% yield, respectively) can also be obtained by an inter-intra-intra-intermolecular version of this queuing cascade involving 1-hydroxyethyl- and 1-aminoethyl-substituted iodoethenes **53**, **54**.

1. Introduction

One of the foremost aims in the development of modern organic synthetic methods is an increase in efficiency,[2] as expressed in the increase in molecular complexity in a minimum number of procedural steps. Both multicomponent[3] and cascade (or domino) reactions[4] bring about remarkable changes in molecular complexity. While multicomponent reactions by definition constitute a subgroup of cascade reactions,[5] not all cascade reactions do necessarily involve more than one component. Thus, multicomponent reactions in which one or more of the reaction partners are involved in more than one step of the overall transformation cascade, are particularly efficient in terms of increasing the molecular complexity.

In recent years, we have found several new examples of such multicomponent molecular queuing cascades,[6] in which palladium-catalyzed cross-couplings and the highly reactive C_6-building block bicyclopropylidene (**1**) play pivotal rules.[6] One of them is a cross-coupling between **1**, an aryl iodide **2** leading to an allylidenecyclopropane **7** which immediately reacts with a dienophile **4**, present in the mixture to yield a 4-arylspiro[2.5]oct-4-ene derivative **3** (Scheme 1).[7] The combinatorial potential of this process has been demonstrated with the automatized preparation of a structurally diverse set of these multifunctional biaryl mimics.[8] A related three-component sequence starts with the same carbopalladation of the unusually reactive double bond in bicyclopropylidene (**1**) and subsequent



Scheme 1. Two recently developed three-component reactions involving bicyclopropylidene (**1**), an aryl iodide and a cyclopropylcarbinyl to homoallylpalladium rearrangement. (A) $Pd(OAc)_2$, PPh_3, K_2CO_3, Et_4NCl, MeCN, 80 °C, 48 h. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, NuH, MeCN, 80 °C, 24 h.

☆ See Ref. 1.

Keywords: π-Allylpalladium species; Bicyclopropylidene; Cascade reactions; Cycloadditions; Small rings; Spiro[2.5]octenes.
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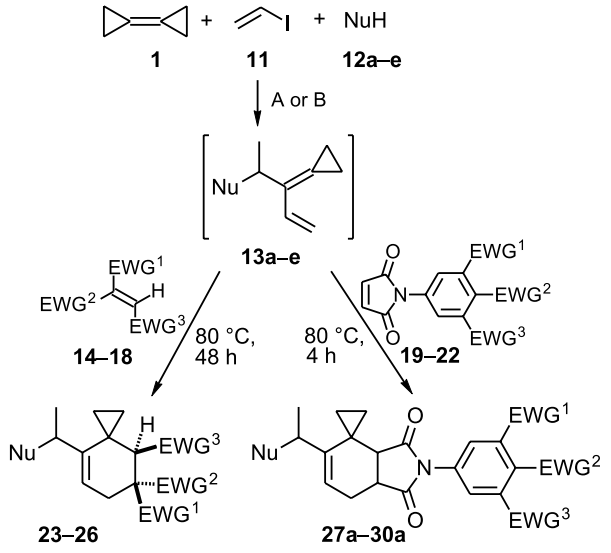
cyclopropylcarbinyl to homoallyl rearrangement of **5** affording the homoallylpalladium species **6**, which rapidly undergoes a β-hydride elimination to yield the diene **7**. In the absence of a dienophile **4** and favored by the presence of tris(2-furyl)phosphine (TFP) instead of triphenylphosphine, **7** undergoes hydridopalladation with the reverse regioselectivity to form the σ-allylpalladium intermediate **10**. Irrespective of the latter equilibrating with the π-allylpalladium species **9**,[9] it is trapped regioselectively by an added nucleophile, for example, lithium acetate or an amine, to furnish a 2-arylallyl derivative of type **8** (Scheme 1).[10] Since the cross coupling of **1** with an alkenyl iodide in the presence of a dienophile leads to a transmissive Diels–Alder adduct of an intermediately formed cross-conjugated triene, we conceived the possibility of extending the second reaction mode into an overall four-component queuing cascade by coupling an alkenyl iodide with bicyclopropylidene (**1**) in the presence of TFP. This would yield, after trapping of the formed π-allylpalladium intermediate with a nucleophile, a conjugated diene, which would undergo a Diels–Alder reaction with an added dienophile. This concept was tested, and here we present our first results.



Scheme 2. A new one-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoethene (**11**), nucleophiles **12a–e** and dienophiles **14–18**, **19–22**. (A) $Pd(OAc)_2$, TFP, NEt_3, 2 h, 80 °C, DMF. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, 2 h, 80 °C, MeCN. For further details see Table 1.

2. Results and discussion

The palladium-catalyzed cross-coupling with rearrangement and nucleophilic trapping cannot be carried out with the dienophile being present from the beginning, since a Michael addition of the nucleophile onto the dienophile would compete with the desired reaction. Therefore, bicyclopropylidene (**1**) and iodoethene (**11**) in the presence of a secondary amine **12** in dimethylformamide were treated with a typical palladium catalyst cocktail (e.g., $Pd(OAc)_2$, TFP, NEt_3) at 80 °C for 2 h, then a dienophile like methyl acrylate (**14**) was added, and the mixture was heated at 80 °C for 48 h (Scheme 2 and Table 1).

With morpholine (**12a**) as a secondary amine, well known to be a good nucleophile,[11] the yields in this one-pot, two-step queuing cascade were generally good (37–66%), irrespective of the nature of the dienophile (Table 1). With piperidine (**12b**), pyrrolidine (**12c**), *N*-benzylpiperazine (**12d**), and *N*-*tert*-butoxycarbonylpiperazine (**12e**) in combination with **1**, **11** and the best yielding *tert*-butyl acrylate (**15**), the cascade reaction gave the corresponding products **24b–e** mostly in moderate yield (29–49%). In all cases, the products from unsymmetrical dienophiles **14–16** were only 5-substituted spiro[2.5]oct-7-ene derivatives as assigned on the basis of their NMR spectra. This is in agreement with the previously observed regioselectivities in Diels–Alder additions of acrylates to allylidenecyclopropanes.[6a,12]

The reaction with dimethyl fumarate **17** and dimethyl maleate **18** both gave mixtures of dimethyl *cis*- and *trans*-spiro[2.5]octenedicarboxylates (*cis*- and *trans*-**26a**) in slightly different ratios (Table 1), irrespective of the conditions (A or B in Scheme 2) used. Control experiments confirmed that simple heating in dimethylformamide at 80 °C causes **18** to isomerize to **17**, (50% conversion after 1.5 h, ~98% conversion after 6 h), whereas heating of **18** in

Table 1. One-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoethene **11**, nucleophiles **12a–e**, dienophiles **14–18** and **19–22** (see Scheme 2)

Nucleophile **12** NuH	Cond.	Dienophile	EWG^1	EWG^2	EWG^3	Product	Yield (%)[a]	d.r.[b]
a Morpholine	B	**14**	CO_2Me	H	H	**23a**	65	1.1:1
a Morpholine	A	**15**	CO_2tBu	H	H	**24a**	66	1.3:1
a Morpholine	A	**16**	SO_2Ph	H	H	**25a**	62	1.2:1
a Morpholine	B	**17**	CO_2Me	H	CO_2Me	*cis*/*trans*-**26a**	58	1.2:1
a Morpholine	B	**18**	H	CO_2Me	CO_2Me	*cis*/*trans*-**26a**	52	1.7:1
a Morpholine	A	**17**	CO_2Me	H	CO_2Me	*cis*/*trans*-**26a**	39	1.3:1
b Piperidine	A	**15**	CO_2tBu	H	H	**24b**	33	1:1
c Pyrrolidine	A	**15**	CO_2tBu	H	H	**24c**	29	1:1
d *N*-Bn-Piperazine	B	**15**	CO_2tBu	H	H	**24d**	48	1.1:1
e *N*-Boc-piperazine	B	**15**	CO_2tBu	H	H	**24e**	49	1:1
a Morpholine	A	**19**	H	H	H	**27a**	40	1:1
a Morpholine	A	**20**	CF_3	H	H	**28a**	38	1.2:1
a Morpholine	A	**21**	H	CF_3	H	**29a**	44	1.1:1
a Morpholine	A	**22**	CF_3	H	CF_3	**30a**	37	1.6:1

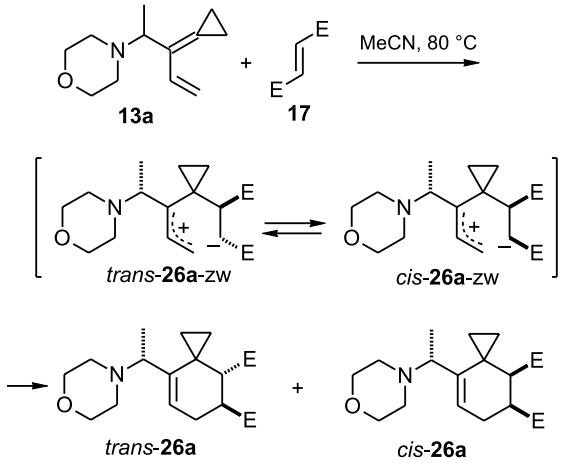
[a] Isolated yields are given.
[b] Diastereomeric ratios were determined by integration of relevant ^1H NMR signals in the spectra of the crude products.

acetonitrile at 80 °C did not lead to any isomerization even after 24 h.

Attention was then turned to the reaction of isolated diene **13a** with dimethyl maleate (**18**) to explain the formation of the *trans*-spirooctenedicarboxylate *trans*-**26a** along with *cis*-**26a** under conditions B (i.e., in acetonitrile), since isomerization of **18** to **17** during the course of the Heck reaction is well known.[13] In other words, in the absence of the catalyst ingredients, *cis*-**26a** would be expected as a single product if the cycloaddition of dimethyl maleate (**18**) to the 1,3-diene **13a** occurred in a concerted mode. Surprisingly, however, the reaction of a fourfold excess of dimethyl maleate (**18**) with diene **13a** in acetonitrile at 80 °C after 24 h again gave virtually the same mixture of *cis*- and *trans*-**26a** in a ratio of 1.4:1 in quantitave yield (based on the diene **13a**) along with a 3:1 mixture of **17** and **18**.

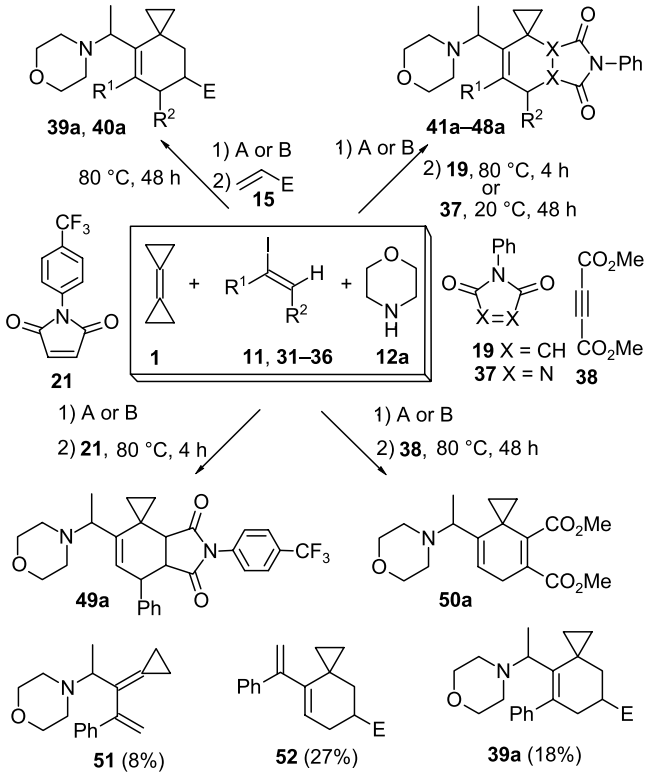
The reaction of **13a** with a twofold excess of **18** was also performed in deuterated acetonitrile and monitored by NMR spectroscopy. After 1 h, some dimethyl fumarate (**17**) was detectable, but none of the cycloadduct *cis*- or *trans*-**26a** from the diene **13a**. The concentration of **17** continued to increase until the formation of *cis*- and *trans*-**26a** set in. Thus, the second order rate of the cycloaddition of **17** to **13a** at the given temperature becomes comparable to that of the first order or pseudo-first order rate of isomerization of **18** to **17** only when the concentration of **17** has reached a certain level (almost one third of that of **18** after 7 h). It is well known that dimethyl fumarate (**17**) is more reactive as a dienophile than dimethyl maleate (**18**) by a factor of about 82.[14] Most probably, the diene **13a**, which is a tertiary amine, catalyzes the isomerization of **18** to **17**. Indeed, in a control experiment, *N*-allylmorpholine as a model for **13a** was shown to cause this isomerization.

Altogether these results imply that the cycloaddition of dimethyl fumarate (**17**) to **13a** must proceed in two steps through the zwitterionic intermediate *trans*-**26a**-zw, just as has been suggested for the reaction of (1′-arylallylidene)-cyclopropanes with **17** and **18** (Scheme 3).[6a] Rather than undergoing immediate cyclization, the initial zwitterion *trans*-**26a**-zw by internal rotation can go to *cis*-**26a**-zw and then cyclize to furnish the cycloadduct of dimethyl maleate (**18**). Since only two diastereomers were obtained from both **17** and **18**, the stereocenter present in the diene **13a** most probably controls the approach of the dienophile **17** in such a way as to only form the zwitterion *trans*-**26a**-zw as shown, and this undergoes rotation only to *cis*-**26a**-zw or ring closure to *trans*-**26a**.



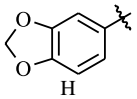
Scheme 3. Rationalizing the formation of both diastereomeric cycloadducts *trans*-**26a** and *cis*-**26a** from the allylidenecyclopropane **13a** and dimethyl fumarate (**17**). E = CO_2Me.

The complexity of the product structure was further increased by the use of heteroatom-containing dienophiles **19**, **21** and **37** with various substituted vinyl iodides **31**–**36** (Scheme 4 and Table 2), which were prepared according to published procedures.[15] In most of these cases, however, the yields were only moderate and, in general, lower than with iodoethene (**11**). In the reactions of α-iodostyrene (**31**) (entries 1, 8 and 10 in Table 2) and 5-(1-iodovinyl)benzo-[1,3]dioxole **32** (entry 2 in Table 2), more than one equivalent of morpholine had to be added, and the reaction mixture with the palladium catalyst had to be heated for more than two hours to drive the first section of the sequential reaction to completion. Indeed, when the reactions of iodoalkenes **31** and **32** were carried out with sterically encumbered dienophiles such as *tert*-butyl acrylate (**15**) (entries 1, 2 in Table 2), prolonged reaction times and higher temperatures than 80 °C were necessary for the Diels–Alder reaction in the second step to be successful. For example, the reaction of α-iodostyrene (**31**) with **1** and one equivalent of morpholine (**12a**) under the usual conditions (80 °C, 2 h for the first step and 80 °C, 48 h for the second step) yielded the diene **51** (8%) and the



Scheme 4. One-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoalkenes **11** and **31**–**36**, morpholine **12a** and dienophiles **15**, **19**, **21**, **37** and **38**. (A) $Pd(OAc)_2$, TFP, NEt_3, 80 °C, DMF. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, 80 °C, MeCN. E = CO_2tBu, For details see Table 2.

Table 2. One-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoalkenes **11** and **31–36**, morpholine **12a** and dienophiles **15**, **19**, **21**, **37** and **38** (see Scheme 4)

Entry	Cond.	Time [h]	Alkenyl Iodide	R^1	R^2	Dienophile	Product	Yield (%)	d.r.
1	B[a,b]	3	**31**	Ph	H	**15**	**39a**	36	1.1:1
2	B[a,b]	3	**32**		H	**15**	**40a**	44	1.2:1
3	A	3	**33**	H	2-Thienyl	**37**	**41a**	26	1:1
4	A[c]	5	**34**	$-(CH_2)_4-$		**37**	**42a**	33	4.6:1
5	B	3	**35**	$[(CH_2)_2NCH_2]$ Bn		**37**	**43a**	17	—[d]
6	A	2	**36**	H	Ph	**37**	**44a**	35	1.4:1
7	B	2	**11**	H	H	**37**	**45a**	50	—[d]
8	B[b]	3	**31**	Ph	H	**37**	**46a**	35	—[d]
9	A[e]	2	**36**	H	Ph	**19**	**47a**	42	2:1
10	A[b,f]	3	**31**	Ph	H	**19**	**48a**	40	1.18:1
11	A[e]	2	**36**	H	Ph	**21**	**49a**	37	2:1
12	B[f]	2	**11**	H	H	**38**	**50a**	30	—[d]

[a] 100 °C, 65 h for the second step.
[b] 1.5 equiv of morpholine (**12a**) used in the first step.
[c] 100 °C for the first step.
[d] Only one diastereomer was isolated.
[e] 80 °C, 4 h for the second step.
[f] 80 °C, 48 h for the second step.

styryl[2.5]spirooctene derivative **52** (27%) along with the expected product **39a** (18%) (Scheme 4). Formation of the by-products **51** and **52** could only be eliminated by applying 1.5 equiv of **12a** in the first step and prolonged heating (65 h) at elevated temperature (100 °C) for the second step (entry 1 in Table 2). Interestingly, however, in the case of (*E*)-1-iodo-2-phenylethene (**36**) (entries 6, 9 and 11 in Table 2) 2 h without using more than one equivalent of morpholine were enough to complete the first step of the reaction.

Yet, even spirocyclopropanated heterooligocyclic systems **42a** and **43a** (entries 4 and 5 in Table 2) were accessible by the use of iodocyclohexene **34** and *N*-benzyl-4-iodotetrahydropyridine **35**, respectively. For the first step of the sequential reaction of iodocyclohexene (**34**), the mixture had to be heated exceptionally long, that is, for 5 h at 100 °C, to reach the maximum yield, whereas the reactions of other iodoalkenes gave lower yields when the temperature for the first steps exceeded 80 °C. The configuration of the major diastereomer **42a** was rigorously proved by an X-ray crystal structure analysis (Fig. 1). A heterocyclic substituent could also be attached to the spirooctene core as in **41a** by means of 2-(2-iodovinyl)thiophene **33** in the cross-coupling step (entry 3 in Table 2).

Furthermore, heteroatoms could be incorporated in the spirooctene moiety of the Diels–Alder products by employing the highly reactive dienophile *N*-phenyltriazolinedione (PTAD) **37**. Whereas with *N*-phenylmaleimide (**19**) the cycloaddition could be completed at 80 °C in 4 h, the reaction with **37** gave better yields when carried out at 20 °C for prolonged times (up to 2 days).

To extend the scope of this cascade reaction even further, functionalized vinyl iodides **53** and **54** were employed to provide, by intramolecular π-allylpalladium trapping in the first step after the cross-coupling and rearrangement, spirocyclopropanated heterobicycles **55**, **56**, albeit in moderate yields only (at best 25 and 38%, respectively) (Scheme 5).[17] Although this is not a four-component reaction, this inter-intra-intra-intermolecular queuing cascade proceeds by the same number of individual steps and with formation of the same number of carbon–carbon and carbon-heteroatom bonds (altogether four) as the four-component cascades discussed above.

Interestingly, the iodohomoallyl alcohol **53** gave the best results under conditions B in acetonitrile with potassium carbonate and the phase transfer agent (Et_4NCl), whereas the *N*-tosylhomoallylamine **54** gave the best yield of 38% under conditions A ($Pd(OAc)_2$, TFP, NEt_3, DMF, 80 °C, 3 h), and the product **56** was obtained as a single diastereomer along with the tosylaminobutenylspiro[2.5]-octenecarboxylate **57** resulting from β-hydride elimination in the intermediate of type **6** and immediate Diels–Alder addition of **15**. The configuration of **56** was also rigorously proved by an X-ray crystal structure analysis (Fig. 2). All

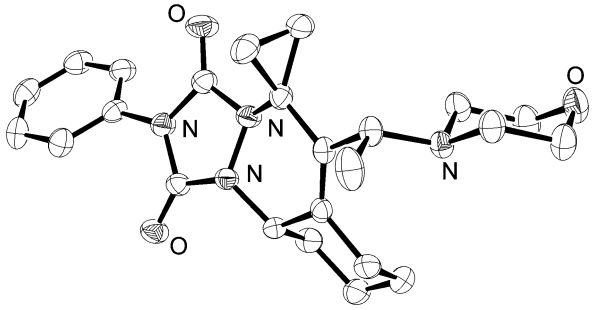
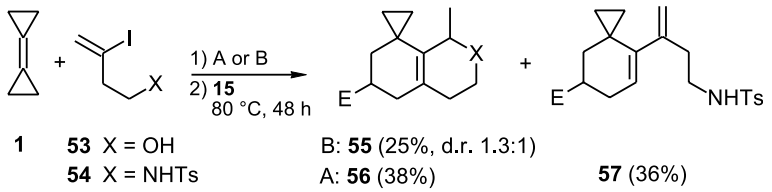


Figure 1. Structure of compound **42a** in the crystal.[16] $C_{24}H_{30}N_4O_3$ (422.52); crystal size $0.50\times0.50\times0.50\ mm^3$, orthorhombic, $a=919.67$ (18), $b=1352.8$ (3), $c=1733.3$ (4) pm, $\alpha=90°$ $\beta=90°$, $\gamma=90°$, $V=2.1565$ (7) nm^3; $Z=4$, space group $P2_1/2_1/2_1$, $T=200$ (2) K, $\rho=1.301\ mg\ m^{-3}$, absorption coefficient $=0.087\ mm^{-1}$, $F_o=904$, θ range for data collection $=3.56–24.96°$, reflection collected $=2892$, $R_{int}=2575[0.0374]$, data/restraints/parameters $=2575/0/281$, Goof on $F^2=1.037$, Final R indices $[I>2\sigma(I)]=R_1$ (0.0374), wR_2 (0.0912), R indices (all data) $=R_1$ (0.0400), wR_2 (0.0943), Largest diff. peak and hole $=0.144$ and $-0.227\ e\ Å^{-3}$.



Scheme 5. An inter-intra-intra-intermolecular queuing cascade involving bicyclopropylidene (**1**) a functionalized iodoalkene **53**, **54**, and a dienophile **15**. (A) $Pd(OAc)_2$, TFP, NEt_3, 80 °C, DMF. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, 80 °C, MeCN. E=CO_2tBu.

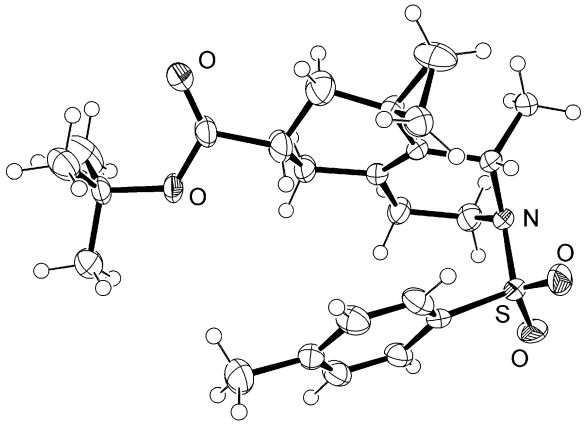


Figure 2. Structure of compound **56** in the crystal.[16] $C_{24}H_{33}NO_4S$ (431.57); crystal size 0.30×0.20×0.20 mm^3, monoclinic, a=1135.4(2), b=1289.1(3), c=1632.3(3) pm, α=90° β=108.0(3)°, γ=90°, V=2.2723(8) nm^3; Z=4, space group $P2_1/c$, T=133(2) K, ρ=1.262 mg m^{-3}, absorption coefficient =0.172 mm^{-1}, F_o=928, θ range for data collection=1.89–24.82°, reflection collected =33280, R_{int}=3897[0.0774], data/restraints/parameters=3897/0/276, Goof on F^2=1.021, Final R indices [$I>2\sigma(I)$]=R_1(0.0536), wR_2(0.1333), R indices (all data)=R_1(0.0873), wR_2(0.1439), Largest diff. peak and hole=0.974 and −0.403 e $Å^{-3}$.

attempts to suppress the formation of **57** by increasing the reaction temperature or the time were unsuccessful.

3. Conclusion

In conclusion, another dimension of diversity has been added to an already powerful combinatorial approach to libraries of spiro[2.5]octene derivatives. The new one-pot, two-step four-component queuing cascade leads to a particularly rich pattern of substituents by variation of the iodoalkenes, the nucleophiles and the dienophiles, exceeding those of the previously described spirocyclopropanated carbo- and heterocyclic skeletons.[6] This sequential transformation may also open up new approaches to natural products containing spiro[2.5]octane substructures.[18]

4. Experimental

4.1. General

NMR spectra were recorded with a Varian Mercury 200 (200 MHz for ^1H and 50.3 MHz for ^{13}C), a Bruker AM 250 (250 MHz for ^1H and 62.9 MHz for ^{13}C NMR), a Varian UNITY-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C NMR) or a Varian Inova 600 (600 MHz for ^1H and 151 MHz for ^{13}C NMR) instruments. Chemical shifts δ are given in ppm relative to residual peaks of deuterated solvents and coupling constants, J, are given in Hertz. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer): +=primary or tertiary (positive DEPT signal), −=secondary (negative DEPT Signal), C_{quat}=quaternary carbon atoms] or APT (attached proton test) measurements. HMQC (heteronuclear multiple quantum coherence) spectra were also measured. IR spectra were recorded on a Bruker IFS 66 spectrometer and measured as KBr pellets or as oils between KBr plates. Low resolution mass spectra (EI at 70 eV or DCI with NH_3) were obtained on a Finnigan MAT 95 spectrometer. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95 spectrometer by preselected-ion peak matching at $R\approx$10,000 to be within ±2 ppm of the exact masses. Elemental analyses were carried out by the Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen. Chromatographic separations were performed with Merck Silica 60 (200–400 or 70–230 mesh). The dimensions of the columns are given as 'diameter×height of the silica gel column'. TLC was performed with Macherey-Nagel TLC Alugram® Sil G/UV 254 plates, detection was under UV light at 254 nm and development with MOPS reagent (10% molybdophosphoric acid in ethanol). Melting points were obtained with a Büchi apparatus according to Dr. Tottoli; values are uncorrected. All reagents were used as purchased from commercial suppliers without further purification. Acetonitrile was dried over P_2O_5, DMF and CH_2Cl_2 were distilled from CaH_2. Ether and THF were freshly distilled from sodium/benzophenone ketyl. Solvents for column chromotography, ethyl acetate and light petroleum were distilled in a rotatory evaporator.

Starting materials: bicyclopropylidene (**1**),[19] iodoalkenes **11**,[20] **31**, **32**, **34**,[15a] **33**,[15c] **35**,[21] **36**,[15e,j] and functionalized iodoalkenes **53**,[15b] **54**,[22] pyrrole-2,5-dione derivatives **19–22**[23] were prepared according to published procedures.

4.2. General procedure for the one-pot, two-step queuing cascade involving bicyclopropylidene (1) an iodoalkene, a secondary amine 12 and a dienophile under conditions A (GP-A)

Palladium acetate (22.4 mg, 100 μmol, 5 mol%) and tri-2-furylphosphine (46.4 mg, 200 μmol, 10 mol%), were suspended in anhydrous DMF (1 mL) in a screw-cap pyrex bottle. Argon was bubbled through the mixture for 5 min, and then the respective amine (2.00 or 2.50 mmol), triethylamine (202 mg, 2.00 mmol), iodoalkene (2.00 mmol) and bicyclopropylidene (**1**) (320 mg, 4.00 mmol) were added. After having stirred the mixture for the given time at the stated temperature the bottle was cooled to ambient temperature, the respective dienophile

(4.00 mmol) was added, (*N*-phenyltriazolinedione was added to the ice-cooled mixture), and then the mixture was stirred for an additional time as stated at the given temperature in a preheated oil bath. After cooling to room temperature, the reaction mixture was taken up in 20 mL of diethyl ether. The solution was washed with water (2× 20 mL). The aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic phases were dried ($MgSO_4$). After removal of the solvent in a rotatory evaporator, the residue was subjected to chromatography on silica gel.

4.3. General procedure for the one-pot, two-step queuing cascade involving bicyclopropylidene (1) an iodoalkene, a secondary amine 12 and a dienophile under conditions B (GP-B)

A screw-cap Pyrex bottle was charged with anhydrous acetonitrile (2 mL), K_2CO_3 (556 mg, 4.00 mmol) and Et_4NCl (332 mg, 2.00 mmol). Argon was bubbled through the mixture for 5 min, $Pd(OAc)_2$ (22.4 mg, 100 μmol, 5 mol%), and tri-2-furylphosphine (46.4 mg, 200 μmol, 10 mol%) were added, and the mixture was stirred once more for an additional 5 min with argon bubbling through, before the respective iodoalkene (2.00 mmol), the nucleophile (2.00 or 2.50 mmol) and bicyclopropylidene (**1**) (320 mg, 4.00 mmol) were added. The bottle was tightly closed, and the mixture was stirred for the given period of time at the stated temperature. After the bottle was cooled to ambient temperature, the respective dienophile (4.00 mmol) was added, (*N*-phenyltriazolinedione was added to the ice-cooled mixture), and then the mixture was stirred for the additional time at the given temperature in a preheated oil bath. After cooling to room temperature, the reaction mixture was taken up in 20 mL of diethyl ether. The solution was washed with water (2×20 mL), the aqueous phase was extracted with diethyl ether (2×20 mL), and the combined organic phases were dried ($MgSO_4$). After removal of the solvent in a rotatory evaporator, the residue was subjected to chromatography on silica gel.

4.3.1. Methyl 8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (23a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature methyl acrylate (**14**, 344 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **23a** (363 mg, 65%, yellowish oil) as a mixture of two diastereomers (ratio 1.1:1 according to NMR).

Major diastereomer. R_f=0.27 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3076, 2973, 2851, 2809, 1738, 1653, 1456, 1329, 1160, 1120, 911, 866 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.32–0.39 (m, 1H, *c*Pr-H), 0.47–0.54 (m, 1H, *c*Pr-H), 0.77–0.95 (m, 2H, *c*Pr-H), 1.02 (d, J=6.23 Hz, 3H, CH_3), 1.24 (ddd, J=12.75, 2.72, 1.2 Hz, 1H, 4- or 6-H), 2.03 (ddd, J=12.5, 12.5, 1.7 Hz, 1H, 4- or 6-H), 2.12 (q, J=6.23 Hz, 1H, 1′-H), 2.29–2.45 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.67–2.80 (m, 1H, 5-H), 3.63–3.69 (m, 4H, CH_2OCH_2), 3.66 (s, 3H; OCH_3), 5.77 (dd, J=4.4, 2.9 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.74 (−, *c*Pr-C), 13.23 (−, *c*Pr-C), 17.78 (+, CH_3), 19.47 (C_{quat}, *c*Pr-C), 28.34 (−, C-4 or -6), 38.56 (−, C-4 or -6), 39.29 (+, C-5), 50.74 (−, CH_2NCH_2), 51.56 (+, OCH_3), 59.17 (+, C-1′), 67.20 (−, CH_2OCH_2), 124.8 (+, C-7), 140.73 (C_{quat}, C-8), 176.09 (C_{quat}, C=O); MS (70 eV, EI), *m*/*z* (%): 279 (29) [M^+], 264 (100) [M^+-CH_3], 250 (11) [$M^+-C_2H_5$], 133 (21), 114 (86), 91 (24), 86 (12); $C_{16}H_{25}NO_3$ (279.38): calcd 279.1834 (correct HRMS); elemental analysis calcd (%) for $C_{16}H_{25}NO_3$: C 68.79, H 9.02; found: C 68.63, H 9.10.

Minor diastereomer. R_f=0.23 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3079, 2952, 2851, 2805, 1740, 1650, 1457, 1257, 1194, 1172, 945, 861 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.35–0.51 (m, 2H, *c*Pr-H), 0.59–0.66 (m, 1H, *c*Pr-H), 1.03 (d, J=6.8 Hz, 3H, CH_3), 1.02–1.14 (m, 1H, *c*Pr-H), 1.48 (dd, J=12.8, 3.1 Hz, 1H, 4- or 6-H), 1.90 (dd, J=10.2, 13 Hz, 1H, 4- or 6-H), 2.20 (q, J=6.8 Hz, 1H, 1′-H), 2.32–2.48 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.69–2.80 (m, 1H, 5-H), 3.63–3.71 (m, 4H, CH_2OCH_2), 3.66 (s, 3H, OCH_3), 5.71 (t, J=3.8 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.75 (−, *c*Pr-C), 12.39 (−, *c*Pr-C), 16.99 (+, CH_3), 18.51 (C_{quat}, *c*Pr-C), 27.80 (−, C-4 or -6), 38.16 (−, C-4 or -6), 38.72 (+, C-5), 50.38 (−, CH_2NCH_2), 51.42 (+, OCH_3), 58.51 (+, C-1′), 67.24 (−, CH_2OCH_2), 121.4 (+, C-7), 143.67 (C_{quat}, C-8), 175.84 (C_{quat}, C=O); MS (70 eV, EI), *m*/*z* (%): 279 (26) [M^+], 264 (100) [M^+-CH_3], 250 (16) [$M^+-C_2H_5$], 133 (19), 114 (94), 91 (22), 86 (16); $C_{16}H_{25}NO_3$ (279.38): calcd 279.1834 (correct HRMS).

4.3.2. *tert*-Butyl 8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (24a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 3:1) to yield **24a** (426 mg, 66%, yellowish oil) as a mixture of two diastereomers (ratio 1.3:1 according to NMR).

Major diastereomer. R_f=0.34 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3077, 2977, 2851, 2809, 2689, 1731, 1455, 1367, 1339, 1253, 1150, 1119, 942, 855 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.32–0.39 (m, 1H, *c*Pr-H), 0.47–0.54 (m, 1H, *c*Pr-H), 0.77–0.92 (m, 2H, *c*Pr-H), 1.02 (d, J=6.2 Hz, 3H, CH_3), 1.19 (ddd, J=12.4, 2.7, 1.2 Hz, 1H, 4- or 6- H), 1.43 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=12.7 Hz, 1H, 4- or 6-H), 2.09 (q, J=6.4 Hz, 1H, 1′-H), 2.27–2.42 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.53–2.68 (m, 1H, 5-H), 3.65 (t, J=4.4 Hz, 4H, CH_2OCH_2), 5.76 (t, J=3.6 Hz, 1H, 7-H);

^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.75 (−, *c*Pr-C), 13.16 (−, *c*Pr-C), 17.87 (+, CH_3), 19.45 (C_{quat}, *c*Pr-C), 28.00 [+, $C(CH_3)_3$], 28.53 (−, C-4 or -6), 38.51 (−, C-4 or -6), 40.32 (+, C-5), 50.75 (−, CH_2NCH_2), 59.11 (+, C-1′), 67.15 (−, CH_2OCH_2), 79.78 [C_{quat}, $C(CH_3)_3$], 120.7 (+, C-7), 140.64 (C_{quat}, C-8), 174.98 (C_{quat}, C=O); MS (70 eV, EI) *m/z* (%): 321 (46) [M^+], 306 (68) [M^+-CH_3], 250 (60) [$M^+-C_2H_5$], 133 (30), 114 (100), 100 (22), 86 (20); elemental analysis calcd (%) for $C_{19}H_{31}NO_3$ (321.5): C 70.99, H 9.72; found: C 70.78, H 9.52.

Minor diastereomer. R_f=0.29 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3079, 2977, 2851, 2804, 2689, 1730, 1454, 1367, 1329, 1256, 1150, 1119, 945, 863 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.35–0.42 (m, 1H, *c*Pr-H), 0.46–0.54 (m, 1H, *c*Pr-H), 0.57–0.64 (m, 1H, *c*Pr-H), 1.03 (d, *J*=6.6 Hz, 3H, CH_3), 1.08–1.17 (m, 1H, *c*Pr-H), 1.43 [s, 10H, $C(CH_3)_3$, 4- or 6-H*], 1.87 (t, *J*=12.9 Hz, 1H, 4- or 6-H), 2.20 (q, *J*=6.5 Hz, 1H, 1′-H), 2.31–2.42 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.57–2.68 (m, 1H, 5-H), 3.64 (t, *J*=4.6 Hz, 4H, CH_2OCH_2), 5.71 (t, *J*=3.6 Hz, 1H, 7-H). *The peak of this proton sits under the broad singlet of the *tert*-butyl group, thus the spin coupling constant of this proton could not be determined. This proton correlates clearly with the carbon peak at 38.14 ppm in the HMQC spectrum.^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.13 (−, *c*Pr-C), 12.43 (−, *c*Pr-C), 17.15 (+, CH_3), 18.63 (C_{quat}, *c*Pr-C), 28.01 [+, $C(CH_3)_3$], 28.01 (−, C-4 or -6), 38.14 (−, C-4 or -6), 39.85 (+, C-5), 50.47 (−, CH_2NCH_2), 58.58 (+, C-1′), 67.17 (−, CH_2OCH_2), 79.88 [C_{quat}, $C(CH_3)_3$], 120.68 (+, C-7), 140.58 (C_{quat}, C-8), 174.81 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 321 (49) [M^+], 306 (94) [M^+-CH_3], 250 (80) [$M^+-C_2H_5$], 133 (30), 114 (100), 100 (26), 86 (22); elemental analysis calcd (%) for $C_{19}H_{31}NO_3$: C 70.99, H 9.72; found: C 70.72, H 9.98. $C_{19}H_{31}NO_3$ (321.46): calcd 321.2304 (correct HRMS).

4.3.3. 4-[1-(7-Benzenesulfonylspiro[2.5]oct-4-en-4-yl)-ethyl]morpholine (25a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature phenyl vinyl sulfone (**16**, 672 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **25a** (450 mg, 62%, yellowish oil) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

Major diastereomer. R_f=0.45 (light petroleum/ethyl acetate, 1:1); IR (KBr): $\tilde{\nu}$=3064, 2972, 2955, 2856, 2814, 1448, 1311 (S=O), 1275 (S=O), 1152 (S=O), 1116 (S=O), 1023, 938, 861, 726 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.30–0.39 (m, 1H, *c*Pr-H), 0.52–0.62 (m, 1H, *c*Pr-H), 0.74–0.84 (m, 1H, *c*Pr-H), 0.92–1.00 (m, 1H, *c*Pr-H), 0.99 (d, *J*=6.3 Hz, 3H, CH_3), 1.38 (ddd, *J*=12.4, 2.7, 1.2 Hz, 1H, 6- or 8-H), 2.04–2.17 (m, 2H, 1′-H, 6- or 8-H), 2.29–2.41 (m, 6H, CH_2NCH_2, 6- or 8-H), 3.28–3.45 (m, 1H, 7-H), 3.65 (t, *J*=4.56 Hz, 4H, CH_2OCH_2), 5.72 (t, *J*=3.8 Hz, 1H, 5-H), 7.52–7.70 (m, 3H, Ph), 7.86–7.90 (m, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.74 (−, *c*Pr-C), 13.37 (−, *c*Pr-C), 17.34 (+, CH_3), 19.49 (C_{quat}, *c*Pr-C), 25.57 (−, C-6 or -8), 34.67 (−, C-6 or -8), 50.46 (−, CH_2NCH_2), 59.00 (+, C-1′), 59.77 (+, C-7), 66.99 (−, CH_2OCH_2), 118.60 (+, C-5), 128.71 (+, Ph-C), 128.99 (+, Ph-C), 133.56 (+, Ph-C), 137.02 (C_{quat}), 141.18 (C_{quat}); MS (70 eV, EI), *m/z* (%): 361 (11) [M^+], 346 (38) [M^+-CH_3], 204 (35), 117 (28), 114 (100), 91 (33); elemental analysis calcd (%) for $C_{20}H_{27}NO_3S$ (361.5): C 66.45, H 7.53; found: C 66.24, H 7.61.

Minor diastereomer. R_f=0.38 (light petroleum/ethyl acetate, 1:1); IR (film): $\tilde{\nu}$=3057, 2967, 2858, 2812, 1447, 1306 (S=O), 1273 (S=O), 1147 (S=O), 1114 (S=O), 944, 751, 725 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.24–0.38 (m, 1H, *c*Pr-H), 0.45–0.55 (m, 2H, *c*Pr-H), 0.92 (d, *J*=6.6 Hz, 3H, CH_3), 1.17–1.23 (m, 1H, *c*Pr-H), 1.33 (ddd, *J*=12.7, 2.7, 1.4 Hz, 1H, 6- or 8-H), 2.04 (t, *J*=12.1 Hz, 1H, 6- or 8-H), 2.16–2.45 (m, 7H, CH_2NCH_2, 1′-H, 6- or 8-H), 3.20–3.36 (m, 1H, 7-H), 3.54 (t, *J*=4.6 Hz, 4H, CH_2OCH_2), 5.72 (dd, *J*=5.5, 4.9 Hz, 1H, 5-H), 7.44–7.63 (m, 3H, Ph), 7.77–7.82 (m, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.83 (−, *c*Pr-C), 13.85 (−, *c*Pr-C), 16.31 (+, CH_3), 19.06 (C_{quat}, *c*Pr-C), 25.65 (−, C-6 or -8), 34.36 (−, C-8 or -6), 50.19 (−, CH_2NCH_2), 58.56 (+, C-1′), 59.67 (+, C-7), 67.25 (−, CH_2OCH_2), 120.09 (+, C-5), 128.82 (+, Ph-C), 129.13 (+, Ph-C), 133.68 (+, Ph-C), 137.23 (C_{quat}), 141.61 (C_{quat}); MS (70 eV, EI), *m/z* (%): 361 (13) [M^+], 346 (47) [M^+-CH_3], 204 (42), 117 (37), 114 (100), 91 (33) 77 (61); elemental analysis calcd (%) for $C_{20}H_{27}NO_3S$ (361.5): C 66.45, H 7.53; found: C 66.21, H 7.62.

4.3.4. 4,5-Dimethyl 8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-carboxylate (*cis*-/*trans*-26a). (a) According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 2 h. After cooling the mixture to room temperature, dimethyl fumarate (**17**, 576 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying over $MgSO_4$, the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield *cis*-/*trans*-**26a** (391.7 mg, 58%, yellowish oil) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

*Major and minor diastereomers**. R_f=0.27 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3083, 2953, 2850, 2809, 2691, 1739, 1466, 1349, 1265, 1197, 1172, 1119, 1021, 945, 918, 864 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.43–0.50 (m, 1H, *c*Pr-H), 0.59–0.68 (m, 3H, *c*Pr-H), 0.70–0.81 (m, 2H, *c*Pr-H), 0.93–0.99 (m, 2H, *c*Pr-H), 1.04 (d, *J*=6.5 Hz, 3H, CH_3), 1.04 (d, *J*=6.5 Hz, 3H, CH_3), 2.08 (q, *J*=6.7 Hz, 1H, 1′-H), 2.19–2.52 (m, 13H, 2×

(CH_2NCH_2), 2×6-H, 1′-H), 2.58 (d, J=4.3 Hz, 1H, 4-H), 2.82 (d, J=7.3 Hz, 1H, 4-H), 3.12 (q, J=7.0 Hz, 1H, 5-H), 3.21–3.26 (m, 1H, 5-H), 3.62–3.68 (m, 8H, 2×CH_2OCH_2), 3.65 (s, 3H, OCH_3), 3.67 (s, 9H, 3×OCH_3), 5.75 (q, J= 3.5 Hz, 2H, 2×7-H); ^{13}C NMR (75.5 MHz, $CDCl_3$, DEPT): δ=9.77 (−, *c*Pr-C), 9.86 (−, *c*Pr-C), 10.65 (−, *c*Pr-C), 11.61 (−, *c*Pr-C), 16.95 (+, CH_3), 17.22 (+, CH_3), 18.61 (C_{quat}, *c*Pr-C), 19.29 (C_{quat}, *c*Pr-C), 24.51 (−, C-6), 26.51 (−, C-6), 40.56 (+, C-5), 41.33 (+, C-5), 49.77 (+, C-4), 50.52 (−, CH_2NCH_2), 50.66 (−, CH_2NCH_2), 50.77 (+, C-4), 51.59 (+, 4×OCH_3), 58.93 (+, C-1′), 59.56 (+, C-1′), 67.22 (−, 2×CH_2OCH_2), 120.04 (+, C-7), 121.09 (+, C-7), 138.76 (C_{quat}, C-8), 139.65 (C_{quat}, C-8), 173.11 (C_{quat}, C=O), 173.24 (C_{quat}, C=O), 174.04 (C_{quat}, C=O), 174.72 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 337 (10) [M^+], 322 (47) [M^+-CH_3], 262 (5), 191 (11), 131 (24), 114 (100), 91 (24) 59 (26); elemental analysis calcd (%) for $C_{18}H_{27}NO_5$ (337.4): C 64.07, H 8.07; found: C 64.26, H 7.86. *Proton and carbon chemical shifts were given for both diastereomers together because ^{1}H NMR and ^{13}C NMR spectra were not proper to classify all of the peaks for major and minor diastereomers. IR, EI mass and elemental analysis were carried out for the mixture of diastereomers.

(b) From the same quantities of reagents, but dimethyl maleate (**18**) instead of dimethyl fumarate (**17**), compound *cis*-/*trans*-**26a** (351 mg, 52%) was obtained as a mixture of two diastereomers (ratio 1.7:1 according to NMR) according to GP-B after column chromatography.

4.3.5. *tert*-Butyl 8-(1-piperidin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (24b). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), piperidine (**12b**, 170.3 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 1:1) to yield **24b** (209 mg, 33%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. R_f=0.28 (light petroleum/ethyl acetate, 1:1); IR (film): $\tilde{\nu}$=3075, 2975, 2932, 2852, 2793, 2747, 1729, 1456, 1391, 1367, 1320, 1255, 1153, 1060, 932, 851 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.29–0.34 (m, 1H, *c*Pr-H), 0.45–0.49 (m, 1H, *c*Pr-H), 0.82–0.91 (m, 2H, *c*Pr-H), 0.99 (d, J=6.7 Hz, 3H, CH_3), 1.13–1.19 (m, 1H, 4- or 6-H), 1.36–1.51 (m, 6H, piperidine), 1.43 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=11.9 Hz, 1H, 4- or 6-H), 2.19–2.45 (m, 7H, 4- or 6-H, piperidine, 1′-H), 2.58–2.71 (m, 1H, 5-H), 5.68–5.71 (m, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.77 (−, *c*Pr-C), 13.70 (−, *c*Pr-C), 16.41 (+, CH_3), 19.91 (C_{quat}, *c*Pr-C), 24.75 (−, piperidine), 26.19 (−, piperidine), 28.02 [+, $C(CH_3)_3$], 28.64 (−, C-4 or -6), 38.79 (−, C-4 or -6), 40.41 (+, C-5), 50.91 (−, piperidine), 59.49 (+, C-1′), 79.71 [C_{quat}, $C(CH_3)_3$], 120.29 (+, C-7), 141.16 (C_{quat}, C-8), 175.21 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 319 (18) [M^+], 304 (58) [M^+-CH_3], 248 (60), 234 (12), 112 (100), 84 (26); elemental analysis calcd (%) for $C_{20}H_{33}NO_2$ (319.5): C 75.19, H 10.41; found: C 74.97, H 10.66.

Diastereomer II. R_f=0.18 (light petroleum/ethyl acetate 1:1); IR (film): $\tilde{\nu}$=3078, 2975, 2932, 2852, 2790, 2748, 1729, 1456, 1391, 1367, 1332, 1257, 1153, 1117, 933, 850 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.27–0.34 (m, 1H, *c*Pr-H), 0.40–0.48 (m, 1H, *c*Pr-H), 0.51–0.58 (m, 1H, *c*Pr-H), 0.98 (d, J=6.7 Hz, 3H, CH_3), 1.09–1.19 (m, 1H, *c*Pr-H), 1.29–1.51 (m, 7H, 4- or 6-H, piperidine), 1.37 [s, 9H, $C(CH_3)_3$], 1.79–1.89 (m, 1H, 4- or 6-H), 2.18–2.40 (m, 7H, 4- or 6-H, piperidine, 1′-H), 2.51–2.63 (m, 1H, 5-H), 5.68 (d, J= 3.9 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.24 (−, *c*Pr-C), 12.60 (−, *c*Pr-C), 16.36 (C_{quat}, *c*Pr-C), 18.76 (+, CH_3), 24.62 (−, piperidine), 26.12 (−, piperidine), 27.94 [+, $C(CH_3)_3$], 28.09 (−, C-4 or -6), 38.25 (−, C-4 or -6), 39.92 (+, C-5), 50.75 (−, piperidine), 58.76 (+, C-1′), 79.68 [C_{quat}, $C(CH_3)_3$], 121.45 (+, C-7), 141.00 (C_{quat}, C-8), 174.87 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 319 (18) [M^+], 304 (58) [M^+-CH_3], 248 (60), 234 (12), 112 (100), 84 (26); elemental analysis calcd (%) for $C_{20}H_{33}NO_2$ (319.5): C 75.19, H 10.41; found: C 74.97, H 10.66.

4.3.6. *tert*-Butyl 8-(1-pyrrolidin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (24c). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), pyrrolidine (**12c**, 142 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate/methanol 3:1:1) to yield **24c** (176 mg, 29%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. R_f=0.33 (light petroleum/ethyl acetate/methanol, 3:1:1); IR (film): $\tilde{\nu}$=3075, 2971, 2932, 2875, 2776, 2712, 1728, 1478, 1457, 1256, 1152, 985, 850 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.34–0.38 (m, 1H, *c*Pr-H), 0.46–0.49 (m, 1H, *c*Pr-H), 0.62–0.66 (m, 1H, *c*Pr-H), 0.80–0.84 (m, 1H, *c*Pr-H), 1.07 (d, J=6.2 Hz, 3H, CH_3), 1.14–1.17 (m, 1H, 4- or 6-H), 1.39 [s, 9H, $C(CH_3)_3$], 1.66–1.71 (m, 4H, pyrrolidine), 1.81 (q, J=6.11 Hz, 1H, 1′-H), 1.96 (td, J=1.8, 12.5 Hz, 1H, 4- or 6-H), 2.21 (ddd, J=17.5, 11.5, 2.5 Hz, 1H, 4- or 6-H), 2.33–2.38 (m, 3H, 4- or 6-H, pyrrolidine), 2.42–2.44 (m, 2H, pyrrolidine), 2.55–2.60 (m, 1H, 5-H), 5.79 (dd, J=2.4, 4.9 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.59 (−, *c*Pr-C), 13.17 (−, *c*Pr-C), 18.66 (C_{quat}, *c*Pr-C), 22.72 (+, CH_3), 23.35 (−, pyrrolidine), 28.04 [+, $C(CH_3)_3$], 28.55 (−, C-4 or -6), 38.30 (−, C-4 or -6), 40.43 (+, C-5), 52.66 (−, pyrrolidine), 59.31 (+, C-1′), 79.78 [C_{quat}, $C(CH_3)_3$], 119.74 (+, C-7), 142.42 (C_{quat}, C-8), 175.16 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 305 (20) [M^+], 290 (56) [M^+-CH_3], 234 (44), 220 (10), 98 (100), 70 (22); elemental analysis calcd (%) for $C_{19}H_{31}NO_2$ (305.5): C 74.71, H 10.23; found: C 74.41, H 10.01.

Diastereomer II. R_f=0.25 (light petroleum/ethyl acetate/methanol, 3:1:1); IR (film): $\tilde{\nu}$=3078, 2971, 2875, 2776, 2710, 1728, 1478, 1457, 1391, 1367, 1256, 1054, 947, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.36–0.42 (m, 1H, *c*Pr-H), 0.44–0.51 (m, 1H, *c*Pr-H), 0.55–0.61 (m, 1H, *c*Pr-H), 0.96–1.03 (m, 1H, *c*Pr-H), 1.07 (d, J=6.5 Hz, 3H, CH_3), 1.40–1.47 (m, 1H, 4- or 6-H), 1.41 [s, 9H, $C(CH_3)_3$], 1.67–1.71 (m, 4H, pyrrolidine), 1.82–1.89 (m, 1′ H, 4- or 6-H), 1.98 (q, J=6.4 Hz, 1H, 1′-H), 2.27–2.34 (m, 2H, 4- or 6-H), 2.43–2.54 (m, 4H, pyrrolidine), 2.54–2.63 (m, 1H, 5-H), 5.79 (t, J=4.0 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.11 (−, *c*Pr-C), 12.27 (−, *c*Pr-C), 18.42 (C_{quat}, *c*Pr-C), 22.64 (+, CH_3), 23.33 (−, pyrrolidine), 28.03 [+, $C(CH_3)_3$], 38.07 (−, C-4 or -6), 39.88 (+, C-5), 52.67 (−, pyrrolidine), 58.19 (+, C-1′), 79.80 [C_{quat}, $C(CH_3)_3$], 120.97 (+, C-7), 142.54 (C_{quat}, C-8), 174.86 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 305 (4) [M^+], 290 (24) [M^+-CH_3], 234 (28), 220 (12), 98 (100), 70 (35), 57 (30), 41 (18); elemental analysis calcd (%) for $C_{19}H_{31}NO_2$ (305.5): C 74.71, H 10.23; found: C 74.41, H 10.01.

4.3.7. *tert*-Butyl 8-[1-(4-benzylpiperazin-1-yl)ethyl] spiro[2.5]oct-7-ene-5-carboxylate (24d). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), *N*-benzylpiperazine (**12d**, 352.5 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **24d** (395 mg, 48%, yellowish oil) as a mixture of two diastereomers (ratio 1.1:1 according to NMR).

Major diastereomer. R_f=0.39 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3063, 2975, 2932, 2808, 2689, 1727, 1495, 1391, 1367, 1330, 1258, 1153, 1013, 910, 849, 823, 734 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.33–0.40 (m, 1H, *c*Pr-H), 0.45–0.52 (m, 1H, *c*Pr-H), 0.56–0.64 (m, 1H, *c*Pr-H), 1.03 (d, J=6.6 Hz, 3H, CH_3), 1.11–1.18 (m, 1H, *c*Pr-H), 1.36–1.43 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.88 (t, J=11.6 Hz, 1H, 4- or 6-H), 2.09 (q, J=6.2 Hz, 1H, 1′-H), 2.31–2.42 (m, 10H, piperazine, 4- or 6-H), 2.56–2.67 (m, 1H, 5-H), 3.48 (s, 2H, Bn), 5.68 (t, J=3.8 Hz, 1H, 7-H), 7.21–7.30 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.11 (−, *c*Pr-C), 12.61 (−, *c*Pr-C), 17.37 (+, CH_3), 18.73 (C_{quat}, *c*Pr-C), 28.03 [+, $C(CH_3)_3$], 28.12 (−, C-4 or -6), 38.30 (−, C-4 or -6), 39.99 (+, C-5), 49.81 (−, piperazine), 53.51 (−, piperazine), 58.23 (+, C-1′), 63.10 (−, Bn), 79.77 [C_{quat}, $C(CH_3)_3$], 121.5 (+, C-7), 126.87 (+, Ph-C), 128.08 (+, Ph-C), 129.21 (+, Ph-C), 138.21 (C_{quat}), 141.16 (C_{quat}), 174.88 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 410 (26) [M^+], 395 (6) [M^+-CH_3], 203 (10), 175 (100), 91 (42); elemental analysis calcd (%) for $C_{26}H_{38}N_2O_2$ (410.6): C 76.06, H 9.33; found: C 75.81, H 9.14.

Minor diastereomer. R_f=0.55 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3063, 3026 2974, 2931, 2807, 1727, 1495, 1455, 1391, 1367, 1318, 1256, 1150, 1013, 906, 849, 825, 736 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.29–0.35 (m, 1H, *c*Pr-H), 0.47–0.52 (m, 1H, *c*Pr-H), 0.80–0.89 (m, 2H, *c*Pr-H), 1.02 (d, J=6.4 Hz, 3H, CH_3), 1.15–1.21 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=12.30 Hz, 1H, 4- or 6-H), 2.17 (q, J=6.42 Hz, 1H, 1′-H), 2.24–2.56 (m, 10H, piperazine, 4- or 6-H), 2.56–2.68 (m, 1H, 5-H), 3.48 (s, 2H, Bn), 5.73 (t, J=3.8 Hz, 1H, 7-H); 7.21–7.30 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.79 (−, *c*Pr-C), 13.38 (−, *c*Pr-C), 17.71 (+, CH_3), 19.62 (C_{quat}, *c*Pr-C), 28.05 [+, $C(CH_3)_3$], 28.59 (−, C-4 or -6), 38.68 (−, C-4 or -6), 40.41 (+, C-5), 49.99 (−, piperazine), 53.43 (−, piperazine), 58.88 (+, C-1′), 63.09 (−, Bn), 79.76 [C_{quat}, $C(CH_3)_3$], 120.48 (+, C-7), 126.88 (+, Ph-C), 128.09 (+, Ph-C), 129.18 (+, Ph-C), 138.22 (C_{quat}), 141.04 (C_{quat}), 175.09 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 410 (36) [M^+], 395 (8) [M^+-CH_3], 337 (19), 203 (14), 175 (100), 91 (35); elemental analysis calcd (%) for $C_{26}H_{38}N_2O_2$ (410.6): C 76.06, H 9.33; found: C 75.81, H 9.14.

4.3.8. *tert*-Butyl 4-[1-(7-*tert*-butoxycarbonylspiro[2.5] oct-4-en-4-yl)ethyl]piperazinecarboxylate (24e). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), *N*-Boc-piperazine (**12e**, 372 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 2 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **24e** (410.7 mg, 49%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. R_f=0.54 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3076, 2976, 2931, 2814, 1727, 1698, 1455, 1422, 1366, 1291, 1248, 1170, 1003, 923, 733 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.31–0.38 (m, 1H, *c*Pr-H), 0.47–0.54 (m, 1H, *c*Pr-H), 0.77–0.92 (m, 2H, *c*Pr-H), 1.02 (d, J=6.4 Hz, 3H, CH_3), 1.16–1.21 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.44 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=12.3 Hz, 1H, 4- or 6-H), 2.18 (q, J=6.3 Hz, 1H, 1′-H), 2.25–2.38 (m, 6H; piperazine, 4- or 6-H), 2.57–2.69 (m, 1H, 5-H), 3.35 (t, J=4.8 Hz, 4H, piperazine), 5.75 (dd, J=2.7, 4.6 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.65 (−, *c*Pr-C), 13.19 (−, *c*Pr-C), 17.22 (+, CH_3), 19.46 (C_{quat}, *c*Pr-C), 27.85 [+, $C(CH_3)_3$], 28.21 [+, $C(CH_3)_3$], 28.39 (−, C-4 or -6), 38.41 (−, C-4 or -6), 40.13 (+, C-5), 43.19 (−, piperazine)*, 49.59 (−, piperazine), 58.60 (+, C-1′), 79.08 [C_{quat}, $C(CH_3)_3$], 79.58 [C_{quat}, $C(CH_3)_3$], 120.63 (+, C-7), 140.59 (C_{quat}), 154.51 (C_{quat}, C=O). 174.79 (C_{quat}, C=O); *It appears as a multiplet of low intensity. This carbon correlates clearly with the triplet at 3.35 ppm in the HMQC spectrum. MS (70 eV, EI), *m/z* (%): 420 (3) [M^+], 397 (8), 284 (17), 213 (52), 157 (100), 57 (48), 41 (14); elemental analysis calcd

(%) for $C_{24}H_{40}N_2O_4$ (420.6): C 68.54, H 9.59; found: C 68.30, H 9.42.

Diastereomer II. R_f=0.48 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3078, 2975, 2931, 2811, 2756, 1727, 1699, 1455, 1422, 1366, 1291, 1248, 1167, 1003, 923, 733 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.34–0.42 (m, 1H, *c*Pr-H), 0.46–0.54 (m, 1H, *c*Pr-H), 0.56–0.64 (m, 1H, *c*Pr-H), 1.02 (d, J=6.6 Hz, 3H, CH_3), 1.08–1.21 (m, 1H, *c*Pr-H), 1.38–1.44 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.44 [s, 9H, $C(CH_3)_3$], 1.88 (dd, J=10.7, 12.8 Hz, 1H, 4- or 6-H), 2.22–2.43 (m, 7H, piperazine, 4- or 6-H, 1′-H), 2.57–2.69 (m, 1H, 5-H), 3.35 (t, J=4.9 Hz, 4H, piperazine), 5.68 (t, J=3.8 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.10 (−, *c*Pr-C), 12.39 (−, *c*Pr-C), 16.43 (+, CH_3), 18.51 (C_{quat}, *c*Pr-C), 27.89 [+, $C(CH_3)_3$], 27.89 (−, C-4 or -6), 28.27 [+, $C(CH_3)_3$], 38.09 (−, C-4 or -6), 39.75 (+, C-5), 43.58 (−, piperazine)*, 49.32 (−, piperazine), 59.74 (+, C-1′), 79.14 [C_{quat}, $C(CH_3)_3$], 79.69 [C_{quat}, $C(CH_3)_3$], 121.65 (+, C-7), 140.58 (C_{quat}), 154.61 (C_{quat}, C=O), 174.64 (C_{quat}, C=O). *It appears as a multiplet of low intensity. This carbon correlates clearly with the triplet at 3.35 ppm in the HMQC spectrum. MS (70 eV, EI), *m/z* (%): 420 (13) [M^+], 405 (18) [M^+-CH_3], 293 (22), 279 (10), 213 (18), 157 (32), 133 (50), 57 (100), 41 (34); elemental analysis calcd (%) for $C_{24}H_{40}N_2O_4$ (420.6): C 68.54, H 9.59; found: C 68.30, H 9.42.

4.3.9. 5-[1′-(Morpholin-4″-yl)ethyl]-2-phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (27a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, 1-phenyl-pyrrole-2,5-dione (**19**, 693 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **27a** (290 mg, 40%, yellow solid) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. Mp 127 °C, R_f=0.42 (light petroleum/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=3087, 3022, 2955, 2906, 2847, 2809, 1708, 1595, 1494, 1456, 1435, 1368, 1298, 1183, 1170, 1135, 1111, 855, 759 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.300.34 (m, 1H, *c*Pr-H), 0.72–0.80 (m, 1H, *c*Pr-H), 1.58 (d, J=6.7 Hz, 3H, CH_3), 1.20–1.26 (m, 1H, *c*Pr-H), 1.75–1.83 (m, 1H, *c*Pr-H), 2.21–2.47 (m, 6H, CH_2NCH_2, 3a-H, 7-H), 2.65 (q, J=6.7 Hz, 1H, 1′-H), 2.81 (ddd, J=2.0, 7.2, 14.8 Hz, 1H, 7-H), 3.29–3.36 (m, 1H, 7a-H), 3.50 (t, J=4.6 Hz, 4H, CH_2OCH_2), 5.85 (dd, J=2.9, 6.9 Hz, 1H, 6-H), 7.18–7.21 (m, 2H, Ph), 7.32–7.45 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.65 (−, *c*Pr-C), 13.04 (−, *c*Pr-C), 15.04 (+, CH_3), 20.05 (C_{quat}, *c*Pr-C), 24.19 (−, C-7), 41.59 (+, C-3a), 50.19 (+, C-7a), 50.57 (−, CH_2NCH_2), 64.02 (+, C-1′), 66.96 (−, CH_2OCH_2), 125.95 (+, Ph-C, C-6), 128.26 (+, Ph), 128.88 (+, Ph-C), 131.89 (C_{quat}), 144.11 (C_{quat}), 177.07 (C_{quat}, C=O), 178.88 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 366 (46) [M^+], 351 (93) [M^+-CH_3], 152 (6), 133 (8), 117 (18), 114 (100), 91 (16), 86 (27); elemental analysis calcd (%) for $C_{22}H_{26}N_2O_3$ (366.5): C 72.11, H 7.15; found: C 71.96, H 7.02.

Diastereomer II. Mp 140 °C, R_f=0.38 (light petroleum/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=3064, 2965, 2891, 2846, 2815, 1773, 1702, 1597, 1500, 1455, 1435, 1390, 1301, 1189, 1172, 1115, 1040, 944, 923, 754 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.35–0.43 (m, 1H, *c*Pr-H), 0.79–0.87 (m, 1H, *c*Pr-H), 0.98 (d, J=6.7 Hz, 3H, CH_3), 1.06–1,18 (m, 1H, *c*Pr-H), 1.47–1.55 (m, 1H, *c*Pr-H), 2.31–2.50 (m, 6H, CH_2NCH_2, 3a-H, 7-H), 2.80–2.92 (m, 2H, 1′-H, 7-H), 3.32–3.40 (m, 1H, 7a-H), 3.52–3.63 (m, 4H, CH_2OCH_2), 5.93 (br s, 1H, 6-H), 7.13–7.17 (m, 2H, Ph), 7.34–7.45 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.71 (−, *c*Pr-C), 11.87 (+, CH_3), 12.73 (−, *c*Pr-C), 22.29 (C_{quat}, *c*Pr-C), 24.56 (−, C-7), 41.60 (+, C-7a), 49.16 (−, CH_2NCH_2), 50.05 (+, C-3a), 60.80 (+, C-1′), 67.28 (−, CH_2OCH_2), 123.30 (+, C-6), 126.33 (+, Ph-C), 128.49 (+, Ph-C), 129.05 (+, Ph-C), 131.98 (C_{quat}), 143.59 (C_{quat}), 177.74 (C_{quat}, C=O), 178.96 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 366 (25) [M^+], 351 (77) [M^+-CH_3], 133 (6), 114 (100), 86 (16); elemental analysis calcd (%) for $C_{22}H_{26}N_2O_3$ (366.5): C 72.11, H 7.15; found: C 71.96, H 7.02.

4.3.10. 5-[1′-(Morpholin-4″-yl)ethyl]-2-(3‴-trifluoromethyl)phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (28a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature 1-(3′-trifluoromethylphenyl)-2,5-dihydro-pyrrole-2,5-dione (**20**, 965 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 2:3) to yield **28a** (327.4 mg, 38%, pale yellow solid) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

Major diastereomer. Mp 147 °C; R_f=0.51 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=3067 (C–H), 1721 (C=O), 1705, 1616, 1526, 1415, 1340, 1223, 1163 (C–F), 1129, 1110, 1071, 842, 824, 818 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.30–0.44 (m, 1H, *c*Pr-H), 0.74–0.89 (m, 1H, *c*Pr-H), 1.06 (d, J=6.9 Hz, 3H, CH_3), 1.19–1.33 (m, 1H, *c*Pr-H), 1.82 (m_c, 1H, *c*Pr-H), 2.19–2.39 (m, 4H, CH_2NCH_2), 2.35 (d, J=9.1 Hz, 1H, 3a-H), 2.45 (ddd, J=15.0, 6.6, 3.3 Hz, 1H, 7-H), 2.67 (q, ^3J=6.9 Hz, 1H, 1′-H), 2.84 (ddd, J=15.0, 6.9, 1.8 Hz, 1H, 7-H), 3.33–3.45 (m, 1H, 7a-H), 3.45–3.59 (m, 4H, CH_2OCH_2), 5.86 (dd, J=7.3, 3.3 Hz, 1H, 6-H), 7.40–7.75 (m, 4H, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.73 (−, *c*Pr-C), 13.3 (−, *c*Pr-C), 15.0 (+, CH_3), 20.6 (C_{quat}, C-4), 24.2 (−, C-7), 41.7 (+, C-7a), 50.3 (+, C-1′), 50.6 (−, CH_2NCH_2), 63.9 (+, C-3a), 67.0 (−, CH_2OCH_2), 123.0 (+, C-6), 123.5 (C_{quat}, q, ^1J(C,F)=247 Hz, CF_3), 125.0 (+, C-5‴), 125.5 (+, Ar-C), 125.9 (+, Ar-C), 129.2 (+, Ar-C), 131.4 (C_{quat},

q, ^2J(C,F)=33.3 Hz, C-3‴), 132.4 (C_{quat}, Ar-C), 144.2 (C_{quat}, C-5), 176.8 (C_{quat}, C=O), 178.5 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 434 (48) [M^+], 419 (100) [M^+-CH_3], 114 (100), 86 (14) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+] 434.1817, correct HRMS.

Minor diastereomer. Mp 146 °C; R_f=0.44 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=3068 (C–H), 1723 (C=O), 1702, 1618, 1529, 1413, 1342, 1225, 1164 (C–F), 1126, 1113, 1074, 841, 823, 817 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.35 (m_c, 1H, *c*Pr-H), 0.74–0.85 (m, 1H, *c*Pr-H), 1.05 (d, ^3J=6.7 Hz, 3H, CH_3), 1.18–1.31 (m, 1H, *c*Pr-H), 1.81 (m_c, 1H, *c*Pr-H), 2.17–2.39 (m, 5H, CH_2NCH_2, 3a-H), 2.45 (ddd, *J*=15.0, 6.6, 3.3 Hz, 1H, 7-H), 2.67 (q, *J*=6.90 Hz, 1H, 1′-H) 2.83 (ddd, *J*=15.0, 6.9, 1.8 Hz, 1H, 7-H), 3.39 (m_c, 1H, 7a-H), 3.44–3.57 (m, 4H, CH_2OCH_2), 5.87 (dd, *J*=7.3, 3.4 Hz, 1H, 6-H), 7.39–7.70 (m, 4H, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.68 (−, *c*Pr-C), 11.8 (+, CH_3), 12.8 (−, *c*Pr-C), 22.9 (C_{quat}, C-4), 24.5 (−, C-7), 41.6 (+, C-7a), 49.1 (−, CH_2NCH_2), 50.1 (+, C-1′), 60.7 (+, C-3a), 67.3 (−, CH_2OCH_2), 123.2 (+, C-6), 123.4 (C_{quat}, q, ^1J(C,F)=245 Hz, CF_3), 125.1 (+, Ar-C), 125.2 (+, Ar-C), 129.5 (+, Ar-C), 129.6 (+, Ar-C), 131.8 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-3‴), 132.4 (C_{quat}, Ar-C), 143.7 (C_{quat}, C-5), 177.4 (C_{quat}, C=O), 178.6 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 434 (48) [M^+], 419 (100) [M^+-CH_3], 114 (100), 86 (14) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+]: 434.1817, correct HRMS.

4.3.11. 5-[1′-(Morpholin-4″-yl)ethyl]-2-(4‴-trifluoromethyl)phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (29a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature 1-(4′-trifluoromethylphenyl)-2,5-dihydropyrrole-2,5-dione (**21**, 965 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (130 g, 3×40 cm, light petroleum/ethyl acetate 2:3) to yield **29a** (384 mg, 44%, pink crystals) as a mixture of two diastereomers (ratio 1.1:1, according to NMR).

Major diastereomer. Mp 158 °C; R_f=0.51 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=2966, 2852, 1714 (C=O), 1616, 1519, 1384 (CH_3), 1326, 1172 (C–F), 1115, 1067, cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.41 (m_c, 1H, *c*Pr-H), 0.79–0.90 (m, 1H, *c*Pr-H), 0.97 (d, *J*=6.8 Hz, 3H, CH_3), 1.04–1.20 (m, 1H, *c*Pr-H), 1.52 (m_c, 1H, *c*Pr-H), 2.31–2.41 (m, 4H, CH_2NCH_2), 2.41–2.47 (m, 1H, 3a-H), 2.47–2.54 (m, 2H, 1′-H, 7-H), 2.86 (m_c, 1H, 7-H), 3.37 (m_c, 1H, 7a-H), 3.61 (m_c, 4H, CH_2OCH_2), 5.94 (d, *J*=7.3, 3.1 Hz, 1H, 6-H), 7.36 (d, *J*=8.5 Hz, 2H, Ar), 7.70 (d, *J*=8.5 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.66 (−, *c*Pr-C), 11.9 (+, CH_3), 12.8 (−, *c*Pr-C), 22.8 (C_{quat}, C-4), 24.4 (−, C-7), 41.6 (+, C-7a), 49.1 (−, CH_2NCH_2), 50.1 (+, C-1′), 60.7 (+, C-3a), 67.3 (−, CH_2OCH_2), 123.2 (+, C-6), 126.1 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-4‴), 126.5 (+, 4×Ar-C), 127.8 (C_{quat}, q, ^1J(C,F)=272 Hz, CF_3), 135.0 (C_{quat}, Ar-C), 143.8 (C_{quat}, C-5), 177.8 (C_{quat}, C=O), 178.7 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 435/434 (10/42) [M^+], 420/419 (22/89) [M^+-CH_3], 117 (13), 114 (100), 91 (12), 86 (13) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+]: 434.1817, correct HRMS.

Minor diastereomer. Mp 149 °C; R_f=0.57 (light petroleum/ethyl acetate 2:3); IR (KBr): $\tilde{\nu}$=2958, 2853, 2810, 1710 (C=O), 1702 (C=O), 1613, 1518, 1384 (CH_3), 1325, 1173 (C–F), 1124, 1066, 1020, 845 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.36 (m_c, 1H, *c*Pr-H), 0.80 (m_c, 1H, *c*Pr-H), 1.06 (d, *J*=6.7 Hz, 3H, CH_3), 1.19–1.31 (m, 1H, *c*Pr-H), 1.85 (m_c, 1H, *c*Pr-H), 2.19–2.40 (m, 4H, CH_2NCH_2), 2.36 (d, *J*=9.2 Hz, 1H, 3a-H), 2.46 (ddd, *J*=15.0, 6.6, 3.3 Hz, 1H, 7-H), 2.67 (q, *J*=6.7 Hz, 1H, 1′-H), 2.84 (ddd, *J*=15.0, 6.9, 1.8 Hz, 1H, 7-H), 3.39 (m_c, 1H, 7a-H), 3.52 (m_c, 4H, CH_2OCH_2), 5.87 (dd, *J*=7.4, 2.9 Hz, 1H, 6-H), 7.42 (d, *J*=8.5 Hz, 2H, Ar), 7.70 (d, *J*=8.5 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.72 (−, *c*Pr-C), 13.3 (−, *c*Pr-C), 15.2 (+, CH_3), 20.6 (C_{quat}, C-4), 24.6 (−, C-7), 41.8 (+, C-7a), 50.4 (+, C-1′), 50.7 (−, CH_2NCH_2), 64.2 (+, C-3a), 67.0 (−, CH_2OCH_2), 126.1 (+, C-6), 126.1 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-4‴), 126.2 (+, 4×Ar), 127.8 (C_{quart}, q, ^1J(C,F)=272 Hz, CF_3), 135.0 (C_{quat}, Ar-C), 144.3 (C_{quat}, C-5), 176.8 (C_{quat}, C=O), 178.5 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 435/434 (10/42) [M^+], 420/419 (22/89) [M^+-CH_3], 117 (13), 114 (100), 91 (12), 86 (13) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+]: 434.1817, correct HRMS.

4.3.12. 5-[1′-(Morpholin-4″-yl)ethyl]-2-[bis-(3‴,5‴-trifluoromethyl)]phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (30a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, 1-[3′,5′-bis(trifluoromethyl)phenyl]-2,5-dihydropyrrole-2,5-dione (**22**, 1236 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (130 g, 3×40 cm, light petroleum/ethyl acetate, 2:3) to yield **30a** (376 mg, 37%, pale yellow crystals) as a mixture of two diastereomers (ratio 1.6:1, according to NMR).

Major diastereomer. Mp 94 °C; R_f=0.60 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=2962, 1791 (C=O), 1628, 1472, 1395 (C–F), 1280, 1176 (C–F), 1137, 892 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.37 (m_c, 1H, *c*Pr-H), 0.82 (m_c, 1H, *c*Pr-H), 1.05 (d, *J*=6.7 Hz, 3H, CH_3), 1.19–1.30 (m, 1H, *c*Pr-H), 1.76–1.90 (m, 1H, *c*Pr-H), 2.19–2.43 (m, 5H, 3a-H, CH_2NCH_2), 2.43–2.55 (m, 1H, 7-H), 2.66 (q, ^3J=6.7 Hz, 1H, 1′-H), 2.84 (ddd, *J*=15.0, 7.8, 1.8 Hz, 1H, 7-H), 3.41 (m_c, 1H, 7a-H), 3.50 (m_c, 4H, CH_2OCH_2), 5.94 (dd, *J*=7.3, 3.2 Hz, 1H, 6-H), 7.75 (s, 2H, Ar), 7.86 (s, 1H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.74 (−, *c*Pr-C), 11.8 (+, CH_3), 13.0 (−, *c*Pr-C), 22.9 (C_{quat}, C-4), 24.5 (−, C-7), 41.7 (+, C-7a), 49.1 (−, CH_2NCH_2), 50.2

(+, C-1′), 60.7 (+, C-3a), 67.2 (−, CH_2OCH_2), 121.9 (+, Ar-C), 122.7 (C_{quat}, q, ^1J(C,F)=271 Hz, 2×CF_3), 123.2 (+, C-6), 126.3 (+, 2×Ar-C), 132.4 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-3‴, C-5‴), 133.4 (C_{quat}, Ar-C), 143.9 (C_{quat}, C-5), 177.0 (C_{quat}, C=O), 178.2 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 502 (27) [M^+], 488/487 (24/100) [M^+-CH_3], 229 (13), 114 (48), 43 (35); HRMS (EI): calcd for $C_{24}H_{24}F_6N_2O_3$ [M^+]: 502.1691, correct HRMS.

Minor diastereomer. Mp 69 °C; R_f=0.59 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=3105 (C–H), 2967, 1720 (C=O), 1627, 1472, 1396 (C–F), 1280, 1176 (C–F), 1135, 892 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.43 (m_c, 1H, *c*Pr-H), 0.77–0.93 (m, 1H, *c*Pr-H), 0.96 (d, *J*=6.8 Hz, 3H, CH_3), 1.02–1.18 (m, 1H, *c*Pr-H), 1.55 (m_c, 1H, *c*Pr-H), 2.20–2.42 (m, 5H, 3a-H, CH_2NCH_2), 2.44–2.59 (m, 1H, 7-H), 2.80–2.94 (m, 2H, 1′-H, 7-H), 3.43 (m_c, 1H, 7a-H), 3.56–3.70 (m, 4H, CH_2OCH_2), 5.88 (dd, *J*=7.1, 3.2 Hz, 1H, 6-H), 7.75 (br s, 1H, Ar), 7.80 (br s, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.87 (−, *c*Pr-C), 12.1 (+, CH_3), 12.8 (−, *c*Pr-C), 22.9 (C_{quat}, C-4), 24.5 (−, C-7), 41.8 (+, C-3a), 49.2 (−, CH_2NCH_2), 50.2 (+, C-1′), 60.9 (+, C-7a), 67.1 (−, CH_2OCH_2), 119.3 (+, Ar-C), 122.1 (+, C-6), 122.7 (C_{quat}, q, ^1J(C,F)=273 Hz, 2×CF_3), 126.4 (+, 2×Ar-C), 132.4 (C_{quat}, q, ^2J(C,F)=33.5 Hz, C-3‴, C-5‴), 133.3 (C_{quat}, Ar-C), 139.3 (C_{quat}, C-5), 177.0 (C_{quat}, C=O), 178.1 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 502 (27) [M^+], 488/487 (24/100) [M^+-CH_3], 229 (13), 114 (48), 43 (35); HRMS (EI): calcd for $C_{24}H_{24}F_6N_2O_3$ [M^+]: 502.1691, correct HRMS).

4.3.13. *tert*-Butyl 8-(1-morpholin-4-ylethyl)-7-phenylspiro[2.5]oct-7-ene-5-carboxylate (39a). (a) According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 261 mg, 3.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 3 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 100 °C for 65 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 10:1) to yield **39a** (286 mg, 36%, yellowish oil) as a mixture of two diastereomers (ratio 1.1:1 according to NMR).

Major diastereomer. R_f=0.48 (light petroleum/ethyl acetate, 10:1); IR (film): $\tilde{\nu}$=3003, 2980, 2951, 2853, 2803, 1723, 1450, 1263, 1149, 1113, 943, 849, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.29–0.36 (m, 1H, *c*Pr-H), 0.59–0.66 (m, 1H, *c*Pr-H), 0.83–0.95 (m, 1H, *c*Pr-H), 1.05–1.13 (m, 1H, 4- or 6-H), 1.11 (d, *J*=7.0 Hz, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$), 1.63–1.70 (m, 1H, *c*Pr-H), 2.02–2.37 (m, 5H, CH_2NCH_2, 4- or 6-H), 2.37–2.59 (m, 2H, 4- or 6-H), 2.75–2.93 (m, 2H, 5-H, 1-H), 3.57 (t, *J*=4.1 Hz, 4H, CH_2OCH_2), 7.05 (d, *J*=9.1 Hz, 2H, Ph), 7.19–7.34 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.78 (−, *c*Pr-C), 14.83 (−, *c*Pr-C), 18.04 (+, CH_3), 19.14 (C_{quat}, *c*Pr-C), 28.02 [+, $C(CH_3)_3$], 36.85 (−, C-4 or -6), 40.35 (−, C-4 or -6), 40.99 (+, C-5), 51.86 (−, CH_2NCH_2), 61.86 (+, C-1′), 67.00 (−, CH_2OCH_2), 79.98 [C_{quat}, $C(CH_3)_3$], 126.12 (+, Ph-C), 128.09 (+, Ph-C), 128.17 (+, Ph-C), 135.69 (C_{quat}), 136.43 (C_{quat}), 144.11 (C_{quat}), 174.77 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 397 (30) [M^+], 382 (8) [M^+-CH_3], 254 (36), 209 (31), 114 (100), 100 (26), 57 (39); elemental analysis calcd (%) for $C_{25}H_{35}NO_3$ (397.6): C 75.53, H 8.87; found: C 75.59, H 8.64.

Minor diastereomer. R_f=0.44 (light petroleum/ethyl acetate 10:1); IR (film): $\tilde{\nu}$=3077, 2975, 2851, 2806, 1726, 1450, 1367, 1265, 1151, 1122, 943, 864, 703 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.37–0.45 (m, 1H, *c*Pr-H), 0.54–0.62 (m, 1H, *c*Pr-H), 1.00 (d, *J*=7.1 Hz, 3H, CH_3), 1.02–1.09 (m, 1H, *c*Pr-H), 1.32 (dd, *J*=12.7, 3.6 Hz, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.83–1.98 (m, 2H, 4- or 6-H, *c*Pr-H), 2.22 (br s, 4H, CH_2NCH_2), 1.83–1.98 (m, 2H, 4- or 6-H), 2.73–2.88 (m, 2H, 5-H, 1-H), 3.55 (t, *J*=4.6 Hz, 4H, CH_2OCH_2), 7.04 (d, *J*=8.1 Hz, 2H, Ph), 7.18–7.33 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.07 (−, *c*Pr-C), 14.13 (−, *c*Pr-C), 18.78 (C_{quat}, *c*Pr-C), 19.07 (+, CH_3), 27.97 [+, $C(CH_3)_3$], 36.56 (−, C-4 or -6), 39.69 (−, C-4 or -6), 40.56 (+, C-5), 51.55 (−, CH_2NCH_2), 61.11 (+, C-1′), 67.06 (−, CH_2OCH_2), 79.93 [C_{quat}, $C(CH_3)_3$], 125.91 (+, Ph-C), 127.98 (+, Ph-C), 128.17 (+, Ph-C), 135.63 (C_{quat}), 136.66 (C_{quat}), 144.35 (C_{quat}), 174.65 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 397 (22) [M^+], 382 (8) [M^+-CH_3], 254 (32), 209 (28), 114 (100), 100 (25), 57 (30); elemental analysis calcd (%) for $C_{25}H_{35}NO_3$ (397.6): C 75.53, H 8.87; found: C 75.57, H 8.56.

(b) According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 10:1) to yield **39a** (142.5 mg, 18%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR), **51** (45.6 mg, 8%, yellowish oil) and **52** (170 mg, 27%, yellowish oil).

4.3.14. 4-(2-Cyclopropylidene-1-methyl-3-phenyl-but-3-enyl)morpholine (51). R_f=0.33 (light petroleum/ethyl acetate, 10:1); IR (film): $\tilde{\nu}$=3078, 3052, 2972, 2851, 2807, 1724, 1597, 1492, 1445, 1265, 1118, 1009, 942, 777, 701 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.76 (t, *J*=7.8 Hz, 2H, *c*Pr-H), 1.18 (t, *J*=7.8 Hz, 2H, *c*Pr-H), 1.28 (d, *J*=7.1 Hz, 3H, CH_3), 2.38–2.55 (m, 4H, CH_2NCH_2), 3.39 (q, *J*=6.7 Hz, 1H, 1-H), 3.65 (t, *J*=4.7 Hz, 4H, CH_2OCH_2), 5.25 (d, *J*=1.9 Hz, 1H, vinyl), 5.60 (d, *J*=1.88 Hz, 1H, vinyl), 7.21–7.32 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=2.98 (−, *c*Pr-C), 3.82 (−, *c*Pr-C), 14.70 (+, CH_3), 50.04 (−, CH_2NCH_2), 63.22 (+, C-1), 67.34 (−, CH_2OCH_2), 114.04 (−, vinyl), 125.49 (C_{quat}), 126.66 (+, Ph-C), 127.56 (+, Ph-C), 127.80 (+, Ph-C), 129.78 (C_{quat}), 142.56 (C_{quat}), 149.51 (C_{quat}); MS

(70 eV, EI) *m/z* (%): 269 (18) [M^+], 268 (37), 183 (4) [M^+ −morpholinyl], 114 (100).

4.3.15. *tert*-Butyl 8-(1-phenylvinyl)spiro[2.5]oct-7-ene-5-carboxylate (52). R_f=0.76 (light petroleum/ethyl acetate, 10:1); IR (film): $\tilde{\nu}$=3081, 2977, 2931, 1726, 1367, 1255, 1152, 903, 780 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ= 0.29–0.61 (m, 4H, *c*Pr-H), 1.37 (dd, *J*=2.9, 13.1 Hz, 1H, 4- or 6-H), 1.46 [s, 9H, $C(CH_3)_3$], 2.09 (t, *J*=12.2 Hz, 1H, 4- or 6-H), 2.47 (dd, *J*=3.7, 7.9 Hz, 2H, 4- or 6-H), 2.71–2.86 (m, 1H, 5-H), 4.94 (d, *J*=1.8 Hz, 1H, vinyl), 5.42 (d, *J*= 1.8 Hz, 1H, vinyl), 5.65 (t, *J*=3.8 Hz, 1H, 7-H), 7.23–7.32 (m, 3H, Ph), 7.37–7.41 (m, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.80 (−, *c*Pr-C), 13.69 (−, *c*Pr-C), 19.44 (C_{quat}, *c*Pr-C), 28.07 [+, $C(CH_3)_3$], 28.47 (−, C-4 or -6), 37.29 (−, C-4 or -6), 40.37 (+, C-5), 79.97 [C_{quat}, $C(CH_3)_3$], 114.22 (−, vinyl), 124.82 (+, C-7), 126.04 (+, Ph-C), 127.48 (+, Ph-C), 128.22 (+, Ph-C), 140.16 (C_{quat}), 142.22 (C_{quat}), 147.56 (C_{quat}), 174.88 (C_{quat}, C=O); MS (70 eV, EI) *m/z* (%): 310 (3) [M^+], 254 (60), 209 (41), 181 (30), 167 (39), 115 (19), 103 (32), 91 (46), 77 (27), 57 (100), 41 (52).

4.3.16. *tert*-Butyl 7-(benzo[1,3]dioxol-5-yl)-8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (40a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 261 mg, 3.00 mmol), 5-(1-iodovinyl)benzo[1,3]-dioxole (**32**, 548.1 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 3 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated with stirring at 80 °C for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 4:1) to yield **40a** (386 mg, 44%, yellowish oil) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

Major diastereomer. R_f=0.44 (light petroleum/ethyl acetate 4:1); IR (KBr): $\tilde{\nu}$=2976, 2952, 2806, 1726, 1606, 1485, 1452, 1433, 1367, 1266, 1238, 1211, 1152, 1121, 1039, 939, 810 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.2–0.34 (m, 1H, *c*Pr-H), 0.57–0.65 (m, 1H, *c*Pr-H), 0.78–0.95 (m, 1H, *c*Pr-H), 1.05 (dd, *J*=12.7, 3.3 Hz, 1H, 4- or 6-H), 1.11 (d, *J*=7.0 Hz, 3H, CH_3), 1.41 [s, 9H, $C(CH_3)_3$], 1.62–1.69 (m, 1H, *c*Pr-H), 2.03 (td, *J*=12.0, 2.0 Hz, 1H, 4- or 6-H), 2.22 (br s, 4H, CH_2NCH_2), 2.34–2.55 (m, 2H, 4- or 6-H), 2.77–2.89 (m, 2H, 5-H, 1-H), 3.57 (br s, 4H, CH_2OCH_2), 5.94–5.96 (m, 2H, OCH_2O), 6.47 (dd, *J*=7.8, 1.7 Hz, 1H, Ph), 6.53 (d, *J*=1.6 Hz, 1H, Ph), 6.76 (d, *J*=7.6 Hz, 1H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.69 (−, *c*Pr-C), 14.78 (−, *c*Pr-C), 17.96 (+, CH_3), 19.04 (C_{quat}, *c*Pr-C), 27.93 [+, $C(CH_3)_3$], 36.81 (−, C-4 or -6), 40.18 (−, C-4 or -6), 40.84 (+, C-5), 51.80 (−, CH_2NCH_2), 61.77 (+, C-1), 66.89 (−, CH_2OCH_2), 79.86 [C_{quat}, $C(CH_3)_3$], 100.72 (−, OCH_2O), 108.05 (+, Ph-C), 108.59 (+, Ph-C), 120.94 (+, Ph-C), 135.79 (C_{quat}, Ph-C), 136.05 (C_{quat}, Ph-C), 137.70 (C_{quat}, Ph-C), 145.69 (C_{quat}), 147.27 (C_{quat}), 174.64 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 441 (12) [M^+], 426 (5) [M^+ −CH_3], 298 (56), 131 (22), 114 (95), 100 (28), 57 (100), 41 (45); elemental analysis calcd (%) for $C_{26}H_{35}NO_5$ (441, 6): C 70.72, H 7.99; found: C 70.55, H 7.72.

Minor diastereomer. R_f=0.39 (light petroleum/ethyl acetate 4:1); IR (KBr): $\tilde{\nu}$=3077, 2975, 2852, 2805, 1725, 1505, 1485, 1433, 1367, 1239, 1150, 1121, 1039, 938, 810 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.36–0.44 (m, 1H, *c*Pr-H), 0.53–0.61 (m, 1H, *c*Pr-H), 0.77–0.90 (m, 1H, *c*Pr-H), 0.99 (d, *J*=6.9 Hz, 3H, CH_3), 1.30 (dd, *J*=12.7, 3.6 Hz, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.85–1.94 (m, 2H, *c*Pr-H, 4- or 6-H), 2.24 (br s, 4H, CH_2NCH_2), 2.35–2.58 (m, 2H, 4- or 6-H), 2.72–2.89 (m, 2H, 5-H, 1-H), 3.58 (t, *J*=4.3 Hz, 4H, CH_2OCH_2), 5.92–5.97 (m, 2H, OCH_2O), 6.48 (dd, *J*=8.1, 1.0 Hz, 1H, Ph), 6.54 (d, *J*=1.5 Hz, 1H, Ph), 6.76 (d, *J*= 8.0 Hz, 1H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ= 13.14 (−, *c*Pr-C), 14.17 (−, *c*Pr-C), 18.76 (+, CH_3), 19.03 (C_{quat}, *c*Pr-C), 27.97 [+, $C(CH_3)_3$], 36.55 (−, C-4 or -6), 37.67 (−, C-4 or -6), 40.51 (+, C-5), 51.59 (−, CH_2NCH_2), 61.18 (+, C-1), 67.12 (−, CH_2OCH_2), 79.98 [C_{quat}, $C(CH_3)_3$], 100.74 (−, OCH_2O), 107.98 (+, Ph-C), 108.80 (+, Ph-C), 121.14 (+, Ph-C), 136.07 (C_{quat}, 2× Ph-C), 138.06 (C_{quat}, Ph-C), 145.62 (C_{quat}), 147.24 (C_{quat}), 174.67 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 441 (29) [M^+], 426 (14) [M^+ −CH_3], 298 (100), 253 (17), 131 (14), 114 (42), 100 (13), 57 (22), 41 (5); elemental analysis calcd (%) for $C_{26}H_{35}NO_5$ (441.6): C 70.72, H 7.99; found: C 70.55, H 7.72.

4.3.17. 6′-(1-Morpholin-4-ylethyl)-2′-phenyl-8′-(thiophen-2-yl)spiro[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo-[1,2-a]pyridazine]-1′,3′-dione (41a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), 2-(2-iodovinyl)thiophene (**33**, 472 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 3 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred again at room temperature for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **41a** (232 mg, 26%, colorless solid) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. Mp 160 °C, R_f=0.15 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3102, 3088, 2963, 2859, 2815, 1769, 1715, 1502, 1409, 1310, 1165, 1116, 767, 731 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.14–1.21 (m, 1H, *c*Pr-H), 1.19 (d, *J*=6.8 Hz, 3H, CH_3), 1.59–1.74 (m, 2H, *c*Pr-H), 2.46–2.64 (m, 6H, *c*Pr-H CH_2NCH_2, 1-H), 3.70 (t, *J*= 4.6 Hz, 4H, CH_2OCH_2), 5.88 (d, *J*=5.2 Hz, 1H, 8′-H), 6.17 (d, *J*=5.2 Hz, 1H, 7′-H), 6.99 (dd, *J*=3.6, 5.1 Hz, 1H, thiophene), 7.21 (d, *J*=3.8 Hz, 1H, thiophene), 7.27–7.42 (m, 6H, Ph, thiophene); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.36 (−, *c*Pr-C), 11.32 (−, *c*Pr-C), 16.08 (+, CH_3), 41.85 (C_{quat}, *c*Pr-C), 50.14 (−, CH_2NCH_2), 53.57 (−, C-8′), 57.28 (+, C-1), 67.07 (−, CH_2OCH_2), 121.17 (+, C-7′), 125.45 (+, Ph), 126.38 (+, thiophene), 126.93 (+, thiophene), 127.87 (+, Ph or thiophene), 128.01 (+, Ph or thiophene), 128.87 (+, Ph), 130.76 (C_{quat}), 138.93

(C_{quat}), 139.48 (C_{quat}), 149.94 (C_{quat}, C=O), 152.08 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 450 (27) [M^+], 364 (100) [M^+ −morpholine], 348 (8), 173 (17), 114 (30), 100 (90); elemental analysis calcd (%) for $C_{24}H_{26}N_4O_3S$ (450.6): C 63.98, H 5.82, N 12.43; found: C 63.76, H 5.71, N 12.68.

Diastereomer II. Mp 122 °C, R_f=0.15 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3108, 3062, 2963, 2858, 2796, 1775, 1714, 1502, 1411, 1112, 766, 713 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.17–1.44 (m, 3H, *c*Pr-H), 1.25 (d, *J*=6.4 Hz, 3H, CH_3), 2.32 (q, *J*=6.4 Hz, 1H, 1-H), 2.47 (br s, 4H, *c*Pr-H, CH_2NCH_2), 2.81–2.90 (m, 1H, *c*Pr-H), 3.69 (t, *J*=4.5 Hz, 4H, CH_2OCH_2), 5.89 (d, *J*=5.0 Hz, 1H, 8′-H), 6.29 (d, *J*=4.86 Hz, 1H, 7′-H), 6.98 (dd, *J*=3.5, 5.1 Hz, 1H, thiophene), 7.19 (d, *J*=3.4 Hz, 1H, thiophene), 7.27–7.42 (m, 6H, Ph, thiophene); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=9.37 (−, *c*Pr-C), 11.56 (−, *c*Pr-C), 18.22 (+, CH_3), 41.92 (C_{quat}, *c*Pr-C), 50.76 (−, CH_2NCH_2), 53.19 (−, C-8′), 58.27 (+, C-1), 67.04 (−, CH_2OCH_2), 120.19 (+, C-7′), 125.47 (+, Ph), 126.49 (+, Ph or thiophene), 126.83 (+, thiophene), 127.76 (+, thiophene), 128.06 (+, Ph or thiophene), 128.91 (+, Ph), 130.75 (C_{quat}), 138.75 (C_{quat}), 139.31 (C_{quat}), 150.45 (C_{quat}, C=O), 152.15 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 450 (9) [M^+], 363 (32) [M^+ −morpholine-H], 348 (4), [M^+ − morpholine–H–CH_3], 173 (11), 114 (36), 100 (100); elemental analysis calcd (%) for $C_{24}H_{26}N_4O_3S$(450.6): C 63.98, H 5.82; found: C 63.90, H 6.06.

4.3.18. 6′-[1-Morpholin-4-ylethyl]-2′-phenylspiro[cyclopropane-1,5′(10a'*H*)-5′,7′,8′,9′,10′,10a′-hexahydro-[1,2,4]triazolo[1,2-a]cinnoline]-1,3-dione (42a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), 1-iodo-cyclohexene (**34**, 416 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 100 °C for 5 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred again at room temperature for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **42a** (280 mg, 33%, colorless solid) as a mixture of two diastereomers (ratio 4.6:1 according to NMR).

Major diastereomer. Mp 151 °C, R_f=0.446 (light petroleum/ethyl acetate, 3:1); IR (KBr): $\tilde{\nu}$=3033, 2961, 2926, 2856, 1762, 1709, 1504, 1459, 1415, 1301, 1270, 1128, 1117, 1069, 1033, 866, 765 cm^{-1}; ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.22–1.36 (m, 1H, *c*Pr-H), 1.28 (d, *J*=6.8 Hz, 3H, CH_3), 1.37–1.48 (m, 1H, *c*Pr-H), 1.51–1.67 (m, 1H, cychex), 1.75 (dt, *J*=3.6, 13.1 Hz, 1H, cychex), 1.88–2.00 (m, 5H, *c*Pr-H, cychex), 2.06–2.14 (m, 1H, *c*Pr-H), 2.47–2.54 (m, 1H, 1-H), 2.49 (t, *J*=4.4 Hz, 4H, CH_2NCH_2), 2.65–2.71 (m, 1H, cychex), 3.71 (t, *J*=4.7 Hz, 4H, CH_2OCH_2), 3.77 (br s, 1H, cychex), 4.23 (dd, *J*=4.2, 10.8 Hz, 1H, cychex), 7.35–7.52 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C, DEPT): δ=10.03 (−, *c*Pr-C), 10.48 (−, *c*Pr-C), 18.04 (+, CH_3), 24.28 (−, cychex), 26.80 (−, cychex), 29.91 (−, cychex), 31.99 (−, cychex), 40.88 (C_{quat}, *c*Pr-C), 51.88 (−, CH_2NCH_2), 57.68 (+, C-1), 58.66 (+, cychex), 66.79 (−, CH_2OCH_2), 125.46 (+, Ph-C), 127.66 (+, Ph-C), 127.85 (C_{quat}), 128.62 (+, Ph-C), 131.36 (C_{quat}), 133.92 (C_{quat}), 149.51 (C_{quat}, C=O), 151.98 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 422 (54) [M^+], 393 (16), 337 (22), 336 (100), 217 (16), 114 (14), 100 (42); elemental analysis calcd (%) for $C_{24}H_{30}N_4O_3$ (422.5): C 68.22, H 7.16; found: C 67.91, H 7.07.

Minor diastereomer. R_f=0.108 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3071, 2932, 2853, 1772, 1714, 1546, 1504, 1413, 1295, 1264, 1130, 1117, 1029, 985, 766 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ=0.60–0.67 (m, 1H, *c*Pr-H), 0.70–0.77 (m, 1H, *c*Pr-H), 0.82–0.89 (m, 1H, *c*Pr-H), 0.99–1.06 (m, 1H, *c*Pr-H), 1.13–1.29 (m, 1H, cychex), 1.36 (d, *J*=6.3 Hz, 3H, CH_3), 1.46 (td, *J*=3.2, 12.0 Hz, 1H, cychex), 1.57 (tt, *J*=3.5, 13.0 Hz, 1H, cychex), 1.71 (td, *J*=3.5, 13.7 Hz, 1H, cychex), 1.82–1.86 (m, 2H, cychex), 2.56 (t, *J*=4.6 Hz, 4H, CH_2NCH_2), 2.98–3.03 (m, 1H, cychex), 3.25 (d, *J*=13.60 Hz, 1H, cychex), 3.58 (q, *J*=3.9 Hz, 4H, CH_2OCH_2), 4.17 (dd, *J*=4.1, 11.2 Hz, cychex), 4.67 (q, *J*=6.3 Hz, 1H, 1-H), 7.29–7.34 (m, 1H, Ph), 7.46–7.51 (m, 4H, Ph); ^{13}C NMR (75.478 MHz, $CDCl_3$, DEPT): δ=11.25 (−, *c*Pr-C), 13.51 (−, *c*Pr-C), 19.87 (+, CH_3), 23.83 (−, cychex), 27.25 (−, cychex), 30.26 (−, cychex), 34.44 (−, cychex), 44.07 (C_{quat}, *c*Pr-C), 49.66 (−, CH_2NCH_2), 51.37 (+, C-1), 58.39 (+, cychex), 67.30 (−, CH_2OCH_2), 125.37 (+, Ph-C), 126.99 (C_{quat}), 127.80 (+, Ph-C), 128.95 (+, Ph-C), 131.33 (C_{quat}), 136.57 (C_{quat}), 149.67 (C_{quat}, C=O), 152.78 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 422 (79) [M^+], 407 (11) [M^+ −CH_3], 336 (55), 261 (18), 247 (30), 246 (100), 232 (27), 218 (24), 178 (20), 119 (39), 91 (42), 77 (20), 41 (22) for $C_{24}H_{30}N_4O_3$ (422.53); HRMS(EI):calcd 422.2318 (correct HRMS).

4.3.19. 6′-[1-Morpholin-4-ylethyl]-9′-(*N*)-benzyl-2′-phenylspiro[cyclopropane-1,5′(10a'*H*)-5′,7′,8′,9′,10′,10a′-hexahydro[1,2,4]triazolo[1,2-a]cinnoline]-1,3-dione (43a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), 1-benzyl-4-iodo-1,2,3,6-tetrahydropyridine (**35**, 600 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 3 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **43a** (180 mg, 17%, colorless oil), R_f=0.17 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3028, 2956, 2850, 2798, 1770, 1713, 1503, 1456, 1412, 1361, 1265, 1120, 1071, 1029, 936, 863, 736, 739 cm^{-1}; ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.24–1.33 (m, 1H, *c*Pr-H), 1.29 (d, *J*=6.8 Hz, 3H, CH_3), 1.36–1.43 (m, 1H, *c*Pr-H), 1.79–1.87 (m, 1H, *c*Pr-H), 2.02–2.15 (m, 2H, tetrahydropyridine), 2.24 (t, *J*=10.3 Hz, 1H, tetrahydropyridine), 2.29–2.35 (m, 1H, *c*Pr-H), 2.39–2.51 (m, 1H, 1-H), 2.47 (q, *J*=4.3 Hz, 4H, CH_2NCH_2), 2.94–2.99 (m, 1H, tetrahydropyridine), 3.56–3.78 (AB system: δ_A=3.6, δ_B=3.8, J_{AB}= 13.3 Hz, 2H, Bn), 3.56–3.78 (1H, tetrahydropyridine)*, 3.68

(t, J=4.6 Hz, 4H, CH_2OCH_2), 3.98–4.02 (m, 1H, tetrahydropyridine), 4.47 (dd, J=4.4, 9.9 Hz, 1H, tetrahydropyridine), 7.28–7.48 (m, 10H, Ph); * The peak of this proton sits under the peaks of the AB system, thus the spin couplings of this proton could not be determined. This proton correlates clearly with the carbon peak at 28.49 ppm in the HMQC spectrum. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C, DEPT): δ=9.40 (−, *c*Pr-C), 10.67 (−, *c*Pr-C), 17.85 (+, CH_3), 28.49 (−, tetrahydropyridine), 40.74 (C_{quat}, *c*Pr-C), 51.80 (−, CH_2NCH_2), 52.61 (−, tetrahydropyridine), 57.06 (+, tetrahydropyridine), 57.32 (−, tetrahydropyridine), 57.71 (+, C-1), 61.61 (−, Bn), 66.70 (−, CH_2OCH_2), 125.52 (+, Ph), 126.86 (+, Ph), 127.77 (+, Ph), 127.98 (+, Ph), 128.53 (+, Ph), 128.66 (+, Ph), 128.81 (C_{quat}), 130.99 (C_{quat}), 131.19 (C_{quat}), 137.72 (C_{quat}), 149.24 (C_{quat}, C=O), 152.27 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 513 (34) [M^+], 427 (26) [M^+ −morpholinyl], 397 (9), 307 (6), 134 (46), 100 (46), 91 (100), 42 (14); elemental analysis calcd (%) for $C_{30}H_{35}N_5O_3$ (513.6): C 70.15, H 6.87; found: C 69.98, H 6.71.

4.3.20. 6′-(1-Morpholin-4-ylethyl)-2′,8′-diphenylspiro-[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo-[1,2-a]pyridazine]-1′,3′-dione (44a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (*E*)-1-iodo-2-phenylethene (**36**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. *N*-phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **44a** (310 mg, 35%, colorless solid) as a mixture of two diastereomers (ratio 1.4:1 according to NMR).

Major diastereomer. Mp 171 °C, R_f=0.47 (light petroleum/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=3106, 3058, 3026, 2977, 2857, 2818, 1763, 1706, 1506, 1411, 1290, 1174, 1112, 768 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.18 (d, J=6.7 Hz, 3H, CH_3), 1.21–1.31 (m, 1H, *c*Pr-H), 1.55–1.65 (m, 1H, *c*Pr-H), 1.90–2.00 (m, 1H, *c*Pr-H), 2.32–2.65 (m, 6H, *c*Pr-H, CH_2NCH_2, 1-H), 3.66 (t, J=4.6 Hz, 4H, CH_2OCH_2), 5.54 (d, J=4.6 Hz, 1H, 8′-H), 5.99 (d, J=4.7 Hz, 1H, 7′-H), 7.25–7.44 (m, 10H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$, DEPT): δ=10.96 (−, *c*Pr-C), 11.33 (−, *c*Pr-C), 15.02 (+, CH_3), 41.54 (C_{quat}, *c*Pr-C), 49.86 (−, CH_2NCH_2), 57.92 (+, C-1), 58.98 (−, C-8′), 67.00 (−, CH_2OCH_2), 121.82 (+, C-7′), 125.39 (+, Ph-C), 127.90 (+, Ph-C), 127.98 (+, Ph-C), 128.57 (+, Ph-C), 128.64 (+, Ph-C), 128.82 (+, Ph-C), 130.85 (C_{quat}), 137.07 (C_{quat}), 137.80 (C_{quat}), 149.68 (C_{quat}, C=O), 151.83 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 444 (11) [M^+], 358 (46) [M^+ −morpholinyl], 167 (12), 114 (26), 100 (100) 91 (14); elemental analysis calcd (%) for $C_{26}H_{28}N_4O_3$ (444.5): C 70.25, H 6.35; found: C 70.54, H 6.26.

Minor diastereomer. Mp 170 °C, R_f=0.47 (light petroleum/ethyl acetate, 1:1); IR (KBr): $\tilde{\nu}$=3065, 2962, 2854, 2811, 1769, 1711, 1502, 1414, 1301, 1265, 1116, 765 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.24 (d, J=6.3 Hz, 3H, CH_3), 1.31–1.39 (m, 2H, *c*Pr-H), 1.43–1.51 (m, 1H, *c*Pr-H), 2.36–2.49 (m, 5H, CH_2NCH_2, 1-H), 2.74–2.82 (m, 1H, *c*Pr-H), 3.69 (t, J=4.4 Hz, 4H, CH_2OCH_2), 5.60 (d, J=4.9 Hz, 1H, 8′-H), 6.15 (d, J=5.0 Hz, 1H, 7′-H), 7.29–7.44 (m, 10H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=9.61 (−, *c*Pr-C), 11.59 (−, *c*Pr-C), 17.83 (+, CH_3), 41.97 (C_{quat}, *c*Pr-C), 50.61 (−, CH_2NCH_2), 58.18 (+, C-1), 58.29 (−, C-8′), 67.09 (−, CH_2OCH_2), 120.47 (+, C-7′), 125.43 (+, Ph-C), 128.00 (+, Ph-C), 128.43 (+, Ph-C), 128.59 (+, Ph-C), 128.72 (+, Ph-C), 128.89 (+, Ph-C), 130.81 (C_{quat}), 134.48 (C_{quat}), 138.44 (C_{quat}), 150.56 (C_{quat}, C=O), 151.60 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 444 (25) [M^+], 358 (80) [M^+ −morpholinyl], 357 (94), 167 (14), 119 (15), 114 (26), 100 (100), 91 (16); elemental analysis calcd (%) for $C_{26}H_{28}N_4O_3$ (444.5): C 70.25, H 6.35; found: C 70.43, H 6.07.

4.3.21. 6′-(1-Morpholin-4-ylethyl)-2′-phenylspiro[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo[1,2-a]pyridazine]-1′,3′-dione (45a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, CH_2Cl_2/ethyl acetate, 1:1) to yield **45a** (367.2 mg, 50%, colorless solid), mp 130 °C, R_f=0.25 (CH_2Cl_2/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=2962, 2953, 2852, 2813, 1771, 1709, 1699, 1504, 1421, 1313, 1268, 1142, 1123, 916, 860, 767 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.17 (d, J=6.5 Hz, 3H, CH_3), 1.18–1.26 (m, 1H, *c*Pr-H), 1.34–1.43 (m, 1H, *c*Pr-H), 1.69–1.78 (m, 1H, *c*Pr-H), 2.31–2.52 (m, 6H, *c*Pr-H, CH_2NCH_2, 1-H), 3.68 (t, J=4.6 Hz, 4H, CH_2OCH_2), 4.18–4.40 (m, 2H, 8′-H), 6.01 (t, J=6.6 Hz, 1H, 7′-H), 7.32–7.46 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=9.76 (−, *c*Pr-C), 11.58 (−, *c*Pr-C), 15.91 (+, CH_3), 41.36 (C_{quat}, *c*Pr-C), 44.28 (−, C-8′), 49.94 (−, CH_2NCH_2) 58.20 (+, C-1), 66.93 (−, CH_2OCH_2), 116.49 (+, C-7′), 125.29 (+, Ph), 127.92 (+, Ph), 128.87 (+, Ph), 130.83 (C_{quat}), 138.72 (C_{quat}), 149.66 (C_{quat}, C=O), 152.62 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 368 (20) [M^+], 281 (100) [M^+ −morpholine], 266 (6) [M^+ −morpholine–CH_3], 178 (16), 114 (10), 100 (64); elemental analysis calcd (%) for $C_{20}H_{24}N_4O_3$ (368.4): C 65.20, H 6.57; found: C 64.90, H 6.25.

4.3.22. 6′-(1-Morpholin-4-ylethyl)-2′,7′-diphenylspiro-[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo[1,2-a]pyridazine]-1′,3′-dione (46a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 261 mg, 3.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 3 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the

ice-cooled mixture and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **46a** (311 mg, 35%, colorless solid), mp 70 °C, R_f=0.30 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3050, 2956, 2850, 2805, 1772, 1713, 1598, 1503, 1407, 1265, 1143, 1119, 942, 863 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.25 (d, J=7.0 Hz, 3H, CH_3), 1.29–1.37 (m, 1H, *c*Pr-H), 1.53–1.62 (m, 1H, *c*Pr-H), 2.14–2.22 (m, 2H, *c*Pr-H), 2.30 (br s, 4H, CH_2NCH_2), 3.08 (q, J=6.7 Hz, 1H, 1-H), 3.61 (t, J=4.4 Hz, 4H, CH_2OCH_2), 4.50 (s, 2H, 8′-H), 7.10–7.14 (m, 2H, Ph), 7.33–7.42 (m, 4H, Ph), 7.45–7.50 (m, 4H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$, DEPT): δ=11.77 (−, *c*Pr-C), 13.69 (−, *c*Pr-C), 17.51 (+, CH_3), 38.24 (C_{quat}, *c*Pr-C), 48.67 (−, C-8′), 51.50 (−, CH_2NCH_2), 59.79 (+, C-1), 66.77 (−, CH_2OCH_2), 125.33 (+, Ph-C), 127.63 (+, Ph-C), 127.89 (+, Ph-C), 128.56 (+, Ph-C), 128.88 (+, Ph-C), 131.22 (C_{quat}), 133.44 (C_{quat}), 136.70 (C_{quat}), 137.78 (C_{quat}), 150.39 (C_{quat}, C=O), 152.97 (C_{quat}, C=O); MS (70 eV, EI) *m/z* (%): 444 (22) [M^+], 357 (52) [M^+ −morpholinyl], 254 (7), 167 (16), 114 (27), 100 (100); elemental analysis calcd (%) for $C_{26}H_{28}N_4O_3$ (444.5): C 70.25, H 6.35, N 12.60; found: C 69.98, H 6.52, N 12.42.

4.3.23. 5-(1′-(Morpholin-4″-yl)ethyl)-2,7-diphenylspiro-[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (47a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (*E*)-1-iodo-2-phenylethene (**36**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature 1-phenyl-2,5-dihydropyrrole-2,5-dione (**19**, 693 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 2:3) to yield **47a** (370 mg, 42%, pale yellow solid) as a mixture of two diastereomers (ratio 2:1 according to NMR). R_f=0.51 (light petroleum/ethyl acetate, 2:3); IR (KBr)*: $\tilde{\nu}$=3095 (C–H), 1723 (C=O), 1499, 1456, 1393, 1376 (CH_3), 1314, 1163, 1149, 1123, 1110, 1076, 1057, 1036, 838 cm^{-1}; MS (70 eV, EI)*, *m/z* (%): 442 (14) [M^+], 427 (26) [$M^+ - CH_3$], 173 (63), 88 (14) [morpholinyl$^+$ +H], 70 (24), 61 (38), 43 (100); HRMS (EI)*: calcd for $C_{28}H_{30}N_2O_3$ (442.6): 442.2256, correct HRMS. *IR, low and high resolution mass measurements were carried out for the mixture of diastereomers.

Major diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.41–0.56 (m, 1H, *c*Pr-H), 0.90–1.04 (m, 1H, *c*Pr-H), 1.19 (d, J=6.6 Hz, 3H, CH_3), 1.22–1.32 (m, 1H, *c*Pr-H), 1.61–1.71 (m, 1H, *c*Pr-H), 2.29–2.51 (m, 4H, CH_2NCH_2), 2.46 (d, J=8.6 Hz, 1H, 3a-H), 3.03 (q, J=6.9 Hz, 1H, 1′-H), 3.53–3.70 (m, 5H, CH_2NCH_2, 7-H), 4.00–4.07 (m, 1H, 7a-H), 6.30 (d, J=3.5 Hz, 1H, 6-H), 7.10–7.60 (m, 10H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.56 (−, *c*Pr-C), 11.6 (+, CH_3), 13.7 (−, *c*Pr-C), 21.5 (C_{quat}, C-4), 23.9 (+, C-7), 41.9 (+, C-7a), 50.6 (+, C-1′), 60.7 (−, CH_2NCH_2), 64.7 (+, C-3a), 67.3 (−, CH_2OCH_2), 126.2 (+, C-6), 126.5 (+, Ph-C), 126.9 (+, Ph-C), 128.2 (+, Ph-C), 128.3 (+, Ph-C), 128.9 (+, Ph-C), 129.4 (+, Ph-C), 131.8 (C_{quat}), 139.7 (C_{quat}), 144.2 (C_{quat}), 175.3 (C_{quat}, C=O), 176.9 (C_{quat}, C=O).

Minor diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.41–0.56 (m, 1H, *c*Pr-H), 0.90–1.04 (m, 1H, *c*Pr-H), 1.09 (d, J=6.7 Hz, 3H, CH_3), 1.22–1.32 (m, 1H, *c*Pr-H), 1.61–1.71 (m, 1H, *c*Pr-H), 2.29–2.51 (m, 4H, CH_2NCH_2), 2.45 (d, J=8.6 Hz, 1H, 3a-H), 2.78 (q, J=6.7 Hz, 1H, 1′-H), 3.53–3.70 (m, 5H, CH_2OCH_2, 7-H), 4.00–4.07 (m, 1H, 7a-H), 6.30 (d, J=3.5 Hz, 1H, 6-H), 7.10–7.60 (m, 10H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.62 (−, *c*Pr-C), 13.0 (−, *c*Pr-C), 14.1 (+, CH_3), 21.5 (C_{quat}, C-4), 23.9 (+, C-7), 41.8 (+, C-7a), 48.2 (+, C-1′), 60.3 (−, CH_2NCH_2), 64.2 (+, C-3a), 67.0 (−, CH_2OCH_2), 126.0 (+, C-6), 126.5 (+, Ph-C), 126.9 (+, Ph-C), 128.2 (+, Ph-C), 128.3 (+, Ph-C), 128.9 (+, Ph-C), 129.4 (+, Ph-C), 131.8 (C_{quat}), 139.5 (C_{quat}), 143.7 (C_{quat}), 175.3 (C_{quat}, C=O), 176.4 (C_{quat}, C=O).

4.3.24. 5-(1′-(Morpholin-4″-yl)ethyl)-2,6-diphenylspiro-[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (48a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, 1-Phenyl-2,5-dihydropyrrole-2,5-dione (**19**, 693 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 3:1) to yield **48a** (353 mg, 40%, colorless solid) as a mixture of two diastereomers (ratio 1.18:1 according to NMR).

Major diastereomer. Mp 165 °C, R_f=0.18 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=2969, 2847, 2802, 1777, 1713, 1597, 1493, 1388, 1185, 1115, 862 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.41–0.49 (m, 1H, *c*Pr-H), 0.78–0.86 (m, 1H, *c*Pr-H), 1.15 (d, J=6.8 Hz, 3H, CH_3), 1.21–1.28 (m, 1H, *c*Pr-H), 2.17 (br s, 4H, CH_2NCH_2), 2.31 (d, J=9.2 Hz, 1H, 3a-H), 2.41–2.49 (m, 1H, *c*Pr-H), 2.95–2.98 (m, 2H, 7-H), 3.08 (q, J=7.0 Hz, 1H, 1′-H), 3.42–3.49 (m, 1H, 7a-H), 3.55 (t, J=4.45 Hz, 4H, CH_2OCH_2), 6.94–6.97 (m, 2H, Ph), 7.22–7.52 (m, 8H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=8.44 (−, *c*Pr-C), 13.47 (−, *c*Pr-C), 16.75 (+, CH_3), 21.33 (C_{quat}, *c*Pr-C), 31.72 (−, C-7), 42.07 (+, C-7a), 51.11 (+, C-3a), 51.42 (−, CH_2NCH_2), 59.89 (+, C-1′), 67.01 (−, CH_2OCH_2), 126.11 (+, Ph), 126.66 (+, Ph), 127.58 (+, Ph), 128.26 (+, Ph), 128.43 (+, Ph), 129.15 (+, Ph), 131.99 (C_{quat}), 138.10 (C_{quat}), 139.28 (C_{quat}), 141.69 (C_{quat}), 177.43 (C_{quat}, C=O), 178.44 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 442 (35) [M^+], 427 (33) [$M^+ - CH_3$], 355 (20) [M^+ −morpholinyl–H], 209 (14), 165 (15), 114 (100), 88 (10); elemental analysis calcd (%) for $C_{28}H_{30}N_2O_3$ (442.6): C 75.99, H 6.83; found: C 75.70, H 7.03.

Minor diastereomer. Mp 168 °C, R_f=0.22 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3077, 3051, 2965, 2852,

2791, 1779, 1709, 1596, 1492, 1390, 1181, 1151, 1120, 1113, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=0.41–0.49 (m, 2H, *c*Pr-H), 1.08 (d, J=7.4 Hz, 3H, CH_3), 1.21–1.29 (m, 1H, *c*Pr-H), 1.61 (q, J=7.1 Hz, 1H, *c*Pr-H), 2.12 (br s, 4H, CH_2NCH_2), 2.53 (d, J=9.2 Hz, 1H, 3a-H), 2.83–2.99 (m, 2H, 7-H) 3.05 (q, J=7.0 Hz, 1H, 1′-H), 3.28–3.46 (m, 5H, CH_2OCH_2, 7a-H), 7.05–7.07 (m, 2H, Ph), 7.24–7.49 (m, 8H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ= 9.28 (−, *c*Pr-C), 12.94 (−, *c*Pr-C), 17.53 (+, CH_3), 21.10 (C_{quat}, *c*Pr-C), 32.11 (−, C-7), 42.40 (+, C-7a), 49.71 (+, C-3a), 51.45 (−, CH_2NCH_2), 60.62 (+, C-1′), 66.84 (−, CH_2OCH_2), 126.07 (+, Ph-C), 126.59 (+, Ph-C), 127.75 (+, Ph-C), 128.17 (+, Ph-C), 128.46 (+, Ph-C), 129.07 (+, Ph-C), 131.82 (C_{quat}), 138.98 (C_{quat}), 139.27 (C_{quat}), 141.98 (C_{quat}), 177.60 (C_{quat}, C=O), 178.57 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 442 (34) [M^+], 427 (66) [M^+ − CH_3], 355 (30) [M^+ − morpholinyl–H], 208 (16), 165 (15), 114 (100), 88 (16); elemental analysis calcd (%) for $C_{28}H_{30}N_2O_3$ (442.6): C 75.99, H 6.83; found: C 75.70, H 6.90.

4.3.25. 5-[1′-(Morpholine-4″-yl)ethyl]-2-(4‴-trifluoromethylphenyl)spiro[cyclopropane-1′,4-(7-phenyl-3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (49a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (*E*)-1-iodo-2-phenylethene (**36**) (460 mg, 2.00 mmol), and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature 1-(4′-trifluoromethylphenyl)-2,5 dihydropyrrole-2,5-dione (**21**, 964 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying over $MgSO_4$, the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 2:3) to yield **49a** (380 mg, 37%, pink crystals) as a mixture of two diastereomers (ratio 2:1 according to NMR). R_f=0.60 (light petroleum/ethyl acetate 2:3); IR (KBr)*: $\tilde{\nu}$=2966, 2853 (C–H), 1717 (C=O), 1376 (CH_3), 1326 (C–F), 1170 (C–F), 1117 (C–F), 1068, 1021 cm^{-1} MS (70 eV, EI)*, *m/z* (%): 511/510 (12/55) [M^+], 497/496 (26/100) [M^+ +H–CH_3], 114 (95), 86 (26) [morpholinyl–H], 56 (11), 43 (29), 42 (10), 41 (13); HRMS (EI)*: calcd for $C_{29}H_{29}F_3N_2O_3$ (510.6): 510.2130, correct HRMS. *IR, low and high resolution mass spectrometric measurements were carried out for the mixture of diastereomers.

Major diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.43–0.61 (m, 1H, *c*Pr-H), 0.91–1.05 (m, 1H, *c*Pr-H), 1.08 (d, J=6.6 Hz, 3H, CH_3), 1.23–1.34 (m, 1H, *c*Pr-H), 1.62–1.75 (m, 1H, *c*Pr-H), 2.25–2.56 (m, 5H, CH_2NCH_2, 3a-H), 3.02 (q, J=6.6 Hz, 1H, 1′-H), 3.47–3.78 (m, 5H, CH_2OCH_2, 7-H), 4.01–4.11 (m, 1H, 7a-H), 6.27–6.37 (m, 1H, 6-H), 7.24–7.49 (m, 7H, Ar-H), 7.67 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.73 (−, *c*Pr-C), 11.7 (+, CH_3), 13.0 (−, *c*Pr-C), 23.8 (C_{quat}, C-4), 41.9 (+, C-7a), 48.3 (+, C-7), 50.7 (+, C-1′), 60.7 (−, CH_2NCH_2), 64.7 (+, C-3a), 67.2 (−, CH_2OCH_2), 126.0 (+, Ar-C), 126.1 (+, Ar-C), 126.3 (+, C-6), 127.1 (+, Ar-C), 127.5 (C_{quat}, q, ^1J(C,F)=273 Hz, CF_3), 128.2 (+, 3× Ar-C), 128.8 (+, Ar-C), 129.3 (+, 2×Ar-C), 130.1 (C_{quart}, q, ^2J(C,F)=33 Hz, C-4‴), 134.7 (C_{quat}), 139.4 (C_{quat}), 143.9 (C_{quat}, C-5), 174.9 (C_{quat}, C=O), 176.4 (C_{quat}, C=O) .

Minor diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.43–0.61 (m, 1H, *c*Pr-H), 0.91–1.05 (m, 1H, *c*Pr-H), 1.18 (d, J=6.6 Hz, 3H, CH_3), 1.23–1.34 (m, 1H, *c*Pr-H), 1.62–1.75 (m, 1H, *c*Pr-H), 2.25–2.56 (m, 5H, CH_2NCH_2, 3a-H), 2.79 (q, J=6.6 Hz, 1H, 1′-H), 3.47–3.78 (m, 5H, CH_2NCH_2, 7-H), 4.01–4.11 (m, 1H, 7a-H), 6.27–6.37 (m, 1H, 6-H), 7.24–7.49 (m, 7H, Ar), 7.67 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.62 (−, *c*Pr-C), 13.7 (−, *c*Pr-C), 16.0 (+, CH_3), 21.4 (C_{quat}, C-4), 41.6 (+, C-7a), 48.3 (+, C-7), 50.8 (+, C-1′), 60.3 (−, CH_2NCH_2), 64.7 (+, C-3a), 67.0 (−, CH_2OCH_2), 125.9 (+, Ar-C), 126.0 (+, Ar-C), 127.1 (+, Ar-C), 127.5 (C_{quat}, q, ^1J(C,F)=273 Hz, CF_3), 128.2 (+, 3×Ar-C), 128.8 (+, Ar-C), 129.3 (+, 2×Ar-C), 130.1 (C_{quat}, q, ^2J(C,F)= 33 Hz, C-4‴), 134.7 (C_{quat}), 139.2 (C_{quat}), 144.3 (C_{quat}, C-5), 175.1 (C_{quat}, C=O), 175.9 (C_{quat}, C=O).

4.3.26. Dimethyl 8-(1-morpholin-4-ylethyl)spiro[2.5]octa-4,7-diene-4,5-dicarboxylate (50a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature dimethyl acetylenedicarboxylate (**38**, 568 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **50a** (200 mg, 30%, yellowish oil). R_f=0.5 (light petroleum/ethyl acetate, 1:1), IR (film): $\tilde{\nu}$=3056, 2953, 2895, 2857, 2824, 1733, 1630, 1587, 1436, 1371, 1266, 1162, 1118, 1033, 737, 704 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.00–1.15 (m, 3H, *c*Pr-H), 1.06 (d, J=6.7 Hz, 3H, CH_3), 1.25–1.35 (m, 1H, *c*Pr-H), 2.22 (q, J=6.5 Hz, 1H, 1-H), 2.35–2.50 (m, 4H, CH_2NCH_2), 3.15 (d, J=3.6 Hz, 2H, 6-H), 3.65 (t, J= 4.5 Hz, 4H, CH_2OCH_2), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.85 (t, J=3.7 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.46 (−, *c*Pr-C), 14.15 (−, *c*Pr-C), 17.14 (+, CH_3), 22.21 (C_{quat}, *c*Pr-C), 26.51 (−, C-6), 50.31 (−, CH_2NCH_2), 51.93 (+, OCH_3), 52.13 (+, OCH_3), 57.91 (+, C-1), 67.10 (−, CH_2OCH_2), 119.91 (+, C-7), 124.75 (C_{quat}), 136.82 (C_{quat}), 146.69 (C_{quat}), 165.78 (C_{quat}, C=O), 168.46 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 335 (41) [M^+], 334 (100) [M^+ −H], 320 (12), 276 (16), 216 (13), 189 (17), 157 (11), 114 (26), 100 (34); elemental analysis calcd (%) for $C_{18}H_{25}NO_5$ (335.4): C 64.46, H 7.51; found: C 64.19, H 7.76.

4.3.27. 2-Methyl-8-*tert*-butoxycarbonylspiro[cyclopropane-1′,10-(3-oxabicyclo[4.4.0]dec-1(6)-ene)] (55). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), 3-iodobut-3-en-1-ol (**53**, 396 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (4 mL) at 80 °C for 24 h. After cooling the mixture to

room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated with stirring at 80 °C for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 4:1) to yield **55** (140 mg, 25%, yellowish oil) as a mixture of two diastereomers (ratio 1.3:1 according to NMR).

*Major and minor diastereomers**. R_f=0.56 (light petroleum/ethyl acetate, 4:1); IR (film): $\tilde{\nu}$=3081, 2977, 2932, 1726, 1452, 1392, 1367, 1318, 1259, 1153, 1107, 1036, 984, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.34–0.72 (m, 6H, *c*Pr-H), 0.76–0.89 (m, 2H, *c*Pr-H), 1.11 (d, J=6.5 Hz, 3H, CH_3), 1.15–1.23 (m, 2H), 1.28 (d, J=6.4 Hz, 3H, CH_3), 1.44 [s, 18H, 2×$C(CH_3)_3$], 1.69–2.27 (m, 10H), 2.68–2.82 (m, 2H), 3.58–3.78 (m, 3H), 3.80–3.99 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.23 (−, *c*Pr-C), 11.87 (−, *c*Pr-C), 13.08 (−, *c*Pr-C), 13.43 (−, *c*Pr-C), 18.37 (C_{quat}, *c*Pr-C), 19.03 (C_{quat}, *c*Pr-C), 19.80 (+, CH_3), 20.58 (+, CH_3), 28.02 [+, 2×$C(CH_3)_3$], 29.09 (−), 30.08 (−), 32.69 (−), 33.54 (−), 38.06 (−), 39.32 (−), 40.13 (+), 40.43 (+), 57.45 (−), 54.49 (−), 66.13 (+), 68.77 (+), 79.99 [C_{quat}, 2×$C(CH_3)_3$], 124.40 (C_{quat}), 127.22 (C_{quat}), 132.29 (C_{quat}), 133.58 (C_{quat}), 174.68 (C_{quat}, C=O), 174.79 (C_{quat}, C=O); MS (DCI), *m*/*z* (%): 296 (100) [$M+NH_4^+$], 279 (2) [$M+H^+$], 240 (73), 232 (20); elemental analysis calcd (%) for $C_{17}H_{26}O_3$ (278.4): C 73.35, H 9.41; found: C 73.59, H 9.41. *Proton and carbon chemical shifts are given in one series for both diastereomers together because ^1H NMR and ^{13}C NMR spectra were not appropriate to classify all of the peaks for major and minor diastereomers. IR, DCI mass and elemental analysis were carried out for the mixture of diastereomers.

4.3.28. 2-Methyl-3-(toluene-4-sulfonyl)-8-*tert*-butoxycarbonylspiro[cyclopropane-1′,10-(3-azabicyclo[4.4.0]dec-1(6)-ene)](56) and 2,2-dimethylpropionic acid 8-[1-methylene-3-toluene-4-sulfonylamino)propyl]spiro[2.5]oct-7-en-5-yl ester (57). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), *N*-(3-iodobut-3-enyl)-4-methylbenzenesulfonamide (**54**, 702.4 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (2 mL), at 80 °C for 3 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 4:1) to yield **56** (328 mg, 38%, colorless solid) and **57** (311 mg, 36%, yellowish oil), **56**: mp 110 °C, R_f=0.35 (light petroleum/ethyl acetate 4:1); IR (KBr): $\tilde{\nu}$=3097, 3072, 3002, 2978, 2909, 2869, 2829, 1716, 1597, 1448, 1433, 1372, 1367, 1338, 1263, 1158, 1089, 1033, 942, 815, 694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.36–0.44 (m, 1H, *c*Pr-H), 0.49–0.67 (m, 2H, *c*Pr-H), 0.80–0.89 (m, 1H, *c*Pr-H), 1.05–1.11 (m, 1H), 1.18 (d, J=6.5 Hz, 3H, CH_3), 1.42 [s, 9H, $C(CH_3)_3$], 1.63–1.98 (m, 4H), 2.03–2.18 (m, 1H), 2.41 (s, 1H, CH_3), 2.47–2.59 (m, 1H), 3.26–3.38 (m, 1H), 3.63–3.79 (m, 2H), 7.25 (d, J=7.8 Hz, 2H, Ph), 7.65 (d, J=8.3 Hz, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.91 (−, *c*Pr-C), 13.17 (−, *c*Pr-C), 18.75 (C_{quat}, *c*Pr-C), 20.21 (+, CH_3), 21.10 (+, CH_3), 28.01 [+, $C(CH_3)_3$], 28.25 (−), 33.09 (−), 37.42 (−), 38.15 (−), 40.47 (+), 46.93 (+), 79.52 [C_{quat}, $C(CH_3)_3$], 125.59 (C_{quat}), 127.45 (+, Ph-C), 129.42 (+, Ph-C), 132.62 (C_{quat}), 139.07 (C_{quat}), 142.67 (C_{quat}), 174.13 (C_{quat}, C=O); MS (70 eV, EI), *m*/*z* (%): 431 (4) [M^+], 416 (4) [M^+-CH_3], 375 (6), 361 (17), 360 (100), 220 (26), 204 (10), 174 (18), 133 (11), 105 (15), 91 (66), 57 (52), 41 (24); elemental analysis calcd (%) for $C_{24}H_{33}NO_4S$ (431.6): C 66.79, H 7.71; found: C 66.68, H 7.50. **57**: R_f=0.31 (light petroleum/ethyl acetate 4:1); IR (film): $\tilde{\nu}$=3275 (N–H), 3080, 3003, 2976, 2924, 2872, 1728 (C=O), 1599, 1457, 1421, 1392, 1367, 1337, 1257, 1167, 1095, 985, 903, 847, 814, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=0.20–0.28 (m, 1H, *c*Pr-H), 0.37–0.44 (m, 2H, *c*Pr-H), 0.46–0.57 (m, 1H, *c*Pr-H), 1.14–1.20 (m, 1H), 1.35 [s, 9H, $C(CH_3)_3$], 1.80 (t, J=12.1 Hz, 1H), 2.02–2.09 (m, 2H), 2.11–2.18 (m, 2H), 2.34 (s, 3H, CH_3), 2.48–2.58 (m, 1H, 5-H), 2.77–2.99 (m, 2H), 4.27 (t, J=5.9 Hz, 1H), 4.53 (d, J=2.7 Hz, 1H, vinyl), 4.66 (br s, 1H, vinyl), 5.00–5.03 (m, 1H, 7-H), 7.23 (d, J=8.0 Hz, 2H, Ph), 7.68 (d, J=8.0 Hz, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.71 (−, *c*Pr-C), 13.12 (−, *c*Pr-C), 18.43 (C_{quat}, *c*Pr-C), 21.26 (+, CH_3), 27.81 (−)*, 27.81 [+, $C(CH_3)_3$], 36.50 (−), 36.81 (−), 39.94 (+, C-5), 40.82 (−), 79.78 [C_{quat}, $C(CH_3)_3$], 115.14 (−, vinyl), 122.46 (+, C-7), 126.91 (+, Ph-C), 129.44 (+, Ph-C), 136.56 (C_{quat}), 141.52 (C_{quat}), 143.08 (C_{quat}), 144.14 (C_{quat}), 174.50 (C_{quat}, C=O). *The peak of this carbon sits under the broad singlet of the *tert*-butyl group. This carbon peak correlates clearly with the multiplet between 2.11–2.18 ppm in the HMQC spectrum. MS (ESI, MeOH) *m*/*z* (%): 885 (100) $[2M+Na]^+$, 454 (63) $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{33}NO_4S$ $[M+H]^+$432.22031; found 432.22036

4.3.29. 5-(1-Iodovinyl)benzo[1,3]dioxole (32). To an ice-cold solution of 5-[(1-diethoxyphosphinyl)oxo-vinyl]-benzo[1,3]dioxole* (2 g, 6.66 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Me_3SiI (2.85 mL, 20.0 mmol) dropwise with a syringe. After stirring 15 min at 0 °C, the reaction mixture was quenched by addition of saturated $NaHCO_3$ (20 mL) and saturated Na_2SO_3 (20 mL) solutions. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The vinyl iodide was purified by column chromatography using *n*-pentane as an eluent. **36** was isolated as a very sensitive pink oil (1.092 g, 60%) and immediately used after isolation. *This precursor was prepared according to a known procedure from the corresponding ketone and directly used for the preparation of **32** without further purification.[24]

^1H NMR (250 MHz, $CDCl_3$) δ=5.98 (s, 2H, OCH_2O), 6.35 (d, J=1.4 Hz, 1H, vinyl), 6.71–6.75 (m, 1H, vinyl), 7.01–7.05 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=101.36 (−), 106.68 (C_{quat}), 107.49 (+, Ph), 108.16 (+, Ph-C), 122.13 (+, Ph-C), 126.13 (−), 135.84 (C_{quat}), 147.16 (C_{quat}), 147.93 (C_{quat}).

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