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Functionalized Organolithium Compounds: Generation via Reductive Lithiation and Nucleophilic Addition to *N*-Phenethylimides. Access to Functionalized Dihydropyrrolo[2,1-*a*]isoquinolinones

Izaskun Manteca, Begoña Etxarri, Ainhoa Ardeo, Sonia Arrasate, Iñaki Osante, Nuria Sotomayor, and Esther Lete*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, Apdo. 644-48080 Bilbao, Spain.

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Abstract: A procedure for producing 1,4-dianion equivalents consists of reductive lithiation, induced by 4,4,-di-*tert*-butylbiphenylide, of functionalized phenyl sulfides. Nucleophilic addition of 4-lithio-2-(trimethylsilylmethyl)but-1-ene **1** and 2-(3-lithiopropyl)-2-trimethylsilyl-1,3-dithiane **2** thus prepared to *N*-phenethyl-*cis*-norbor-5-en-2,3-dicarboximide **9** afforded the corresponding α-hydroxy lactams in good yields. Besides, access to C-10b substituted α,β-unsaturated pyrroloisoquinolinones **3** was efficiently achieved *via* a tandem organolithium nucleophilic addition — *N*-acyliminium ion cyclization sequence and subsequent retro Diels-Alder reaction. The methodology can be extended to functionalized organolithiums, but the *N*-acyliminium cyclization fails if the allylsilane moiety is present.

Functionalized organolithium compounds[1] are interesting building blocks in synthetic organic chemistry because by reaction with carbon electrophiles they produce, together with the formation of a carbon-carbon bond, the transference of functionality to the electrophilic reagent, so polyfunctionalized molecules are prepared in one step.

Reductive lithiation of phenyl sulfides[2] or halides[3] with aromatic radical-anions is a particularly versatile method of preparing organolithium reagents and, in particular, functionalized organolithium compounds. Thus, this procedure has become an extremely popular synthetic tool and new developments in this field are frequently reported. An important development involves the use of catalytic amounts of an arene in the lithiation of chlorinated precursors at low temperature.[4] This often results in largely improved rates and yields *vs.* the original stoichiometric conditions. Among the many subsequent applications of this catalytic procedure, it has been shown that this method can be used not only for chlorine-lithium exchange, but for the preparation of organolithiums from non halogenated precursors, through reductive opening of saturated heterocycles, or to prepare polylithiated synthons, or functionalized organolithium compounds. [5]

On the other hand, we have described a method for preparing pyrroloisoquinolines by a tandem carbophilic addition — *N*-acyliminium ion cyclization sequence from *N*-phenethylimides and alkyllithiums.[6] This strategy allows the efficient preparation of various types of the isoquinoline class of alkaloids just by changing the substitution pattern on the readily available starting imide. Thus, 5-arylpyrrolo[2,1-*a*]isoquinolinones, benzo[*a*]quinolizidones and their 2-oxa analogues, isoindoloisoquinolinones,

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dibenzo[*a*,*h*]quinolizidones, thiazolo-, oxazolo-, and imidazolo [4,3-*a*]isoquinolinones were prepared.[7] An advantage of this strategy is that construction of the heterocyclic system may result in the introduction of functionality on the pendant side chain at the C-1 position of the isoquinoline ring, by the appropriate choice of the organolithium reagent at the first step.

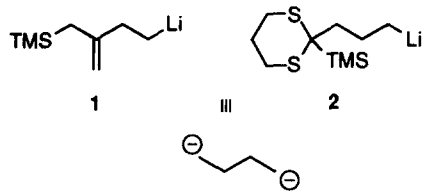


Figure 1

On the basis of these results, it was envisioned that this methodology could be applied to functionalized organolithium compounds. In this context, we thought that 4-lithio-2-(trimethylsilylmethyl)but-1-ene **1** and 2-(3-lithiopropyl)-2-trimethylsilyl-1,3-dithiane **2** (Figure 1) would be of great interest, as they carry allylsilane and 1,3-dithiane moieties that, *a priori*, would be stable under the nucleophilic addition—*N*-acyliminium ion cyclization sequence reaction conditions and, therefore, they could transfer their functionality to the *N*-phenethylimides. We have designed strategies for the preparation of these organolithiums from the corresponding phenyl sulfides or halides, based on reductive lithiation processes. Both methods of organolithium generation involve alkylation of thioacetals and, aside form the ease of preparation of the substrates, have the attractive feature of producing 1,4-dianion equivalents.

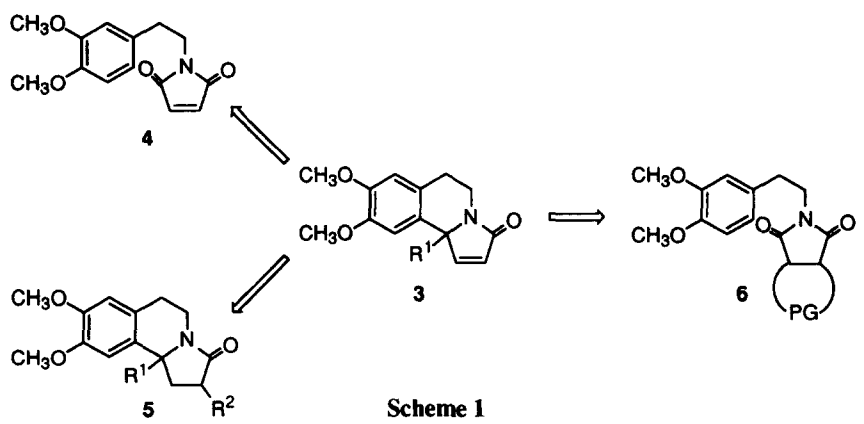
On the other hand, we chose α,β–unsaturated lactams **3** as targets for testing the scope of our methodology, because these nitrogen heterocycles could be adequate precursors of more complex alkaloids, as they would allow further transformations of the C-10b functionalized pyrroloisoquinoline *via* inter- or intramolecular conjugate additions. Besides, recently much interest has been focused on the effectiveness of pyrrolo[2,3-*a*]isoquinolines as antidepressant agents or on their use as PET radiotracers for imaging serotonin uptake sites.[8] We have subsequently developed methodology by which efficient access to pyrrolo[2,3-*a*]isoquinolinones with the α,β–unsaturated lactam unit is achieved, thus significantly expanding the validity nucleophilic addition—*N*-acyliminium ion cyclization sequence.

We now present our results in the synthesis of the functionalized organolithium compounds **1** and **2** and their use for the construction of the pyrrolo[2,3-*a*]isoquinolinone skeleton.

RESULTS AND DISCUSSION

Access to pyrroloisoquinolinone skeleton

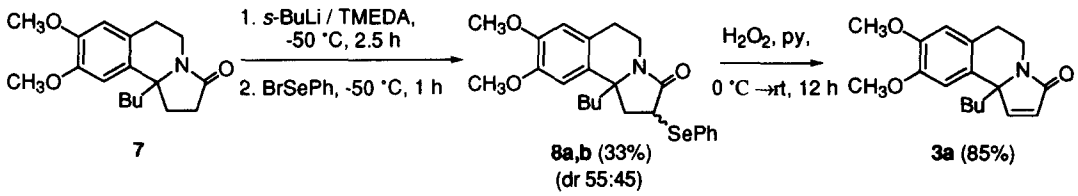
Three different approaches to pyrroloisoquinolines **3** using the tandem carbophilic addition — *N*-acyliminium ion cyclization sequence were examined (Scheme 1). The most direct approach would be the use of *N*-phenethylmaleimide **4** as a precursor, although polymerization might be a competitive process upon treatment with organolithiums. Alternatively, the double bond could be introduced at the final stages of the sequence, *via* oxidative elimination of an adequate precursor **5**, or by carrying a masked double bond in the starting imide **6**.



Scheme 1

A preliminary study of the most adequate approach to pyrroloisoquinoline skeleton **3** was carried out using simple alkyllithiums. As expected, treatment of *N*-phenethylmaleimide **4**[9] with *n*-BuLi at -78 °C led only to polymerization products.[10] In fact, these reaction conditions do not differ from the ones used in anionic polymerization of related substrates.[11]

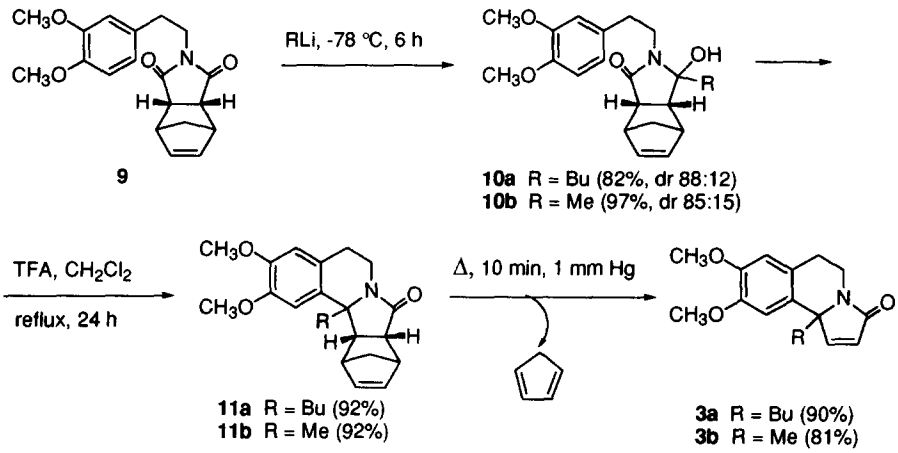
The second method implied the introduction of an adequate substituent on C-2 of a tetrahydropyrroloisoquinolinone, that could be eliminated to afford the desired double bond. In this context, oxidative elimination *via* selenoxides, obtained from the corresponding selenides, has proven to be a highly efficient procedure in the synthesis of α,β–unsaturated lactams.[12] Thus, 10b-butylpyrroloisoquinoline **7**, prepared from *N*-[2-(3,4-dimethoxyphenyl)ethyl]-succinimide by tandem *n*-BuLi addition — *N*-acyliminium ion cyclization,[7d] was treated with LDA and PhSeBr at -78 °C to afford a mixture of the diastereomeric alkylated products **8a,b** in a 60:40 ratio, with an overall yield of 21%. The corresponding dialkylated product was also isolated in minor amounts (5-6%). The use of *s*-BuLi / TMEDA gave a somewhat better yield of the diastereomeric mixture **8a,b** (33%) (Scheme 2).



Scheme 2

The stereochemistry of the products **8a,b** was not determined at this point, as the phenylselenyl group was going to be eliminated in the next step. Therefore, the diastereomeric mixture of **8a,b** was treated with H_2O_2 and pyridine in CH_2Cl_2, to afford the desired pyrroloisoquinolinone **3a** in high yield (83%). The low yield obatined in the alkylation step was related to the unstability of the selenides during work up and purification processes, and not to a poor deprotonation by LDA or *s*-BuLi, as shown by the ^1H NMR spectra of the crude reaction mixtures. Thus, when the alkylation — oxidative elimination sequence was carried out without purification of the intermediate selenides **8a,b**, the overall yield of **3a** raised to 49% (*vs.* 18-28%).

Our third alternative involved the use of *cis*-norbor-5-en-*endo*-2,3-dicarboximide **9** as a substrate for the nucleophilic addition — *N*-acyliminium ion cyclization sequence, as it bears a masked α,β-unsaturated imide moiety, that can be released at the final stages of the synthesis by a retro-Diels-Alder reaction.[13] Imide **9** was prepared by condensation of 2-(3,4-dimethoxyphenyl)ethylamine with *cis*-norbor-5-en-*endo*-2,3-dicarboxylic anhydride in refluxing acetic acid (84%). The viability of this approach was tested using simple alkyllithiums, under the previously optimized reaction conditions.[6,7] Thus, treatment of **9** with *n*-BuLi or MeLi at -78 °C for 6 h afforded the corresponding hydroxy lactams **10a** and **10b** in good yields, as diastereomeric mixtures in a 88:12 and 85:15 ratio, respectively (Scheme 3). Both pairs of diastereomers could not be chromatographically separated, and their relative stereochemistry at C-3 was not determined at this point, as a planar *N*-acyliminium ion was going to be generated in the cyclization step. Though most of the protons appear at the same δ values for both diastereomers, diastereomeric ratios (dr) were obtained by integration of representative signals in the ^{1}H NMR spectra of the mixtures. Subsequent cyclization of **10a** and **10b** with TFA in refluxing CH_2Cl_2 yielded pyrroloisoquinolinones **11a** and **11b**, respectively, which upon heating at 500 °C at reduced pressure (1 mm Hg)[14], afforded almost quantitatively the α,β-unsaturated pyrroloisoquinolinones **3a** and **3b**.



Scheme 3

From the results obtained we may conclude that the latter methodology is a convenient route for the three-steps construction of the dihydropyrroloisoquinolinone skeleton with a high overall yield (*ca.* 80% from imide **9**). The alternative alkylation — oxidative elimination sequence implies one more synthetic step (two steps are required for the preparation of **7** from *N*-[2-(3,4-dimethoxyphenyl)ethyl]succinimide in a 92% overall yield[7d]), and offers a significantly lower yield (80% *vs.* 45% overall for **3a**).

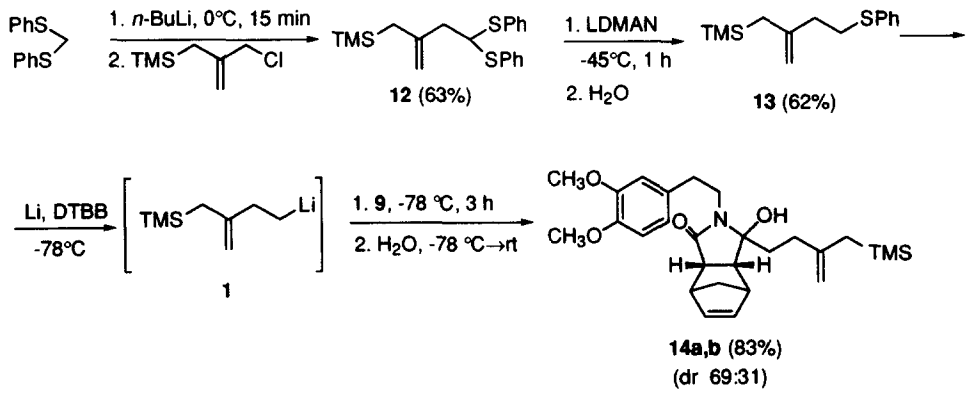
Generation and reactivity of functionalized organolithium compounds

Having established that norbornenimide **9** behaved as an appropriate protected maleimide in this type of reactions, we decided to extend this procedure to functionalized organolithiums **1** and **2**. Homoallyllithiums (β-lithioalkenes), which can be prepared by reductive lithiation of the corresponding homoallyl phenyl sulfides, are rare materials of considerably synthetic and mechanistic interest.[15] In our case, the 4-lithio-2-

(trimethylsilylmethyl)but-1-ene **1** was one of the reagents of choice, because it represents a convenient synthon of an 1,4-dianion, due to the presence of the trimethylsilylallyl group. Though this type of organolithium has no special stabilizing features, primary homoallyllithiums can be prepared in a synthetically useful manner, as they do not present the rearrangements associated with their secondary and tertiary homologous.[15c]

On the other hand, though there are several examples of lithium bishomoenolates in which the carbonyl group is masked as a cyclic acetal,[16] the 2-(3-lithiopropyl)-2-trimethylsilyl-1,3-dithiane **2** (a sulfur-stabilized organolithium compound) would represent a new type of functionalized organolithium, because it could be considered both as an acyl anion equivalent and a masked lithium bishomoenolate, that is a synthon for the $^{-}$C-C-C-C=O unit (a d^4 reagent following Seebach's nomenclature[17]).

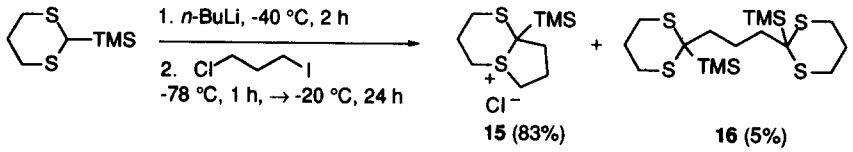
Access to homoallyllithium **1** was achieved as depicted in Scheme 4. Alkylation of bis(phenylthio)methane with 4-chloro-2-(trimethylsilylmethyl)-prop-1-ene proceeded efficiently to afford the bisphenylthioacetal **12**. Reductive lithiation with lithium 1-dimethylaminonaphthalenide (LDMAN)[18], followed by proton quench, yielded sulfide **13** though in a moderate yield (62%, based on a 55% conversion). Several reaction conditions and arenes were tested, but the conversion could not be improved. However, reductive lithiation of **15** was much more efficiently achieved using lithium and 4,4.-di-*tert*-butylbiphenyl (DTBB) as arene in catalytic quantities,[4] affording organolithium **1**. The homoallyllithium has to be manipulated at low temperature in order to avoid its total or partial decomposition under the reaction conditions, mainly by abstraction of a proton from the solvent. The primary organolithium thus prepared **1** is capable of 1,2-addition to carbonyl compounds, hence the reaction of **1** with norbornenimide **9** proceeded smoothly at -78 °C to yield a diastereomeric mixture of hydroxy lactams **14a,b** in a 69:31 ratio (Scheme 4). As in the previous cases, the diastereomers could not be chromatographically separated, and the relative stereochemistry was not determined.



Scheme 4

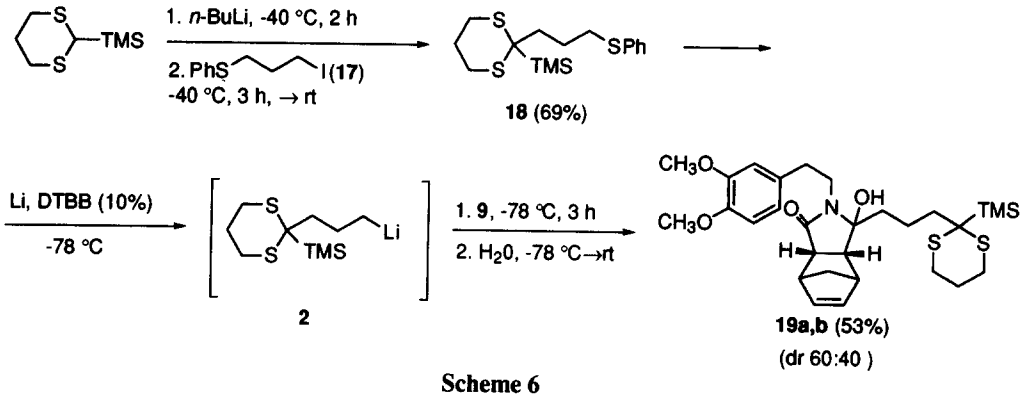
Two procedures were examined for the preparation of sulfur-stabilized organolithium compound **2**, which involved reductive lithiation of chlorides and phenyl sulfides, respectively. Initial attempts to alkylate 2-trimethylsilyl-1,3-dithiane with 1-chloro-4-iodobutane at -78 °C failed to yield the desired 2-(3-chloropropyl)-2-trimethylsilyl-1,3-dithiane and, instead, the bicyclic sulfonium salt **15** was obtained as the major product

(83%). Its formation could be explained *via* an intramolecular cyclization of the chlorothioacetal initially formed.[19] The dialkylated product **16**, obtained in minor amounts (5%) at -78 °C, was the major product when the alkylation was carried out at higher temperatures (*ca.* - 40 °C) (Scheme 5).



Scheme 5

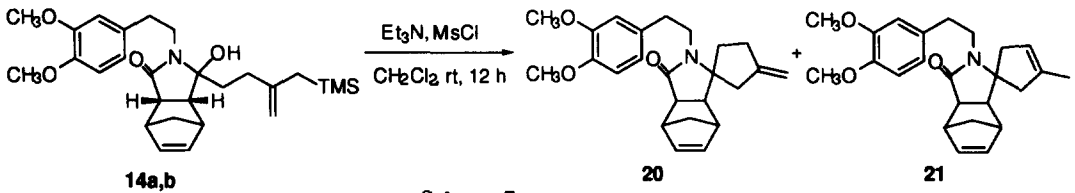
Alternatively, alkylation of 2-trimethylsilyl-1,3-dithiane with iodide **17**[20] afforded phenylsulfide **18**, which was an efficient precursor of organolithium **2** upon treatment with lithium and DTBB under the same conditions used for reductive lithiation of **1** (Scheme 6). The resulting γ-lithio thioketal **2** was treated with the electrophile, the norbornenimide **9**, to afford a diastereomeric mixture of hydroxy lactams **19a,b** in a 60:40 ratio with an overall yield of 53% (76% conversion).



Scheme 6

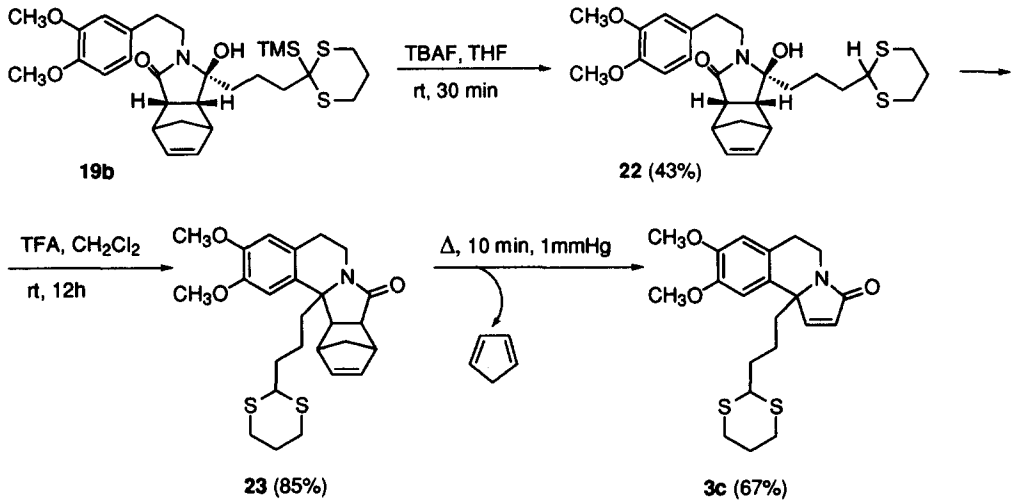
Our next concern was the cyclization *via N*-acyliminium ions applied to the hydroxy lactams **14** and **19** in order to construct the isoquinoline nucleus of pyrrolo[2,1-*a*]isoquinolinones. It should be noted that in the case of hydroxy lactams **14a,b**, the molecules have two types of π-nucleophiles: the aromatic ring and the allylsilane moiety, both could be reactive towards the *N*-acyliminium ion formed. In fact, when hydroxy lactams **14a,b** were subjected to the usual cyclization conditions (TFA) a mixture of products was obtained. It could be deduced from the ^{1}H NMR spectra of the crude reaction mixture that cyclization to the isoquinolinone skeleton had taken place, but also desilylation yielding a mixture of double bond isomerization and degradation products, that was not separated. Other reaction conditions were tested, but no evolution of the starting material was observed using HCl or $BF_3.Et_2O$. However, under basic reaction conditions (Et_3N and MsCl) the allylsilane was the most reactive nucleophile. Thus, a 50: 50 mixture of unseparable spiro-compounds, whose structures were assigned as **20** and **21**, was obtained. No isoquinoline products could be isolated or even detected (Scheme 7). NMR resonaces were used in the determination of the regioisomers ratio from the

mixture. The most significant signals were those of the olefinic protons and the methyl group of the cyclopentane ring of both compounds (see experimental section). A GC-MS analysis showed the presence of both spiro-compounds with a characteristic peak at m/z 313 (M^+ - cyclopentadiene).



Scheme 7

Access to functionalized pyrroloisoquinoline **3c** was finally achieved *via* intramolecular cyclization of hydroxy lactams **19** as depicted in Scheme 8. First, desilylation of diastereomeric hydroxy lactams **19a,b** was carried out using TBAF and afforded hydroxy lactam **22**.[21] We thought that the low yield obtained (15%), could be related to the stereochemistry of the diastereomeric hydroxy lactams. Thus, hydroxy lactams **19a** and **19b** were separated and unambiguously identified.



Scheme 8

Owing to the complex NMR spectra, the ^1H and ^{13}C NMR resonances were assigned by analysis of 2D ^1H-^1H COSY and HMQC spectra. Their relative stereochemistry was finally assigned on the basis of NOESY experiments. The most significant results are shown on Figure 2.

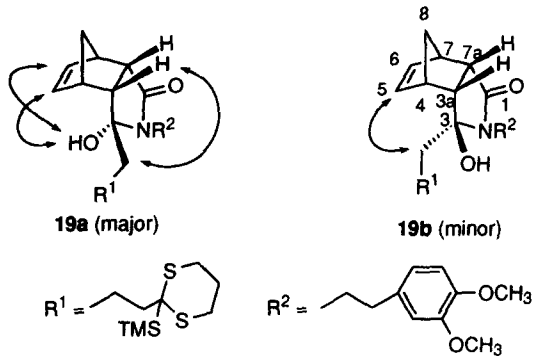


Figure 2. Selected NOE enhancements observed for **19a** and **19b**

The major diastereomer **19a** resulted from organolithium attack from the less hindered side of the starting imide, leaving the hydroxyl group in the *endo* part of the molecule. Thus, a NOE enhancement could be observed between the hydroxylic proton and H-5 and H-6, and between H-3a and the methylenic protons of the substituent on C-3. On the contrary, the minor diastereomer **19b**, with an *exo* hydroxyl, showed an enhancement of the signal due to the methylenic protons of the side chain upon irradiation on H-5, and *vice versa*. **19a** and **19b** were separately submitted to deprotection with TBAF, observing that the expected product **22** was only obtained from **19b** in a 43% yield, whereas **19a** does not yield the desylilated product. Several deprotection conditions were used, but other desylilating agents, as CsF, were not effective, recovering unreacted starting material. Despite the low yield obtained, **22** was submitted to *N*-acyliminium ion cyclization and successfully annelated upon treatment with TFA at rt, affording the functionalized pyrroloisoquinolinone **23** in high yield. The retro-Diels-Alder reaction was accomplished by heating **23** at 500 °C under vacuum to yield α,β-unsaturated lactam **3c**.

CONCLUSIONS

In summary, we have achieved for the first time the preparation of two new functionalized organolithium reagents (1,4-dianion equivalents): 4-lithio-2-(trimethylsilylmethyl)but-1-ene **1** and 2-(3-lithiopropyl)-2-trimethylsilyl-1,3-dithiane **2**, by reductive lithiation of the corresponding phenyl sulfides. It should be noted that the sulfur-stabilized organolithium **2** can be considered both as an acyl anion equivalent and a masked lithium bishomoenolate. Both organolithiums are capable of 1,2-addition to the carbonyl group of imides and thus transfer their functionality to the corrresponding α-hydroxy lactams. On the other hand, convenient approaches to the target C-10b substituted α,β-unsaturated pyrroloisoquinolinones have been developed. It has been demonstrated that the use of *N*-phenethyl-*cis*-norbor-5-en-2,3-dicarboximide **9** as substrate allows to carry the double bond conveniently protected throughout the sequential organolithium nucleophilic addition — *N*-acyliminium ion cyclization, being released by a simple retro Diels-Alder reaction in the last step. This sequence offers better overall yields than an alternative alkylation — oxidative elimination sequence.

EXPERIMENTAL SECTION

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20-25 °C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solutions, unless otherwise stated. Assignment of individual ^{13}C resonances are supported by DEPT experiments. ^1H-{^1H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[22] ^1H-{^1H} COSY, NOESY, and HMQC spectra were recorded at 300 or 500 MHz for ^1H and 75.5 or 126 MHz for ^{13}C in $CDCl_3$ solutions. Mass spectra were recorded under electron impact at 70 eV. GC-MS analyses were performed using a HP-5 column (5% phenyl methyl polysiloxane, 30 m × 0.25 mm × 0.25 μm). HRMS spectra were performed at the corresponding service of the Universidad Autónoma de Madrid. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}). Visualization was accomplished by UV light or by spraying with a 10% fosfomolibdic acid in EtOH.[23] Flash column chromatography[24] on silica gel was performed with Merck Kiesegel 60 (230-400 mesh). HPLC was performed using a LiChrosorb Si60 (7μm) column with a refraction index detector. All solvents used in reactions were anhydrous and purified according to standard procedures.[25] Organolithium reagents were titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

N-[2-(3,4-Dimethoxyphenyl)ethyl]maleimide (**4**)

A solution of 2-(3,4-dimethoxyphenyl)ethylamine (1.5 g, 8.3 mmol) and maleic anhydride (1.60 g, 16.4 mmol) in glacial acetic acid (20 mL) was heated under reflux for 4 h. The mixture was cooled and the acetic acid was evaporated under reduced pressure. H_2O (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 5% CH_2Cl_2/MeOH) afforded the imide **4** (1.64 g, 76%) as white crystals: mp (MeOH) 122-124 °C; IR (KBr) 1720, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) 2.83 (t, J = 7.8 Hz, 2H), 3.73 (t, J = 7.8 Hz, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 6.67 (s, 2H), 6.61-6.80 (m, 3H); ^{13}C NMR ($CDCl_3$) 33.9, 39.1, 55.8, 111.2, 111.9, 120.8, 130.2, 134.0, 147.7, 148.9, 170.6; MS (EI) *m/z* (rel intensity) 261 (M^+, 27), 164 (52), 151 (100), 107 (13), 91 (9), 77 (10), 65 (9), 54 (7); Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.37, H, 5.75, N, 5.36. Found: C, 64.07, H, 5.86, N, 5.04.

10b-Butyl-8,9-dimethoxy-2-phenylselenyl-1,5,6,10b-tetrahydro-pyrrolo[2,1-a]isoquinolin-3(2H)-ones (**8a,b**)

To a solution of the pyrroloisoquinoline **7** (240 mg, 0.8 mmol) in dry THF (20 mL), was added LDA (0.90 mL of a 1.03 M solution in THF, 0.93 mmol) at -78 °C. After stirring for 1 h, a solution of PhSeBr (184 mg, 0.8 mmol) in dry THF (5 mL) was added, and the resulting mixture was stirred at this temperature for further 1 h. The reaction was quenched by the addition of a saturated NH_4Cl solution and allowed to warm to 20 °C. Et_2O (10 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 50% Hexane/AcOEt) afforded the diastereomeric pyrroloisoquinolinones **8a** and **8b**, in a 60:40 ratio (75 mg, 21% overall) as oils. **8a** (major diastereomer): IR ($CHCl_3$) 1682 cm^{-1}; ^1H NMR ($CDCl_3$) 0.86 (t, J = 6.8 Hz, 3H), 1.22-1.28 (m, 4H), 1.72-1.80 (m, 2H), 2.27 (dd, J = 13.6, 8.7 Hz, 1H), 2.51-2.62 (m, 1H), 2.65-2.78 (m, 1H), 2.86 (dd, J = 13.6, 9.3 Hz, 1H), 3.01-3.08 (m, 1H), 3.83 (s,

3H), 3.84 (s, 3H), 4.14 (t, J = 9.0 Hz, 1H), 4.27-4.38 (m, 1H), 6.40 (s, 1H), 6.46 (s, 1H), 7.10-7.19 (m, 3H), 7.53-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) 13.9, 22.7, 26.1, 27.5, 35.0, 40.6, 41.6, 41.8, 55.8, 56.1, 62.7, 107.7, 111.4, 124.3, 128.0, 128.8, 134.3, 135.2, 147.7, 147.8, 171.2; MS (EI) *m/z* (rel intensity) 301 (M^+-157, 1), 246 (2), 244 (100), 228 (4), 200 (11), 183 (3), 165 (2), 130 (3), 77 (4). **8b** (minor diastereomer): IR ($CHCl_3$) 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.84 (t, J = 7.0 Hz, 3H), 1.01-1.22 (m, 4H), 1.74-1.81 (m, 2H), 2.47 (dd, J = 14.0, 5.6 Hz, 1H), 2.57-2.69 (m, 2H), 2.87-3.02 (m, 1H), 3.14 (td, J = 12.1, 5.0 Hz, 1H), 3.82 (s, 3H) *, 3.83 (s, 3H)*, 3.82-3.91 (m, 1H)*, 4.30 (ddd, J = 12.1, 5.9, 1.7 Hz, 1H), 6.52 (s, 1H), 6.53 (s, 1H), 7.25-7.30 (m, 3H), 7.68-7.72 (m, 2H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 13.9, 22.8, 26.4, 27.2, 35.6, 39.4, 40.2, 41.7, 55.9, 56.2, 63.2, 108.0, 111.6, 125.1, 128.0, 129.1, 134.0, 134.7, 147.7, 147.8, 172.7; MS (EI) *m/z* (rel intensity) 246 (M^+ - 212, 100), 230 (9), 202 (6), 185 (4), 165 (5), 123 (8), 77 (5). Alternatively, a solution of **7** (639 mg, 2.1 mmol) in dry THF (20 mL), was added to a solution of *s*-BuLi (2.34 mL of a 1.7 M solution in THF, 2.8 mmol) and TMEDA (0.41 mL, 2.8 mmol) in THF (8 mL) at -50 °C. After stirring for 2.5 h, a solution of PhSeBr (654 mg, 2.8 mmol) in dry THF (5 mL) was added, and the resulting mixture was stirred at this temperature for further 1 h. Usual work up and column chromatography afforded **8a,b** (248 mg, 33%) in a 55:45 ratio.

10b-Butyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinolin-3(10bH)-one (**3a**)

To a solution of **8a** and **8b** (diastereomeric mixture in a 60:40 ratio) (160 mg, 0.4 mmol) in CH_2Cl_2 (25 mL) was added pyridine (0.07 mL, 0.9 mmol) and 30% H_2O_2 (0.04 mL, 1.1 mmol) dropwise. The resulting mixture was allowed to warm to 20 °C, and stirred for 12 h. The reaction was quenched by the addition of 5% aqueous HCl (5 mL). The organic layer was separated and washed successively with 5% aqueous HCl (2 × 5 mL), brine (2 × 5 mL), and H_2O (2 × 5 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 80% Hexane/AcOEt) afforded pyrroloisoquinolinone **3a** (90 mg, 85%) as an oil: IR ($CHCl_3$) 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.84 (t, J = 7.1 Hz, 3H), 1.08-1.26 (m, 4H), 1.85-1.96 (m, 2H), 2.64 (dd, J = 16.2, 4.1 Hz, 1H), 2.91 (td, J = 16.2, 6.7 Hz, 1H), 3.15 (td, J = 12.4, 4.1 Hz, 1H), 3.83 (s, 3H), 3.88 (s, 3H), 4.41 (dd, J = 12.4, 6.7 Hz, 1H), 6.13 (d, J = 5.7 Hz, 1H), 6.59 (s, 1H), 6.69 (s, 1H), 7.22 (d, J = 5.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 13.9, 22.7, 25.3, 29.0, 34.7, 38.7, 55.9, 56.2, 68.5, 109.2, 112.1, 125.2, 126.1, 129.7, 147.6, 148.1, 151.9, 170.8; MS (EI) *m/z* (rel intensity) 301 (M^+, 2), 244 (100), 228 (3), 200 (11); HRMS Calcd for $C_{18}H_{23}NO_3$: 301.1678. Found: 301.1685.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-cis-norborn-5-en-endo-2,3-dicarboxyimide (**9**)

A solution of 2-(3,4-dimethoxyphenyl)ethylamine (1.5 g, 8.3 mmol) and *cis*-norborn-5-en-*endo*-2,3-dicarboxylic anhydride (2.7 g, 16.5 mmol) in glacial acetic acid (20 mL) was heated under reflux for 4 h. The mixture was cooled and the acetic acid was evaporated under reduced pressure. H_2O (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 80% Hexane/AcOEt) afforded the imide **9** (2.3 g, 84%) as white crystals: mp (MeOH) 112-114 °C; IR (KBr) 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.44 (d, J = 8.7 Hz, 1H), 1.62 (d, J = 8.7 Hz, 1H), 2.61 (t, J = 7.8 Hz, 2H), 3.09-3.17 (m, 2H), 3.21-3.30 (m, 2H), 3.49 (t, J = 7.8 Hz, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 5.88 (br s, 2H), 6.59-6.72 (m, 3H); ^{13}C NMR ($CDCl_3$) 32.9, 39.2, 44.6, 45.4, 51.9, 55.6, 110.9, 111.7, 120.6, 130.1, 134.1, 147.4, 148.6, 177.3;

MS (EI) *m/z* (rel intensity) 327 (M^+, < 1), 261 (24), 164 (54), 151 (100), 107 (10), 91 (7), 65 (9). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71, H, 6.46, N, 4.28. Found: C, 64.58, H, 5.6.52, N, 4.19.

Addition of RLi to imide **9**. *Typical procedure A*

3-Butyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-3-hydroxy-3a,4,7,7a-tetrahydro-4,7-methanoisoindolin-1-one (**10a**). To a solution of the imide **9** (327 mg, 1 mmol) in dry THF (30 mL), *n*-BuLi (1.83 mL of a 1.2 M solution in hexanes, 2.2 mmol) was added at -78 °C. The resulting mixture was stirred at this temperature for 6 h, quenched by the addition of H_2O (10 mL), and allowed to warm to 20 °C. Et_2O (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 5% CH_2Cl_2/MeOH) afforded hydroxy lactam **10a** (a 88:12 mixture of diastereomers) as an oil (315 mg, 82%). NMR data of major diastereomer are given: IR ($CHCl_3$) 3320, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 0.87 (t, *J* = 6.9 Hz, 3H), 1.39 (d, *J* = 8.1 Hz, 1H), 1.23-1.40 (m, 4H), 1.53 (d, *J* = 8.1 Hz, 1H), 1.51-1.73 (m, 2H), 1.98 (s, 1H), 2.70-2.80 (m, 3H), 2.91-3.05 (m, 3H), 3.25 (br s, 1H), 3.40-3.51 (m, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 5.99 (dd, *J* = 5.5, 2.7 Hz, 1H), 6.12 (dd, *J* = 5.5, 2.7 Hz, 1H), 6.68-6.71 (m, 3H); ^{13}C NMR ($CDCl_3$) 13.9, 22.5, 25.2, 34.5, 39.8, 40.8, 45.1, 45.7, 47.6, 49.3, 51.9, 55.7, 55.8, 91.1, 111.0, 112.1, 120.7, 131.7, 133.1, 136.5, 147.4, 148.7, 173.8; MS (EI) *m/z* (rel intensity) 367 (M^+ - 18, < 1), 343 (1), 328 (1), 310 (1), 244 (3), 164 (100); HRMS Calcd for $C_{23}H_{31}NO_4$: 385.2252. Found: 385.2246.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-hydroxy-3-methyl-3a,4,7,7a-tetrahydro-4,7-methanoisoindolin-1-one (**10b**). According to Typical Procedure A, described for **10a**, imide **9** (327 mg, 1 mmol) was treated with MeLi (1.37 mL of a 1.6 M solution in Et_2O, 2.2 mmol) to afford hydroxy lactam **10b** as a 85:15 mixture of diastereomers, that was used without further purification (332 mg, 97%). NMR data of major diastereomer are given, obtained from the spectra of the diastereomeric mixture (oil): IR ($CHCl_3$) 3354, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) 1.30 (s, 3H)*, 1.31 (d, *J* = 8.3 Hz, 1H)*, 1.48 (d, *J* = 8.3 Hz, 1H), 2.44-2.50 (m, 1H), 2.64-2.75 (m, 2H), 2.95 (br s, 1H), 3.02-3.17 (m, 3H), 3.22-3.47 (m, 1H), 3.74 (s, 3H), 3.76 (s, 3H); 5-87-5.90 (m, 1H), 5.96-6.00 (m, 1H), 6.65-6-78 (m, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 22.6, 34.6, 40.6, 44.3, 44.5, 46.9, 51.1, 51.6, 55.5, 89.1, 110.8, 111.7, 120.4, 131.5, 133.11, 135.2, 147.1, 148.4, 175.9; MS (EI) *m/z* (rel intensity) 325 (M^+ - 18, 4), 259 (1), 164 (100), 151 (15), 135 (2), 121 (3), 108 (15); HRMS Calcd for $C_{20}H_{25}NO_4$: 343.1783. Found: 343.1776.

Cyclization Reactions. Typical Procedure B

12b-Butyl-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-a]isoquinolin-8-one (**11a**). To a solution of hydroxy lactam **10a** (385 mg, 1 mmol) in CH_2Cl_2 (10 mL), TFA (0.38 mL, 5 mmol) was added and the resulting solution was heated at reflux for 24 h. The reaction mixture was treated with saturated aqueous Na_2CO_3, the organic layer was decanted and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (silica gel, 80% Hexane/AcOEt) afforded pyrroloisoquinolinone **11a** as an oil (354 mg, 92%): IR ($CHCl_3$) 1775 cm^{-1}; ^1H NMR ($CDCl_3$) 0.89 (t, *J* = 6.9 Hz, 3H), 1.43 (d, *J* = 8.3 Hz, 1H), 1.18-1.53 (m, 4H), 1.62 (d, *J* = 8.3 Hz, 1H), 1.73-1.85 (m, 2H), 2.78 (dd, *J* = 16.4, 6.3 Hz, 1H), 3.06 (ddd, *J* = 16.4, 10.2, 9.5 Hz, 1H), 3.30-3.40 (m, 3H), 3.41 (br s, 1H), 3.48-3.51 (m, 1H), 3.86 (s, 3H), 3.92 (s, 3H), 4.17 (dd, *J* = 13.4, 7.4 Hz, 1H), 6.20 (dd, *J* = 5.5, 2.3

Hz, 1H), 6.31 (dd, J = 5.5, 2.3 Hz, 1H), 6.61 (s, 1H), 6.76 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.8, 23.3, 26.5, 27.9, 35.1, 37.7, 44.6, 45.9, 48.9, 49.1, 52.4, 55.8, 56.3, 65.4, 109.3, 112.1, 125.5, 133.2, 134.6, 135.4, 146.7, 148.1, 177.6; MS (EI) *m/z* (rel intensity) 367 (M^+, 1), 310 (22), 244 (100), 228 (3), 200 (10), 183 (3), 164 (15); HRMS Calcd for $C_{23}H_{29}NO_3$: 367.2147. Found: 367.2141.

2,3-Dimethoxy-12b-methyl-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin[2,3-a]isoquinolin-8-one (**11b**). According to Typical Procedure B, described for **10a**, hydroxy lactam **10b** (343 mg, 1 mmol) was treated with TFA (0.38 mL, 5 mmol) to afford pyrroloisoquinolinone **11b**, that was purified by column chromatography (silica gel, 80% Hexane/AcOEt) (300 mg, 92%): white crystals, mp (Et_2O) 158-160 °C; IR (KBr) 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.36 (d, J = 8.2 Hz, 1H), 1.37 (s, 3H), 1.55 (d, J = 8.2 Hz, 1H), 2.29-2.42 (m, 1H), 2.80-2.98 (m, 2H), 3.00-3.08 (m, 2H), 3.10-3.20 (m, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 4.01-4.10 (m, 1H), 6.10-6.16 (m, 2H), 6.41 (s, 1H), 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$) 25.8, 26.4, 34.4, 44.1, 45.4, 48.5, 49.5, 51.8, 55.3, 55.7, 60.9, 107.6, 111.3, 125.3, 134.2, 134.7, 136.4, 147.0, 147.2, 174.7; MS (EI) *m/z* (rel intensity) 325 (M^+, 10), 310 (18), 245 (17), 244 (100), 200 (10), 91 (6), 85 (12), 83 (18), 77 (4)); Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82, H, 7.12, N, 4.30. Found: C, 73.50, H, 6.98, N, 4.36.

Retro Diels-Alder Reaction. Typical Procedure C

10b-Butyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinolin-3(10bH)-one (**3a**). Pyrroloisoquinolinone **11a** (367 mg, 1 mmol) was heated at 500 °C under vacuum (1 mm Hg). Heating was continued until no more evolution of cyclopentadiene was observed (10 min). The crude product was purified by column chromatography (silica gel, 80% Hexane/AcOEt) (270 mg, 90%), whose data were identical to those previously reported (*vide supra*).

8,9-Dimethoxy-10b-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-3(10bH)-one (**3b**). According to Typical Procedure C, **11b** (325 mg, 1 mmol) was heated under vacuum, affording pyrroloisoquinolinone **3b**, The crude product was crystalized from Et_2O to afford **11** as pale yellow crystals (210 mg, 81%): mp (Et_2O) 148-150 °C; IR (KBr): 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.45 (s, 3H), 2.52 (dd, J = 16.0, 4.2 Hz, 1H), 2.71-2.85 (m, 1H), 3.09 (td, J = 4.2, 3.1 Hz, 1H), 3.68 (s, 3H), 3.74 (s, 3H) 4.26 (dd, J = 13.1, 7.0 Hz, 1H), 5.94 (d, J = 5.7 Hz, 1H), 6.47 (s, 1H), 6.62 (s, 1H), 7.29 (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 26.2, 28.7, 34.1, 55.4, 55.7, 65.2, 108.7, 111.6, 124.3, 124.7, 128.7, 147.2, 147.6, 153.1, 169.7; MS (EI) *m/z* (rel intensity) 259 (M^+, 11), 245 (16), 244 (100), 228 (6), 200 (20), 183 (5), 170 (5), 130 (5), 115 (7), 77 (9); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48, H, 6.61, N, 5.40. Found: C, 69.23, H, 6.87, N, 5.22.

4,4-Bis(phenylthio)-2-[(trimethylsilyl)methyl]but-1-ene (**12**)

To a solution of bis(phenylthio)methane (532 mg, 2.3 mmol) in dry THF (10 mL), was added *n*-BuLi (1.94 mL of a 1.3 M solution in THF, 2.5 mmol) at 0 °C. After stirring for 15 min, a solution of 2-chloromethyl-3-trimethylsilylprop-1-ene (648 mg, 4 mmol) was added, the resulting mixture was allowed to warm to 20 °C, and it was stirred for 1 h. The reaction was quenched by addition of H_2O (5 mL). Et_2O (10 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 5% Hexane/AcOEt) afforded **12** as an oil (520 mg, 63%): IR ($CHCl_3$) 3072, 2952 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.00 (s, 9H), 1.57 (s, 2H), 2.57 (d, J = 7.1 Hz, 2H), 4.59 (t, J = 7.1 Hz, 1H), 4.77 (br s, 1H), 4.82 (br s, 1H), 7.33-7.56 (m, 10 H); ^{13}C NMR ($CDCl_3$) -1.5, 26.3, 44.3, 56.4, 110.9, 127.6,

128.8, 132.8, 134.2, 143.1; MS (EI) *m/z* (rel intensity) 358 (M^+, 1), 249 (17), 233 (1), 231 (1), 175 (2), 167 (4), 73 (100). Anal. Calcd for $C_{20}H_{26}S_2Si$: C, 66.98, H, 7.31. Found: C, 66.86, H, 7.11.

4-Phenylthio-2-[(trimethylsilyl)methyl]but-1-ene (**13**)

N,N-dimethylaminonaphthalene (DMAN) (2.10 mL, 12.7 mmol) was added dropwise over a suspension of Li powder (103 mg, 14.7 mmol) in dry THF (25 mL) at -45 °C, and the resulting mixture was stirred at this temperature for 3.5 h. A solution of **12** (1.42 g, 3.98 mmol) in dry THF (5 mL) was added dropwise, and the mixture was stirred at -45 °C for 1.5 h. The reaction was quenched by the addition of H_2O (10 mL), the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 1% Hexane/AcOEt) afforded **13** as an oil (339 mg, 62% based on a 55% conversion): IR ($CHCl_3$): 3070, 2952 cm^{-1}; ^1H NMR ($CDCl_3$) -0.02 (s, 9H), 1.52 (s, 2H), 2.27 (t, J = 7.7 Hz, 2H), 3.01 (t, J = 7.7 Hz, 2H), 4.59 (br s, 1H), 4.64 (br s, 1H), 7.12-7.51 (m, 5H); ^{13}C NMR ($CDCl_3$) -1.4, 26.8, 32.0, 37.7, 108.2, 125.8, 127.5, 128.8, 129.1, 145.7; MS (EI) *m/z* (rel intensity) 250 (M^+, 4), 235 (5), 177 (14), 167 (6), 144 (4), 119 (13), 109 (3), 91 (3), 73 (100), 59 (6). Anal. Calcd for $C_{14}H_{22}SSi$: C, 67.13, H, 8.85. Found: C, 67.30, H, 9.18.

(3R,3aR*,7aS*)- and (3S*,3aR*,7aS*)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-hydroxy-3-[3-[(trimethylsilyl)methyl]but-3-enyl]-3a,4,7,7a-tetrahydro-4,7-methaneisoindolin-1-one* (**14a,b**)

To a blue suspension of Li powder (530 mg, 76.3 mmol) and DTBB (425 mg, 0.5 mmol) in THF (10 mL) at -78 °C, was added a solution of sulfide **13** (1.32 g, 5.3 mmol) in THF (10 mL), and the reaction mixture was stirred for 1 h, resulting in the formation of organolithium **1**. A solution of imide **9** (1.74 g, 5.3 mmol) in dry THF (100 mL) was then added, and the reaction mixture was stirred for 3 h. H_2O (15 mL) was added and the reaction mixture was allowed to warm to 20 °C. Et_2O (20 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 70% Hexane/AcOEt) afforded a diastereomeric mixture of hydroxy lactams **14a,b** in a 69:31 ratio (2.10 g, 83%) as an oil: IR ($CHCl_3$) 3300, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) -0.02 (s, 9H, major diastereomer), 0.00 (s, 9H, minor diastereomer), 0.53-0.64 (m, 2H, minor diastereomer), 1.31-1.50 (m, 3H, both diastereomers), 1.71-2.03 (m, 4H, both diastereomers), 2.35 (d, J = 14.4 Hz, 1H, major diastereomer), 2.50 (d, J = 14.4 Hz, 1H, major diastereomer), 2.62-2.83 (m, 2H, both diastereomers), 2.89-3.12 (m, 4H, both diastereomers), 3.26 (br s, 1H, both diastereomers), 3.41-3.57 (m, 1H, both diastereomers), 3.83 (s, 3H, both diastereomers), 3.85 (s, 3H, both diastereomers), 4.52 (s, 1H, minor diastereomer), 4.57 (s, 1H, minor diastereomer), 4.84 (s, 1H, major diastereomer), 5.00 (s, 1H, major diastereomer), 5.98-6.19 (m, 2H, both diastereomers), 6.70-6.80 (m, 3H, both diastereomers); ^{13}C NMR ($CDCl_3$) -1.8 (major diastereomer), -1.4 (minor diastereomer), 14.9 (major diastereomer), 27.1 (minor diastereomer), 31.4 (major diastereomer), 31.6 (minor diastereomer), 34.5 (minor diastereomer), 34.6 (major diastereomer), 38.2 (minor diastereomer), 40.8 (minor diastereomer), 41.3 (major diastereomer), 45.1 (both diastereomers), 45.7 (major diastereomer), 45.8 (minor diastereomer), 45.9 (both diastereomers), 46.9 (major diastereomer), 47.7 (minor diastereomer), 49.1 (major diastereomer), 49.3 (minor diastereomer), 51.8 (major diastereomer), 52.0 (minor diastereomer), 55.8 (both diastereomers), 55.9 (both diastereomers), 90.6 (major diastereomer), 91.0 (minor diastereomer), 107.1 (minor

diastereomer), 111.1 (major diastereomer), 112.1 (minor diastereomer), 113.6 (major diastereomer), 120.8 (both diastereomers), 131.7 (minor diastereomer), 131.8 (major diastereomer), 133.1 (minor diastereomer), 133.1 (major diastereomer), 136.4 (major diastereomer), 136.7 (minor diastereomer), 146.2 (minor diastereomer), 146.7 (major diastereomer), 147.5 (minor diastereomer), 148.8 (major diastereomer), 173.6 (minor diastereomer), 173.7 (major diastereomer); MS (EI) *m/z* (rel intensity) 469 (M^+, < 1), 451 (1), 385 (1), 328 (3), 262 (3), 221 (2), 206 (1), 164 (100), 151 (100), 107 (5), 73 (33); HRMS Calcd for $C_{27}H_{39}NO_4Si$: 469.2648. Found: 469.2646.

Alkylation of 2-trimethylsilyl-1,3-dithiane. 4-Thia-7a-thioniaperhydroindene chloride (**15**) *and 1,3-bis(2-trimethylsilyl-1,3-dithian-2-yl)propane* (**16**)

To a solution of 2-trimethylsilyl-1,3-dithiane (400 mg, 2.1 mmol) in dry THF (7 mL), was added *n*-BuLi (1.9 mL of a 1.2 M solution in THF, 2.3 mmol) at -40 °C. After 2 h, the reaction mixture was cooled to -78 °C, and a solution of 1-chloro-3-iodopropane (0.22 mL, 2.1 mmol) in dry THF (1 mL) was added. The resulting solution was slowly allowed to warm to -20 °C, and was stirred at this temperature for 24 h. The reaction was quenched by the addition of H_2O (5 mL) at 20 °C. Et_2O (10 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 50% Hexane/AcOEt) afforded the sulfonium salt (**15**) and the dialkylated product (**16**) as oils. *Sufonium salt* **15** (402 mg, 83%): ^1H NMR ($CDCl_3$) 0.17 (s, 9H), 1.77-2.09 (m, 4H), 2.30-2.64 (m, 4H), 3.58 (t, J = 6.1, 2H), 2.95-3.02 (m, 2H); ^{13}C NMR ($CDCl_3$) -2.7, 23.1, 24.9, 30.6, 34.3, 48.4; MS (EI) *m/z* (rel intensity) 160 (M^+ - 73, 18), 127 (3), 113 (15), 106 (30), 87 (33), 86 (70), 85 (100). *Dithiane* **16** (22 mg, 5%): ^1H NMR ($CDCl_3$) 0.87 (s, 18H), 1.57-2.03 (m, 6H), 2.20-2.26 (m, 4H), 2.41-2.50 (m, 4H), 2.98-3.09 (m, 4H); ^{13}C NMR ($CDCl_3$) -2.6, 23.3, 25.1, 26.0, 37.7, 38.5; MS (EI) *m/z* (rel intensity) 424 (M^+, 2), 351 (2), 318 (1), 145 (65), 113 (22), 73 (100).

3-Iodopropyl phenyl sulfide (**17**)

To a solution of thiophenol (0.51 mL, 5 mmol) in dry THF (10 mL), was added *n*-BuLi (3.44 mL of a 1.6 M solution in THF, 5.5 mmol) at -50 °C. The reaction mixture was allowed to warm to 20 °C during 1 h, then was transferred over a solution of 1,3-diiodopropane (0.57 mL, 5 mmol) in dry THF (50 mL), at -50 °C, and the resulting mixture was stirred at this temperature for further 1.5 h. The reaction was quenched by the addition of H_2O. Et_2O (25 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 2.5% Hexane/AcOEt) afforded sulfide **17** as an oil (460 mg, 33%): IR ($CHCl_3$) 3000, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) 2.11 (quin, *J* = 6.8 Hz, 2H), 3.03 (t, *J* = 6.9 Hz, 2H), 3.30 (t, *J* = 6.6 Hz, 2H), 7.19-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) 4.9, 32.2, 34.1, 126.1, 128.8, 129.4, 135.4; MS (EI) *m/z* (rel intensity) 278 (M^+, 46), 151 (100), 123 (93), 109 (52), 77 (21). Anal. Calcd for $C_9H_{11}IS$: C, 38.86, H, 3.98. Found: C, 38.47, H, 3.74.

2-[(3-Phenylthio)propyl]-2-trimethylsilyl-1,3-dithiane (**18**)

To a solution of 2-trimethylsilyl-1,3-dithiane (0.19 mL, 1 mmol) in dry THF (3 mL), was added *n*-BuLi (0.66 mL of a 1.6 M solution in THF, 1.05 mmol) at -40 °C. After 2 h, a solution of sulfide **17** (278 mg, 1 mmol) in dry THF (10 mL) was added at -40 °C, and the resulting solution was stirred at this temperature for further 3 h, and then was allowed to warm to 20 °C. H_2O (10 mL) and Et_2O (25 mL) were added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 2.5% Hexane/AcOEt) afforded dithiane **18** as an oil (240 mg, 69%): IR ($CHCl_3$) 3000, 2960, 1480, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) 0.15 (s, 9H), 1.81-2.07 (m, 4H), 2.31-2.46 (m, 4H), 2.95-3.06 (m, 4H), 7.13-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) -2.7, 23.2, 24.9, 27.0, 34.0, 36.0, 38.3, 125.8, 128.7, 129.0, 136.5; MS (EI) *m/z* (rel intensity) 342 (M^+, 1), 327 (1), 269 (10), 159 (35), 110 (23), 73 (100). Anal. Calcd for $C_{16}H_{26}S_3Si$: C, 56.14, H, 7.60. Found: C, 56.44, H, 7.39.

(3R,3aR*,7aS*)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-hydroxy-3-[3-(2-trimethylsilyl-1,3-dithian-2-yl)-propyl]-3a,4,7,7a-tetrahydro-4,7-methaneisoindolin-1-one* (**19a**) *and (3S*,3aR*,7aS*)-N-[2-(3,4-dimethoxyphenyl)ethyl]-3-hydroxy-3-[3-(2-trimethylsilyl-1,3-dithian-2-yl)propyl]-3a,4,7,7a-tetrahydro-4,7-methaneisoindolin-1-one* (**19b**)

To a blue suspension of Li powder (530 mg, 76.36 mmol) and DTBB (425 mg, 0.5 mmol) in THF (10 mL) at -78 °C, was added a solution of dithiane **18** (1.83 g, 5.3 mmol) in THF (10 mL), and the reaction mixture was stirred for 1 h, resulting in the formation of organolithium **2**. A solution of imide **9** (1.74 g, 5.3 mmol) in dry THF (100 mL) was then added, and the reaction mixture was stirred for 3 h. H_2O (15 mL) was added and the reaction mixture was allowed to warm to 20 °C. Et_2O (20 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 60% Hexane/AcOEt) afforded diastereomeric hydroxy lactams **19a** and **19b** in a 60:40 ratio. **19a** (710 mg, 32%), colorless oil: IR ($CHCl_3$) 3421, 1674 cm^{-1}; ^1H NMR ($CDCl_3$) -0.02 (s, 9H), 0.39-0.48 (m, 2H), 1.41 (d, J = 7.6 Hz, 1H), 1.53 (d, J = 7.6 Hz, 1H)*, 1.54-1.75 (m, 4H)*, 1.82-2.01 (m, 2H), 2.79 (s, 1H)#, 2.61-2.91 (m, 4H)#, 2.96-3.04 (m, 2H), 3.12-3.29 (m, 3H), 3.40 (dd, J = 8.9, 4.20 Hz, 1H), 3.55-3.74 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 6.06 (dd, J = 5.6, 2.8 Hz, 1H), 6.15 (dd, J = 5.6, 2.7 Hz, 1H), 6.71-6.80 (m, 3H) (*,# designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) -1.6, 17.4, 19.6, 23.4, 27.4, 27.7, 34.2, 40.6, 44.0, 46.0, 46.1, 47.0, 49.3, 51.6, 55.8, 55.9, 63.0, 98.4, 111.1, 112.1, 120.7, 132.3, 133.8, 135.7, 147.4, 148.7, 175.4; MS (EI) *m/z* (rel intensity) 561 (M^+, < 1), 328 (71), 262 (100), 233 (12), 165 (81), 73 (62); HRMS Calcd for $C_{29}H_{43}NO_4S_2Si$: 561.2403. Found: 561.2398.

19b (480 mg, 21%), yellow oil: IR ($CHCl_3$) 3400, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) 0.17 (s, 9H), 1.36 (d, J = 7.6 Hz, 1H), 1.69 (s, 1H), 1.34-2.41 (m, 9H), 2.39-2.51 (m, 2H), 2.72-2.83 (m, 3H), 2.90-3.04 (m, 3H), 3.04-3.12 (m, 2H), 3.28 (br s, 1H), 3.44-3.55 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 6.00-6.02 (m, 1H), 6.15-6.19 (m, 1H), 6.71-6.80 (m, 3H); ^{13}C NMR ($CDCl_3$) -2.5, 21.5, 23.6, 24.9, 34.6, 37.5, 38.3, 40.4, 40.8, 45.1, 45.9, 47.9, 49.3, 52.2, 55.9, 63.2, 91.0, 111.1, 112.2, 120.8, 131.7, 132.8, 137.2, 147.6, 148.8, 173.6; MS (EI) *m/z* (rel intensity) 544 (M^+ -17, 1), 478 (1), 396 (37), 371 (2), 272 (89), 205 (46), 164 (100), 73 (81); HRMS Calcd for $C_{29}H_{43}NO_4S_2Si$: 561. 2403. Found: 561.2397.

[N-[2-(3,4-Dimethoxyphenyl)ethyl]-3a,4,7,7a-tetrahydro-4,7-methaneisoindolin-1-one]-3-spiro-1'-(3-methylidencyclopentane) (**20**) *and [N-[2-(3,4-Dimethoxyphenyl)ethyl]-3a,4,7,7a-tetrahydro-4,7-methane-isoindolin-1-one]-3-spiro-1'-(3-methylcyclopent-3-ene)* (**21**)

To a solution of **14a,b** (diastereomeric mixture in a 69:31 ratio) (245 mg, 0.5 mmol) in dry CH_2Cl_2 (1 mL), were added triethylamine (0.1 mL, 0.7 mmol) and mesyl chloride (0.05 mL. 0.7 mmol). The reaction mixture was stirred at room temperature for 12 h. H_2O (3 mL) and Et_2O (5 mL) were added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with HCl (3 mL, 1% aqueous), H_2O (3 mL), Na_2CO_3 (3 mL, 5% aqueous), and H_2O (3 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, 70% Hexane/AcOEt) afforded a mixture of spiro compounds **20** and **21** in a 50:50 ratio (135 mg, 71%), as an oil: IR ($CHCl_3$) 1700, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) 1.20-1.78 (m, 10H, both regioisomers), 1.81 (s, 3H, spiro compound **21**), 2.54-2.75 (m, 4H, both regioisomers), 2.90 (d, J = 7.5 Hz, 2H, spiro compound **21**), 3.01-3.12 (m, 1H, one regioisomer), 3.15-3.45 (m, 9H, both regioisomers), 3.57 (d, J = 17.9 Hz, 2H, one regioisomer), 3.60-3.82 (m, 2H, one regioisomer), 3.85 (s, 6H, both regioisomers), 3.89 (s, 6H, both regioisomers), 4.66 (t, J = 7.5 Hz, 1H, spiro compound **21**), 4.72-4.85 (m, 2H, spiro compound **20**), 5.85-6.05 (m, 4H, both regioisomers), 6.68-6.82 (m, 6H, both regioisomers). MS (EI) *m/z* (rel intensity) *one regioisomer* 313 (M^+-66, 3), 258 (16), 165 (15), 164 (100), 151 (15), 149 (16), 134 (3), 120 (4), 107 (6), 91 (9), 79 (6), 77 (10), 65 (6), 55 (6). *The other regioisomer* 313 (M^+-66, 6), 258 (1), 165 (13), 164 (100), 151 (9), 149 (13), 148 (5), 147 (5), 134 (7), 132 (5), 120 (5), 107 (5), 105 (5), 91 (11), 79 (6), 77 (9), 65 (7), 55 (6). Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96, H, 7.70, N, 3.69. Found: C, 76.21, H, 7.45, N, 3.37.

(3S,3aR*,7aS*)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-3-hydroxy-3-[3-(1,3-dithian-2-yl)propyl]-3a,4,7,7a-tetrahydro-4,7-methaneisoindolin-1-one* (**22**)

To a solution of **19b** (62 mg, 0.1 mmol) in dry THF (3 mL), was added TBAF (0.55 mL of a 1 M solution in THF, 0.55 mmol) at 20 °C. After 30 min, H_2O (3 mL) and Et_2O (5 mL) were added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, AcOEt) afforded hydroxy lactam **22** as an oil (23 mg, 43%): IR ($CHCl_3$): 3336, 1657 cm^{-1}; ^1H NMR ($CDCl_3$) 1.35-1.50 (m, 2H), 1.51-1.92 (m, 7H)*, 1.80 (s, 1H)*, 2.02-2.16 (m, 1H), 2.71-2.92 (m, 7H), 2.96-3.13 (m, 3H), 3.28 (br s, 1H), 3.40-3.56 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.98 (t, J = 6.8 Hz, 1H), 5.98 (dd, J = 5.5, 2.6 Hz, 1H), 6.15 (dd, J = 5.5, 2.9 Hz, 1H), 6.69-6.80 (m, 3H) (* designates partially overlapped signals); ^{13}C NMR ($CDCl_3$) 20.4, 25.9, 34.4, 34.5, 35.1, 39.5, 40.8, 45.1, 45.9, 47.1, 47.6, 49.3, 52.1, 55.9, 90.9, 111.1, 112.2, 120.8, 131.7, 132.8, 137.1, 147.5, 148.8, 173.8; MS (EI) *m/z* (rel intensity) 489 (M^+, < 1), 471 (M^+-18, 2), 415 (1), 372 (4), 331 (3), 272 (4), 164 (100), 151 (8), 119 (6), 105 (12); HRMS Calcd for $C_{26}H_{35}NO_4S_2$: 489.2041. Found: 489.2033.

12b-[3-(1,3-Dithian-2-yl)propyl]-2,3-dimethoxy-5,6,8a,9,12,12a-hexahydro-9,12-methaneisoindolin-[2,3-a]isoquinolin-8-one (**23**)

According to Typical Procedure B, described for **11a**, hydroxy lactam **22** (500 mg, 1 mmol) was treated with TFA (0.38 mL, 5 mmol) at 20 °C for 12 h, to afford isoquinoline **23**, that was purified by column chromatography (silica gel, AcOEt), oil (400 mg, 85 %): IR ($CHCl_3$) 1654 cm^{-1}; ^1H NMR ($CDCl_3$) 1.42 (d, J

= 8.3 Hz, 1H), 1.66 (d, J = 8.3 Hz, 1H), 1.38-1.91 (m, 7H), 2.06-2.18 (m, 1H), 2.48-2.57 (m, 1H), 2.79-2.88 (m, 4H), 2.89-3.01 (dd, J = 16.6, 5.6 Hz, 1H), 3.03-3.20 (m, 3H), 3.22 (s, 1H), 3.33 (s, 1H), 3.83 (s, 3H), 3.91 (s, 3H), 3.99 (t, J = 6.4 Hz, 1H), 4.18 (dd, J = 11.9, 5.9 Hz, 1H), 6.21 (s, 2H), 6.51 (s, 1H), 6.71 (s, 1H); ^{13}C NMR ($CDCl_3$) 23.1, 25.9, 26.4, 30.4, 34.7, 36.0, 38.1, 44.5, 46.1, 47.2, 48.9, 49.1, 52.4, 55.8, 56.4, 63.8, 109.3, 112.0, 126.2, 133.6, 134.2, 135.7, 146.6, 147.9, 175.4; MS (EI) *m/z* (rel intensity) 471 (M^+, < 1), 310 (31), 272 (1), 258 (1), 244 (100), 200 (9), 183 (2), 164 (5); HRMS Calcd for $C_{26}H_{33}NO_3S_2$: 471.1935. Found: 471.1906.

10b-[3-(1,3-Dithian-2-yl)propyl]-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinolin-3(10bH)-one (**3c**)

According to Typical Procedure C, described for **3a**, **23** (300 mg, 0.6 mmol) was heated under vacuum, affording pyrroloisoquinolinone **3c**, that was purified by column chromatography (silica gel, 80% Hexane/AcOEt), oil (168 mg, 67%): IR ($CHCl_3$) 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.19-1.43 (m, 2H), 1.61-1.75 (m, 2H), 1.75-2.15 (m, 4H), 2.63 (dd, J = 15.8, 3.9 Hz, 1H), 2.75-3.01 (m, 5H), 3.15 (td, J = 12.2, 4.5 Hz, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 3.95 (t, J = 6.9 Hz, 1H), 4.40 (dd, J = 12.8, 6.5 Hz, 1H), 6.13 (d, J = 5.9 Hz, 1H), 6.59 (s, 1H), 6.68 (s, 1H), 7.21 (d, J = 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) 20.4, 25.8, 28.9, 30.3, 30.4, 34.7, 35.2, 38.3, 47.1, 55.8, 56.2, 68.2, 109.9, 111.9, 125.2, 126.4, 129.3, 147.5, 148.1, 151.5, 170.8; MS (EI) *m/z* (rel intensity) 405 (M^+, 1), 286 (1), 258 (1), 244 (100), 228 (4), 200 (11), 161 (10); HRMS Calcd for $C_{21}H_{27}NO_3S_2$: 405.1432. Found: 405.1427.

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