A DITOX derived α-sulfinyl carbanion as nucleophile in conjugate addition reactions to pyrrolo[2,1-*a*]isoquinolones

Cristina Camarero, Sonia Arrasate, Nuria Sotomayor, and Esther Lete*

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco, Apdo. 644. 48080 Bilbao, Spain
E-mail: esther.lete@ehu.es

Dedicated to Professor Benito Alcaide on occasion of his 60th birthday

Abstract
The synthesis of DITOX, both in racemic and enantioenriched forms, was accomplished *via* sulfur oxidation of 1,3-dithiane or 2-acyl-1,3-dithiane derivatives, using chiral oxaziridines for the asymmetric process. The conjugate addition reaction of the α-sulfinyl carbanion derived from DITOX, prepared by deprotonation using the mixture of bases NaHMDS/*n*-BuLi, to the bicyclic γ-lactam unit of C-10b substituted dihydropyrrolo[2,1-*a*]isoquinolones led diastereoselectively to the corresponding *trans* isomer.

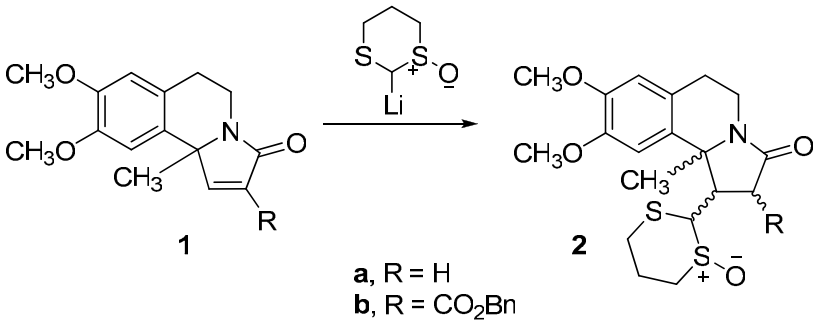
Keywords: DITOX**,** pyrroloisoquinolines, conjugate addition, asymmetric oxidation, α-sulfinyl carbanion

Introduction

Asymmetric 1,4-addition reactions to α,β-unsaturated carbonyl compounds are among the most frequently used methods for stereoselective C-C bond construction.[1] The utilization of chiral sulfur-based stabilized carbanions has shown great promise as a powerful method in asymmetric Michael-type reactions.[2] Thus, Toru et al. have reported that the reaction of chiral α-sulfinyl carbanions derived from *p*-tolyl β-(trimethylsilyl)ethyl sulfoxides with α,β-unsaturated carbonyl compounds or esters gives the conjugate addition products with complete stereoselectivity.[3] Álvarez-Ibarra and co-workers reported high levels of stereoselectivity in 1,4-additions of anions derived of a α-sulfinylketimine to an α,β-unsaturated ester, which has culminated in the enantioselective synthesis of methyl (+)-(*2S*,4*S*)-4-methylpipecolate.[4] Similar results were achieved by Metzner,[5] who has used anions prepared from chiral α-sulfinylthioamide in the same type of reaction with α,β-unsaturated ester and nitriles as substrates.

1,3-Dithiane 1-oxide (DITOX) derivatives, which both enantiomers can be accessed with excellent enantioselectivities by asymmetric sulfur oxidation of the corresponding 1,3-dithianes, can act as combined chiral auxiliaries and asymmetric building blocks.[6] It has been shown that chiral and achiral carbanions derived from DITOX and its 2-acyl derivatives undergo a variety of transformations with excellent diastereoselectivities, including nucleophilic substitution of alkyl halides,[7] nucleophilic addition to aldehydes, ketones, esters or *N*-acylimidazoles,[8] and electrophilic amination.[9] In addition, different types of stereoselective reactions using the DITOX unit as the stereocontrolling element, have been described, as well as its application to the enantioselective synthesis of several interesting compounds, such as α-hydroxyacids or α-arylpropano acids.[10] However, to the best of our knowledge, there are no precedents in the literature for the 1,4-addition of α-sulfinyl carbanions derived from DITOX to α,β-unsaturated carbonyl compounds.

In this context, our group has been involved in the application of conjugate addition reactions to α,β-unsaturated lactams in the synthesis of polyfunctionalized nitrogen heterocycles. In this context, we have recently described a stereocontrolled 1,4-addition of α-lithiodithioacetals to tetrahydrobenzo[*a*]benzoquinolizines, which led to the synthesis of emetine-like derivatives.[11] On the other hand, the introduction of a carbomethoxy group in the α-position of α,β-unsaturated bicyclic γ-lactams[12] has allowed us to achieve the conjugate addition of hard nucleophiles to pyrrolo[2,1-*a*]isoquinolones,[13] as we had previously illustrated in the synthesis of erythrinanes.[14] In this paper, we describe the use of α-sulfinyl carbanions derived from DITOX in 1,4-addition reactions to the α,β-unsaturated lactam unit of pyrrolo[2,1-*a*]isoquinolone **1** (Scheme 1).



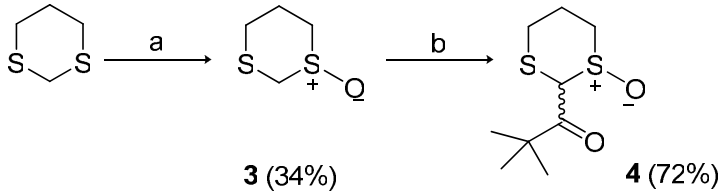
Scheme 1

Results and Discussion

Our first task was the synthesis of racemic DITOX (**3**), which was accomplished by treatment of 1,3-dithiane with *m*-CPBA at room temperature overnight. Although several experimental

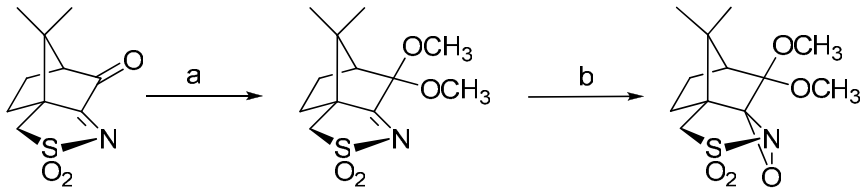
conditions were tried, the low yields of the monoxide could not be improved, due to the formation of the corresponding dioxide and/or sulfone.[15]

To check that α-sulfinyl carbanion derived from DITOX was efficiently formed, we carried out the deprotonation of **3** using Page procedure,[7c,8b] with sodium hexamethyldisilazide at −78 °C in THF solution, subsequent treatment with *n*-BuLi and addition of the electrophile (ethyl 2,2-dimethylpropanoate), obtaining the corresponding 2-acyl-DITOX **4** as a diastereomeric mixture in a 70:30 ratio (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) *m*-CPBA, K_2CO_3, CH_2Cl_2, 0° C to rt, 16 h. (b) NaHMDS, THF, -78 º C, 10min; *n*-BuLi, -78 ºC, 10min; $(CH_3)_3CCO_2Et$, -78 º C to rt, 2h.

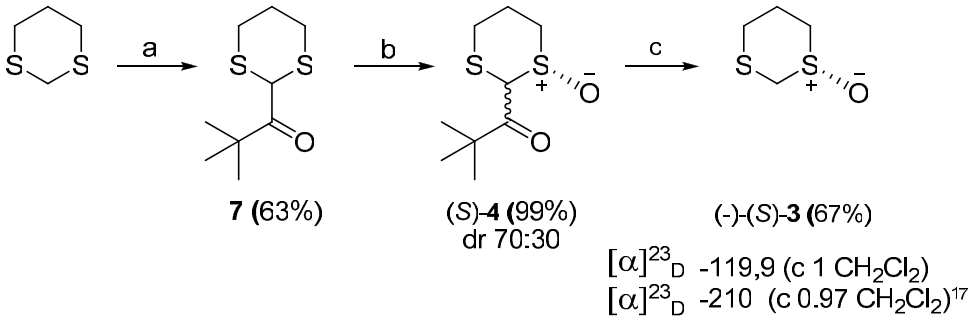
We next undertook the asymmetric synthesis of (+)-(*S*)-DITOX by asymmetric sulfur oxidation of 1,3-dithiane using Davies' oxaziridines.[16] As shown in Scheme 3, treatment of commercial (–)-(3-oxocamphorylsulfonyl)imine with $CH(OCH_3)_3$ and H_2SO_4 in MeOH afforded imine **5** in quantitative yield and excellent enantiomeric excess. Subsequent oxidation with *m*-CPBA gave oxaziridine **6**, again in excellent yields and with very high enantiomeric excess. The enantiomeric purity of both compounds was determined by comparison of the $[\alpha]^{23}_D$ value with the literature values.[17]



Scheme 3. *Reagents and conditions*: (a) $CH(OCH_3)_3$, H_2SO_4, MeOH, 85-90 º C, 4 h; $CH(OCH_3)_3$, MeOH, rt to 85-90 º C, 1 h. (b) *m*-CPBA, K_2CO_3, CH_2Cl_2, rt 16h.

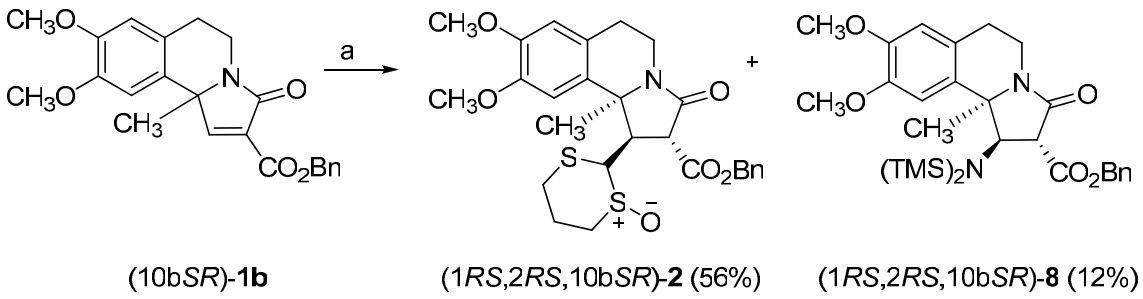
It is known that asymmetric sulfur oxidation on 1,3-dithianes requires the introduction of an acyl group at C-2 to be successful.[6] Thus, 1,3-dithiane was deprotonated by sequential addition of NaHMDS and *n*-BuLi at 0ºC as described above, and the so-obtained 1,3-dithianyllithium

reacted with $(CH_3)_3CCO_2Et$ to afford the 2-acyl-1,3-dithiane **7** in a 63% yield. Asymmetric sulfur oxidation was accomplished upon treatment of a solution of **7** in CCl_4 with oxaziridine **6** to afford sulfoxide **4** in quantitative yield as a mixture of diastereomers. Finally, elimination of the pivaloyl group by treatment with aqueous (5%) NaOH under reflux gave (-)-(*S*)-DITOX **3** in good yield. The enantiomeric excess determined by CSP HPLC was 66% (lit.[17] 87%) by comparison with the racemic mixture (Chiralcel OD, 9% hexane/2-propanol). The value of the specific rotation (see scheme 4) allowed us to assign the absolute configuration of sulfoxide as *S*.



Scheme 4. *Reagents and conditions*: (a) NaHMDS, THF, 0 º C to rt, 1h; *n*-BuLi, 0 º C to rt, 30min; $(CH_3)_3CCO_2Et$, rt, 2.5 h (b) Oxaziridine **6**, CCl_4, 0 º C to rt, 2 days. (c) aqueous (5%) NaOH, EtOH, rt to reflux, 24 h.

Conjugate addition reaction was next examined. We had previously shown that conjugate addition reactions of α-lithiodithioacetals to the α,β-unsaturated lactam unit of pyrrolo[2,1-*a*]isoquinolones does not need the presence of an activating group attached to the unsaturated system to give regio and stereoselectively 1,4-addition.[18] Thus, we studied the addition of the α-sulfinyl carbanion derived from racemic DITOX to pyrrolo[2,1-*a*]isoquinolone **1a**. The 1,3-dithianyllithium could be efficiently prepared by using the mixture of bases NaHMDS/*n*-BuLi at 0ºC. However, although several reaction conditions were tested, the DITOX derived anion was not reactive enough, and no reaction was observed if the lactam **1a** was added at this temperature, and the reaction mixture was allowed to warm up to rt. Therefore, we focused our attention on the conjugate addition to α,β–unsaturated lactam **1b** with an activating benzyloxycarbonyl group at the α position of the lactam carbonyl group. After extensive screening of conditions, it was found that conducting the reaction with α-sulfinyl carbanion derived from DITOX (prepared as described above) provided diastereoselectively the *trans* isomer **2** in moderate yield (56%). However, variable amounts of the product **8**, formed by addition of lithium trimetylsilylamide were always obtained. The use of the mixture of NaHMDS and n-BuLi is crucial for an efficient deprotonation, as no addition product was observed when the bases were used separately.



Scheme 5. *Reagents and conditions*: (a) DITOX, NaHMDS, THF, – 78 ºC, 10 min; *n*-BuLi, – 78 ºC, 10 min; lactam **1b**, rt, 24h.

NOESY and COSY experiments confirmed the stereochemistry of tetrahydropyrroloisoquinoline **2**. Thus, the *J* value of the system formed by H-1 and H-2 protons (*J* = 2.6 Hz) indicates that both protons are in a *pseudo*-equatorial disposition. Besides, NOE difference spectroscopy showed an enhancement between the methyl group in C-10b and H-1 and between the methine proton of the 1-oxodithianyl group and H-2. The absence of NOE enhancement between methyl group on C-1 and the 1-oxodithianyl group on C-10b, confirms that they are in a relative *trans* disposition. The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry.

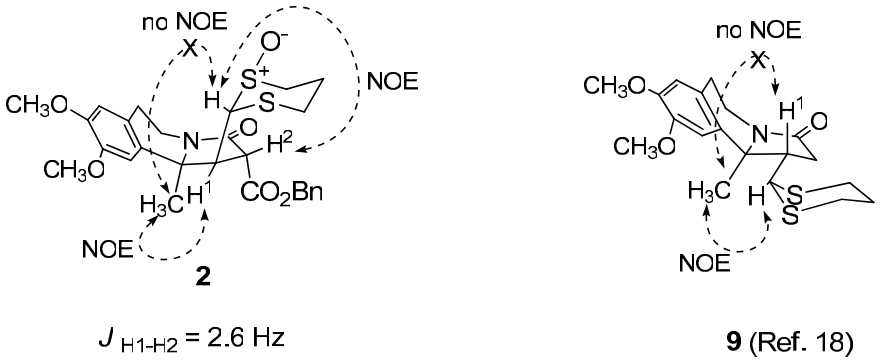
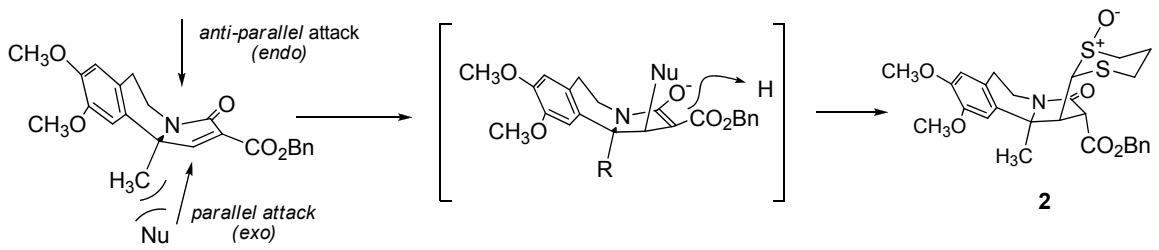


Figure 1. Selected NOE enhancements for **2**.

It is interesting to note that the 1,10b-*trans* stereochemistry observed in **2** is the opposite of that obtained for the addition of 2-lithio-1,3-dithiane to pyrroloisoquinoline **1a**, that afforded the 1,10b-*cis* adduct **9** as a single diastereomer.[18] In this case, the increased bulk of the nucleophile precludes the parallel attack from the exo face, leading to a 1,10b-*trans* enolate intermediate, which is protonated to give the more stable 1,2-*trans* adduct (Scheme 6).



Scheme 6. Stereochemical outcome of the conjugate addition reaction.

In conclusion, in contrast with our previous results with sulfur stabilized anions[18] the addition of a DITOX derived sulfinyl anion to the γ-lactam requires the introduction of an electron withdrawing group on C-2, leading to the *trans* substituted adduct **2** in moderate yield and high stereoselectivity.

Experimental Section

General Procedures. 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 or 300 MHz for ^{1}H and 62.8 or 75.47 MHz for ^{13}C in $CDCl_3$ solutions. Assignment of individual ^{13}C resonances are supported by DEPT experiments. Mass spectra were recorded under electron impact at 70 eV. Exact mass was obtained using a TOF detector. GC-MS analyses were performed using a TRB-1 column (methyl polysiloxane, 30 m × 0.25 mm × 0.25 μm). Elemental analyses were performed with a 2400 CHN Perkin-Elmer analyzer at the Servicios Generales de Investigación (SGIker) of the University of the Basque Country. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography[19] on silica gel was performed with Kiesegel 60 (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures.[20] Organolithium reagents were titrated with diphenylacetic acid or *N*-benzyl benzamide periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 ˚C) and purged with argon.

(1*RS*)-DITOX (3). A solution of *m*-CPBA (2.1 g, 12.5 mmol) in dry CH_2Cl_2 (62 mL) was added over a solution of 1,3-dithiane (1 g, 8.3 mmol) in dry CH_2Cl_2 (42 mL) at 0 °C. The reaction mixture was allowed to reach rt and stirred for 16 h. Then the mixture was washed with (sat.) Na_2SO_3 (3 × 15 mL), H_2O (1 × 15 mL) and (sat.) NaCl (1 × 15 mL). 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*. Crystallization from Et_2O afforded (1*RS*)-DITOX (**3**) (385 mg, 34%) as a white solid: mp (Et_2O): 87-88 ºC; IR (KBr) 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.16-2.28 (m, 1H),

2.46-2.71 (m, 4H), 3.28-3.36 (m, 1H), 3.64 (d, *J* = 12.7 Hz, 1H), 4.01 (d, *J* = 12.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 27.1, 28.2, 50.3, 52.8; MS (EI) *m/z* (rel intensity) 136 (M^+, 77), 120 (6), 119 (37), 106 (41), 91 (13), 90 (73), 87 (90), 85 (26), 83 (18), 78 (17), 74 (40), 73 (100), 72 (22), 71 (14), 69 (19), 64 (17), 63 (25), 61 (87), 60 (67), 59 (30), 57 (27), 55 (41), 54 (14); HRMS calcd for C_4H_8OS: 136.0017. Found: 136.0005.

(1*RS*)-2-(2,2-Dimethylpropanoyl)-DITOX (4). A solution of NaHMDS (1.15 mL of a 0.70 M solution in hexanes, 0.81 mmol) was added over a solution of (*RS*)-DITOX (**3**) (100 mg, 0.73 mmol) in dry THF (10 mL) at – 78 °C. After 10 min, *n*-BuLi (0.6 mL of a 1.36 M solution in hexanes, 0.81 mmol) was added. The resulting solution was stirred at this temperature for 10 min and $(CH_3)_3CCO_2Et$ (0.56 mL, 3.68 mmol) was added. The reaction mixture was stirred for 2.5 h. The reaction was quenched by the addition of saturated NH_4Cl (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (1 × 15 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with 10% aq. NaOH (2 × 25 mL), brine (2 × 25 mL), and H_2O (2 × 25 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (silicagel, CH_2Cl_2 100%→AcOEt 100%) afforded 2-acyl DITOX **4** as mixture of diastereomers in an *anti/syn* 70:30 diastereomeric ratio (1.37 g, 72%); IR **(**KBr) 1701, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.16 (s, 9H, *syn*), 1.18 (s, 9H, *anti*), 2.03-3.06 (m, 10H, both diastereomers), 3.37-3.46 (m, 1H, *anti*), 3.81-3.92 (m, 1H, *syn*), 4.69 (s, 1H, *anti*), 4.93 (s, 1H, *syn*); ^{13}C NMR ($CDCl_3$) 23.2; 23.6, 25.8; 25.9, 27.7, 28.0, 45.6 (*syn*), 45.9 (*syn*), 49.9 (*anti*), 63.5 (*anti*), 206.5; 207.4. HRMS calcd for $C_9H_{16}O_2S_2$: 220.0592. Found: 204.0598.

(+)-[(8,8-Dimethoxycamphoryl)sulfonyl]imine (5)[16] A solution of (-)-[(3-oxocamphoryl)sulfonyl]imine (3.0 g, 13.2 mmol) was added to a solution of $CH(OCH_3)_3$ (16.5 mL, 150.8 mmol) and conc. H_2SO_4 (0.66 mL) in MeOH (9 mL). The resulting mixture was heated at 85-90 ºC for 4h. After allowing the reaction mixture to cooled to rt, $CH(OCH_3)_3$ (4 mL, 36.6 mmol) and MeOH (1.32 mL) were added and it was heated at 85-90 ºC for 1 h. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (2 × 15 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Crystallization from EtOH afforded imine (+)-**5** (3.6 g, 99%) as a yellow solid: mp (EtOH): 186-188 ºC; $[\alpha]^{23}_D$ +7.6 (c 1, $CHCl_3$); IR (KBr) 1654, 1331 cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.95 (s, 3H), 1.05 (s, 3H), 1.73-2.02 (m, 4H), 2.3 (broad s, 1H), 2.95 (d, *J* = 13.1 Hz, 1H), 3.14 (d, *J* = 13.1 Hz, 1H), 3.32 (s, 3H), 3.41 (s, 3H);^{13}C NMR ($CDCl_3$) 20.4, 20.5, 29.2, 45.9, 48.8, 50.2, 50.5, 51.9, 64.2, 102.9, 188.8; MS (EI) *m/z* (rel intensity) 273 (M^+, ‹ 1), 209 (19), 204 (21), 194 (37), 129 (100), 101 (22), 73 (8). HRMS calcd for $C_{12}H_{19}NO_4S$: 273.1035. Found:273.1042.

(+)-(2*R*,8a*R*)-[(8,8-Dimethoxycamphoryl)sulfonyl]oxaziridine (6).[16] To a solution of (+)-imine **4** (460 mg, 1.68 mmol) in dry CH_2Cl_2 (2 mL) at 0 ºC, a saturated K_2CO_3 solution (10 mL) was added. After 5 min under vigorous stirring, a solution of *m*-CPBA (465 mg, 2.69 mmol) in dry CH_2Cl_2 (8 mL) was added. The reaction mixture was stirred at this temperature for 16 h. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (1 × 15 mL), (sat.) Na_2SO_3 (2 × 15 mL), H_2O

(1 × 15 mL), and brine (2 × 15 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Crystallization from EtOH afforded oxaziridine (+)-**6** (479 mg, 98%) as a pink solid: mp (EtOH) 198-200 ºC; $[\alpha]^{23}_D$: +89.0 (c 2.7, $CHCl_3$); IR (KBr) 1353 cm^{-1}; ^1H NMR ($CDCl_3$) 1.04 (s, 3H), 1.30 (s, 3H), 1.75-1.95 (m, 4H), 2.26 (d, *J* = 4.0 Hz, 1H), 3.05 (d, *J* = 13.9 Hz, 1H), 3.24 (d, *J* = 13.9 Hz, 1H), 3.25 (s, 3H), 3.32 (s, 3H); ^{13}C NMR ($CDCl_3$) 20.4, 21.6, 28.0, 45.1, 47.4, 50.5, 50.8, 52.8, 54.5, 97.6, 102.7; MS (EI) *m/z* (rel intensity) 289 (M^+, <1), 129 (14), 109 (100), 108 (19), 93 (54), 91 (11), 67 (16). HRMS calcd for $C_{12}H_{19}NO_5S$: 289.0984. Found:289.0992.

2-(2,2-Dimethylpropanoyl)-1,3-dithiane (7).[17] A solution of NaHMDS (18.3 mL of a 0.70 M solution in hexanes, 12.8 mmol) was added over a solution of 1,3-dithiane (1.32 g, 10.7 mmol) in dry THF (20 mL) at 0 °C. The resulting solution was stirred at rt for 1h and *n*-BuLi (9.15 mL of a1.4 M solution in hexanes, 12.8 mmol) was added. After 30 min at rt, $(CH_3)_3CCO_2Et$ (1.96 mL, 12.8 mmol) was added and the reaction mixture was stirred for 2.5 h. The reaction was quenched by the addition of saturated NH_4Cl (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (1 × 15 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford 2-acyl-1,3-dithiane **7** (1.37 g, 63%) as a white solid: mp (Et_2O): 109-111 ºC; IR **(**KBr) 1688 cm^{-1}; ^1H NMR ($CDCl_3$) 1.17 (s, 9H), 1.85-2.15 (m, 2H), 2.45-2.53 (m, 2H), 3.31-3.42 (m, 2H), 4.45 (s, 1H); ^{13}C NMR ($CDCl_3$) 24.9, 25.3, 26.8, 38.0, 44.2, 208.6; MS (EI) *m/z* (rel intensity) 204 (M^+, < 1), 119 (3), 87 (5), 85 (51), 83 (100), 71 (5), 57 (9), 55 (3). HRMS calcd for $C_9H_{16}OS_2$: 204.0643. Found: 204.0650.

(1*S*,2*R*) and (1*S*,2*S*)-2-(2,2-Dimethylpropanoyl)-DITOX (4).[17] Oxaziridine **6** (3 g, 10.35 mmol) was added to a solution of 2-acyl-1,3-dithiane **7** (1.37 g, 6.73 mmol) in CCl_4 (80 mL) at 0 ºC. The reaction mixture was allowed to reach rt, stirred at this temperature for 2 days, and then filtered off. Column chromatography (silicagel, CH_2Cl_2 100%→AcOEt 100%) afforded 2-acyl-DITOX **4** as mixture of diastereomers in an *anti/syn* 70:30 diastereomeric ratio (1.47 g, 99%). The spectroscopic data were identical to those of the corresponding racemate. To the diastereomeric mixture of **(**1*S*,2*R*) and (1*S*,2*S*)-2-(2,2-dimethylpropanoyl)-DITOX (**4**) (237 mg, 1.08 mmol) aqueous (15%) NaOH (1.44 mL) and EtOH (3.6 mL) were added. The reaction mixture was heated under reflux for 24 h. Crystallization from Et_2O afforded (1*S*)-(-)-DITOX (**3**) (98 mg, 67%) as a white solid: mp (Et_2O): 91-93 ºC; $[\alpha]^{23}_D$ –119.9 (c 1, $CHCl_3$). The enantiomeric excess determined] by CSP HPLC was > 99% by comparison with the racemic mixture. Chiralcel OC, 9% hexane/2-propanol, 1 mL/min; t_r = 39.3 min (83%); t_r[(1*R*)-1a]= 48.9 min (17%). The spectroscopic data were identical to those of the corresponding racemate.

Conjugate addition of DITOX to pyrrolo[2,1-*a*]isoquinolones. Synthesis of *(1RS,2SR,10bSR)*-2-benzyloxycarbonyl-8,9-dimethoxy-10b-methyl-1-(1-oxo-1,3-dithian-2-yl)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (2) and *(1RS,2SR,10bSR)*-2-benzyloxycarbonyl-1-(1,1,1,3,3,3-hexamethyldisilazan-2-yl)-10b-methyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (8). A solution of NaHMDS (0.36 mL of a 0.70 M solution in hexanes, 0.25 mmol) was added over a solution of DITOX (**3**) (32 mg, 0.23 mmol) in dry THF (10 mL) at – 78 °C. After 10 min, *n*-BuLi (0.19 mL, of a 1.36 M solution in hexanes, 0.25 mmol) was added. After 10 min, a solution of pyrroloisoquinolone **1b** (109.3 mg,

0.28 mmol) in dry THF (5 mL) was added. The resulting solution was stirred at rt for 24 h. The reaction was quenched by addition of NH_4OH (12% aq.) (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (10 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (silicagel, 96% hexane/AcOEt) afforded adducts **2** and **8**. Both compounds were separated by chromatography and characterized separately. *(*1*RS,*2*SR,*10b*SR)*-2-benzylcarbonyl-8,9-dimethoxy-10b-methyl-1-(1-oxo-1,3-dithian-2-yl)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (**2**), oil (83 mg, 56%): IR (KBr) 1736, 1698, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) 1.55 (s, 3H), 1.72-2.01 (m, 1H), 2.24-2.28 (m, 1H), 2-33-2.44 (m, 3H), 2.57-2.62 (m, 1H), 2.89-2.97 (m, 1H), 3.02-3,08 (m, 1H), 3.20-3.23 (m, 1H), 3.55 (d, *J* = 2.6 Hz, 1H), 3.60 (s, 1H·), 3.88 (s, 3H), 3.99 (s, 3H), 3.95-4.02 (m, 1H), 4.36-4.39 (m, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 5.31 (d, *J* = 12.2 Hz, 1H),6.55 (s, 1H), 6.99 (s, 1H), 7.30-7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) 28.7, 29.3, 30.5, 31.6, 35.6, 45.4, 55.7, 55.8, 56.0, 63.1, 67.8, 72.4, 110.5, 111.3, 126.6, 128.0, 135.1, 128.5, 128.6, 128.7, 147.1, 148.2, 165.8, 168.7; MS (EI) *m/z* (rel intensity) 530 (M^+ +1, 3), 529 (M^+, 9), 514 (M^+-15, 2), 395 (11), 378 (2), 316 (23), 273 (5), 272 (8), 244 (6), 207 (14), 206 (100), 205 (9), 204 (9), 197 (5), 190 (9), 119 (9), 108 (12), 107 (9), 106 (6), 91 (58), 90 (18), 85 (6), 79 (15), 77 (9), 71 (7), 57 (9), 55 (6). Anal. Calcd for $C_{27}H_{31}NO_6S_2$: C, 61.22; H, 5.90; N, 2.64. Found: C, 60.97; H, 5.84; N, 2.72. Minor compound **8**, oil (19 mg, 12%); IR (KBr) 1740, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) -0.12 (s, 6H,), -0.08 (s, 3H), 0.35 (s, 6H), 0.40 (s, 3H), 1.61 (s, 3H), 2.56-2.62 (m, 1H), 2.84-2,91 (m, 2H), 3.86-3.93 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.10 (d, *J* = 11.1 Hz, 1H, 4.35-4.41 (m, 1H), 5.19 (d, *J* = 4.8 Hz, 2H), 6.58 (s, 1H), 6.78 (s, 1H), 7.33-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) 3.1, 5.6, 24.0, 29.3, 35.0, 55.2, 55.7, 56.3, 63.8, 67.0, 67.4, 110.2, 111.8 , 125.6, 128.1, 128.2, 128.4, 131.5, 135.3, 147.3, 147.9, 166.8, 169.6; MS (EI) *m/z* (rel intensity) 555 (M^+ +1, 5), 554 (M^+, 12), 539 (6), 455 (8), 378 (22), 364 (19), 306 (15), 262 (8), 258 (11), 244 (11), 214 (13), 206 (47), 205 (100), 204 (9), 190 (12), 146 (14), 130 (8), 100 (7), 99 (6), 91 (63), 79 (5), 77 (5), 73 (39), 65 (5). Anal. Calcd for $C_{29}H_{42}N_2O_5Si_2$: C, 62.78; H, 7.63; N, 5.05. Found: C, 62.49; H, 7.46; N, 5.12.

Acknowledgements

Financial support from MICINN (CTQ2006-01903), Gobierno Vasco (GIC07/92-IT-227-07), and Universidad del País Vasco is gratefully acknowledged.

References

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Baldwin, J. E.; Magnus, P. D., Eds; Tetrahedron Organic Chemistry Series, Pergamon Press: Oxford, 1992,

Vol. 9. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92,* 771. (c) Leonard, J.; Díez-Barra, E.; Merino, S. *E. J. Org. Chem.* **1998***,* 2051. (d) Yamamguchi, M. In *Comprehensive Asymmetric Catalysis I-III*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: Berlin, 1999, Vol. 3, pp 1121. (e) Jha, S. C.; Joshi, N. N. *Arkivoc* **2002**, 167. (f) Iguchi, M.; Yamada, K.; Tomioka, K. In *Organolithiums in Enantioselective Synthesis*, Hodgson, D. M., Ed.; Topics in Organometallic Chemistry, Springer: Berlin, 2003, Vol. 5, pp 21-36. (g) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16,* 2833. (h) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106,* 2596. (i) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40,* 179. (j) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108,* 2796. (k) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108,* 2824.

2. For reviews on asymmetric conjugate additions with sulfoxide stabilized carbanions, see: (a) Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp 157. (b) Posner, G. H. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Striling, C. J. M., Eds.; Wiley-Interscience: New York, 1988; pp 823-849. (c) Walker, A.-J. *Tetrahedron: Asymmetry* **1992**, *3*, 961. (d) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717. (e) Allin, S. M.; Shuttleworth, S. J.; Page, P. C. B. *Organosulfur Chem.* **1998**, *2*, 97. (f) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. (g) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559.
3. (a) Nakamura, S.; Takemoto, H.; Ueno, Y.; Toru, T.; Kakumoto, T.; Hagiwara, T. *J. Org. Chem.* **2000**, *65*, 469. (b) Nakamura, S.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 17586. (c) Nakamura, S.; Uchiyama, Y.; Ishikawa, S.; Fukinbara, R.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **2002**, *43*, 2381.
4. Acherki, H.; Alvarez-Ibarra, C.; de Dios, A.; Gutiérrez, M.; Quiroga, M. L. *Tetrahedron: Asymmetry* **2001**, *12*, 3173.
5. Nowaczyk, S.; Alayrac, C.; Metzner, P.; Averbuch-Pouchot, M-T. *J. Org. Chem.* **2002**, *67*, 6852.
6. (a) Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.;Andrews, D. M. *Synlett* **1995**, 773. (b) Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2911. (c) Allin, S. M.; Page, P. C. B. *Org. Prep. Proc. Int.* **1998,** *30*, 145.
7. (a) Carey, F. A.; Dailey, O. D.; Hernandez, O. *J. Org. Chem.* **1976**, *41*, 3979. (b) Auret, B. J.; Boyd, D. R.; Cassidy, E. S.; Hamilton, R.; Turley, F.; Drake, A. F. *J. Chem. Soc., Perkin Trans. I* **1985**, 1547. (c) Page, P. C. B.; Shuttleworth, S. J.; Schilling, M. B.; Tapolczay, D. J. *Tetrahedron Lett.* **1993**, *34*, 6947.
8. (a) Carlson, R. M.; Helquist, P. M. *J. Org. Chem.* **1968**, *33*, 2596. (b) Page, P. C. B.; Gareh, M. T.; Porter, R. A. *Tetrahedron Lett.* **1993**, *34*, 5159. (c) Page, P. C. B.; Purdie, M.;

Lathbury, D. *Tetrahedron Lett.* **1996**, *37*, 8929. (d) Fang, J-M.; Chou, W-C.; Lee, G-H.; Peng, S-M. *J. Org. Chem.* **1990**, *55*, 5515.
9. Page, P. C. B.; McKenzie, M. J.; Allin, S. M.; Buck, D. R. *Tetrahedron* **2000**, *56*, 9683.
10. For some representative examples, see: reductions (a) Barros, M. T.; Leitão, A. J.; Maycock, C. D. *Tetrahedron Lett.* **1995**, *36*, 6537. Nucleophilic additions (b) Page, P. C. B.; Prodger, J. C.; Westwood, D. *Tetrahedron* **1993,** *49*, 10355. (c) García Ruano, J. L.; Barros, D.; Maestro, M. C.; Slawin, A. M. Z.; Page, P. C. B. *J. Org. Chem.* **2000**, *65*, 6027. Ketones α-Alkylation (d) Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *Tetrahedron Lett.* **1994**, *35*, 2607. (e) Page, P. C. B.; McKenzie, M. J.; Allin, S. M.; Klair, S. S. *Tetrahedron* **1997,** *53*, 13149. Dihydroxylation (f) Page, P. C. B.; McKenzie, M. J.; Buckle, D. R. *Tetrahedron* **1998,** *54*, 14581. Conjugate addition (g) Page, P. C. B.; Prodger, J. C.; Hursthouse, M. B.; Mazid, M. *J. Chem. Soc., Perkin Trans. I* **1990**, 167. Cicloaddition (h) Page, P. C. B.; McKenzie, M. J.; Buckle, D. R. *Tetrahedron* **1998,** *54*, 14573.
11. García, E.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2006**, *71,* 6776.
12. For examples of low reactivity of α,β̃-unsaturated amides and lactams in 1,4-addition reactions, see: (a) Brewster, A. G.; Broady, S.; Hughes, M.; Moloney, M. G.; Woods, G. *Org. Biomol. Chem.* **2004**, *2*, 1800, and references therein. For examples for 1,4-addition reactions of sulfur-stabilized anions to lactams, see: (b) Mpango, G. B.; Mahalanabis, K. K.; Damghani, Z. M.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21,* 4823. (c) Mpango, G. B.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21,* 4827. (d) Hashimoto, M.; Hashimoto, K.; Shirahama, H. *Tetrahedron* **1996**, *52,* 1931. (e) Forns, P.; Díez, A.; Rubiralta, M. *Tetrahedron* **1996**, *52,* 3563. (f) Forns, P.; Díez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61,* 7882. (g) Amat, M.; Pérez, P., Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4,* 2787.
13. Camarero, C.; González-Temprano, I.; Lete, E.; Sotomayor, N. *Synlett* **2007**, 1101.
14. Osante, I. Abdullah, M. N.; Arrasate, S.; Sotomayor, N.; Lete, E. *Arkivoc* **2007**; 206.
15. (a) Nickon, A.; Rodríguez, A. D.; Shirhatti, V.; Ganguly, R. *J. Org. Chem.* **1985**, *50*, 4218. (b) Aggarwal, V. K.; Davies, I. W.; Franklin, R. J.; Maddock, J.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. I* **1994**, 2363.
16. Chen, B. C.; Murphy, C. K.; Kumar, A.; Reddy, R. T.; Clark, C.; Zhou, P.; Lewis, B. M.; Gala, D.; Mergelsberg, I.; Scherer, D.; Buckley, J.; Di Benedetto, D.; Davis, F. A. *Org. Synth.*; **1996**, *73*, 159.
17. Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Org. Synth.*; **1999**, *76*, 37.
18. Etxarri, B.; González-Temprano, I.; Manteca, I.; Sotomayor, N.; Lete, E. *Synlett* **1999**, 1486.
19. Still, W. C.; Kann, H.; Mitra, A. J. *J. Org. Chem*. **1978**, *43*, 2923.
20. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1997.