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Conjugate Additions of Sulfur-Stabilized Anions to Unsaturated Lactams. Synthesis of Polyfunctionalized Benzo[*a*]quinolizinone Systems

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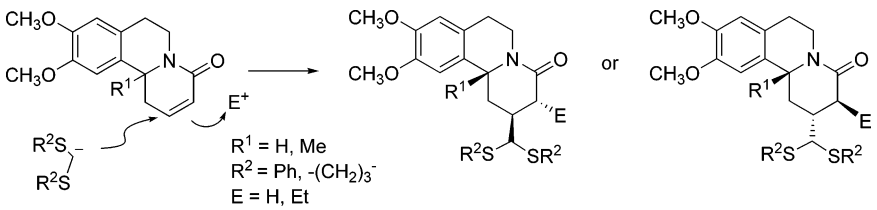

Conjugate addition reactions of sulfur-stabilized nucleophiles to the δ-lactam unit of tetrahydrobenzo[*a*]benzoquinolizines have been studied. The stereochemical outcome of the conjugate addition reaction depends on the nature of the substituent at the angular position, thus 2,11b-cis or 2,11b-trans diastereomers could be obtained selectively. The tandem conjugate addition−alkylation also takes place in good yields and with high diastereoselectivity. The polyfunctionalized hexahydrobenzo[*a*]quinolizinone systems obtained could be further elaborated toward emetine-like structures.

Introduction

The benzo[*a*]quinolizidine ring system is of considerable interest and significance because this heterocyclic template is found within a plethora of isoquinoline alkaloids, including Ipecac alkaloids such as emetine and related bases, which possess multifold interesting biological activity.[1] For instance, emetine shows antiamoebic properties,[2] shows activity against breast tumor cells,[3] and can be used as an emetic.[4] In a recent work on novel classes of anticancer drugs, an extensive analysis of various analogues of the original inhibitors allowed the identification of a common structure that is essential for the inhibition of Hsp induction (i.e., the 2*H*-benzo[*a*]quinolizidine tricyclic system).[5] Because of the toxicological problems associated with many of these drugs,[6] much attention is still directed toward the synthesis of natural or synthetic congeners to study structure−activity relationships.[7]

During the past several years, research in our laboratories has focused on the application of aromatic metalation and α-amidoalkylation reactions for the synthesis of benzo-fused indolizidine and quinolizidine compounds.[8] Thus, we have developed an approach for the construction of the benzo[*a*]-quinolizidone skeleton that involves the Parham[9] or *N*-acyliminium ion[10] cyclization as the key ring-forming step.[8a] The

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presence of the α,β-unsaturated lactam unit in benzo[*a*]-quinolizidones would allow for possible further functionalization en route to natural products or more complex targets. We envisaged the conjugate system could be generated by oxidative elimination via selenoxides,[11] obtained from the corresponding selenides. Therefore, benzo[*a*]quinolizidones would represent late-stage intermediates in the stereocontrolled synthesis of Ipecac alkaloid analogues by a conjugate addition reaction.

The conjugate addition of various organometallic reagents to α,β-unsaturated carbonyl compounds is an important process for carbon−carbon bond formation in organic synthesis.[12] Although compared with some other classes of conjugate acceptors α,β-unsaturated amides and lactams are usually less reactive, it is known that sulfur-stabilized anions do not need the presence of an activating group attached to the unsaturated system to give regioselectively 1,4-addition. Thus, several authors have demonstrated that lithiated 1,3-dithianes undergo conjugate addition to tertiary crotonamides, thioamides, and lactams. The resulting amide enolates may be quenched with electrophiles to give α,β-dialkylated products.[13] These α-lithiodithioacetals are particularly useful acyl anion equivalents because they provide an umpolung to the normal reactivity pattern of carbonyl compounds.[14] In this context, we have previously shown that highly diastereoselective conjugate addition of α-lithiodithioacetals to the α,β-unsaturated bicyclic lactam unit

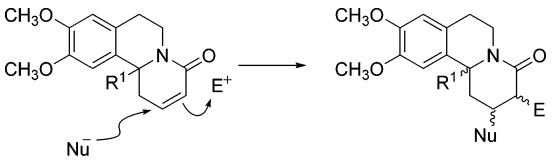

FIGURE 1. Tandem conjugate addition−electrophile trap on benzoquinolizidones.

of dihydropyrrolo[2,1-*a*]isoquinolones can be achieved. Cis or trans 1,10b-disubstituted isomers could be obtained exclusively by using a 1,3-dithianyl anion or bis(phenylthio)methyllithium as nucleophiles, respectively.[15] With these precedents, we decided to study the conjugate additions of sulfur-stabilized anions to the α,β-unsaturated lactam moiety of benzoquinolizidones (Figure 1), paying special attention to the effect of both the nucleophile and the substitution on C-11b (R^1 = H, Me) on the stereoselectivity. To show the synthetic potential of these conjugate additions, the adducts would be further manipulated to access various polyfunctionalized benzo[*a*]quinolizidones.[16]

Results and Discussion

Our first task was the synthesis of benzoquinolizidones **3a**,**b**, which incorporate different substituents on C-11b. The benzoquinolizinone skeleton was assembled through α-amidoalkylation reactions of glutarimide **1**. The addition of organolithium reagents and the reduction of imides are efficient methods to access α-hydroxylactams, immediate precursors of *N*-acyliminium ions, which have been successfully used to access various types of isoquinoline skeletons.[8] Thus, treatment of glutarimide **1** with $NaBH_4$ under the conditions reported by Speckamp[17] yielded a mixture of tautomeric α-hydroxylactam and oxoamide, which, without purification, were cyclized with TFA to give **2a** in good overall yield (Scheme 1).[18] Similarly, treatment of **1** with MeLi (3 equiv) yielded an oxoamide that was cyclized to afford **2b** in similar overall yield. The double bond was introduced then by an oxidative elimination of a selenoxide. Thus, deprotonation with LDA, followed by treatment with PhSeBr, afforded the corresponding diastereomeric selenides. The oxidative elimination was carried out with H_2O_2 to afford **3b**. However, when these conditions were applied to the

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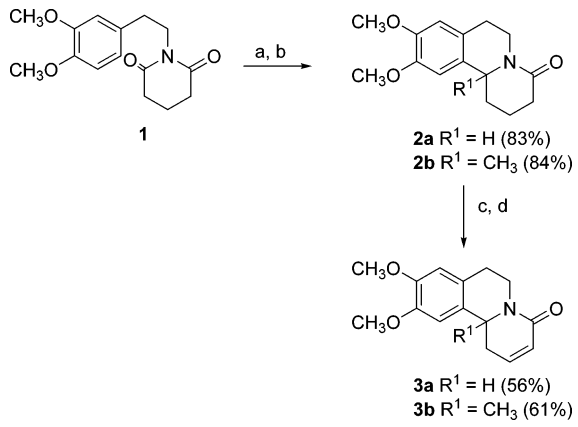
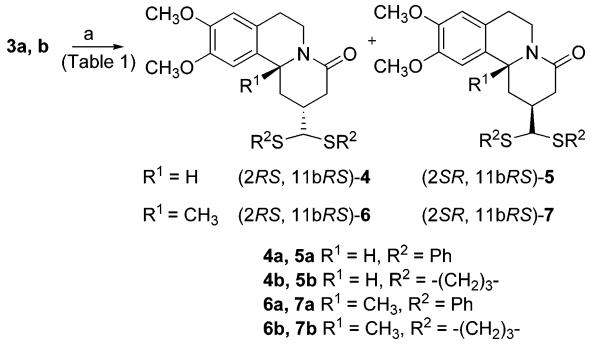
(18) When the reaction was carried out in a larger scale (3 g of **1**), it was not possible to control the partial reduction of the imide, and *N*-(3,4-dimethoxyphenylethyl)-4-hydroxybutyramide was obtained. This hydroxyamide could be oxidized (Swern) to the aldehyde and cyclized with TFA to afford **3a** in good overall yield. See Supporting Information.

SCHEME 1[a]



[a] Reagents: (a) $NaBH_4$, $EtOH/H_2O$, HCl, 0 °C (for **2a**); MeLi, −78 °C (for **2b**). (b) TFA, CH_2Cl_2, rt. (c) LDA, −78 °C, PhSeBr. (d) PIDA, TFA, CH_3CN/H_2O, rt (for **3a**); H_2O_2, pyridine, 0 °C → rt (for **3b**).

SCHEME 2[a]



[a] Reagents: (a) $(R^2S)_2CHLi$, −78 °C, 1 h.

diastereomeric selenides derived from **2a**, only low yields of **3a** were obtained (10%). In this case, the oxidative elimination was finally carried out successfully with PIDA (phenyliodonium diacetate). Although this type of hypervalent iodine reagent is well-known and has been extensively used in organic synthesis,[19] to our knowledge, it had not been used previously for this type of selenoxide elimination.

Then, we studied the conjugate addition reactions of α-lithiodithioacetals to unsaturated bicyclic *δ*-lactams **3a** and **3b**. For this purpose, we chose 2-lithio-1,3-dithiane and bis(phenylthio)methyllithium, which could show different behavior in conjugate additions.[15] The latter anion would be more stable, whereas its acyclic structure allows rotation, optimizing orbital overlap with the conjugate acceptor.[20] First, we studied the addition of bis(phenylthio)methyllithium to lactams **3a**,**b** (Scheme 2, Table 1). The anion could be efficiently prepared by deprotonation of bis(phenylthio)methane with *n*-BuLi at −78 °C for 1 h. However, no reaction was observed if the conjugate acceptor was added at this temperature and allowed to reach

TABLE 1. Conjugate Additions of Stabilized Anions to 3a,b

Entry	RLi	R^1	R^2	t (h)	Prod.	Yield (%)	*dr trans/cis*
1		H	Ph	16	**5a**	5[a]	<5:>95
2		H	Ph	5	**5a**	70	<5:>95
3		H	-$(CH_2)_3$-	5	**5b**	85	<5:>95
4		CH_3	Ph	16	**6a:7a**	93	80:20
5		CH_3	-$(CH_2)_3$-	16	**6b:7b**	84	85:15
6		CH_3	-$(CH_2)_3$-	5	**6b:7b**	75	88:12

[a] Cyclopropane derivative **8** (Figure 2) was isolated as the major product (68%).

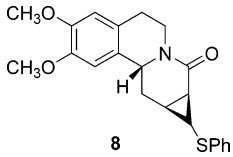


FIGURE 2. Structure of byproduct **8**.

temperatures from −78 °C to room temperature. Optimization of the reaction conditions revealed that 1,4-addition occurred when the anion was prepared at −78 °C, allowed to reach room temperature, and quenched by addition of the lactam **3a** or **3b** (Table 1).

However, in the case of **3a**, if the reaction mixture was stirred overnight (entry 1), the addition product **5a** was isolated in low yield (5%) and the major compound was the cyclopropane derivative **8** (Figure 2).[21] The formation of **8** could be explained by nucleophilic displacement of a thiophenyl group by the enolate formed after the conjugate addition reaction.[22] Thus, a reduction of the reaction time (entry 2) allowed the isolation of the cis diastereomer **5a** in good yield and with complete diastereoselectivity. These conditions were applied to the addition of 2-lithio-1,3-dithiane (entry 3), obtaining the corresponding cis adduct **5b** as a single diastereomer in high yield. Interestingly, a reversal of the stereoselectivity was observed

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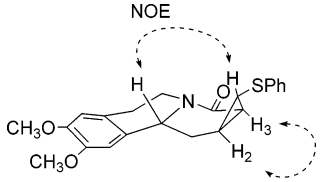
(21) COSY, HMQC, and NOESY experiments were used to confirm the structure of **8**. The value of the coupling constant among the cyclopropane protons and the NOE enhancement between H-11b and the PhSCH were consistent with the stereochemistry shown in the figure.



(22) The formation of this type of cyclopropane derivatives has been previously reported in the conjugate addition of this sulfur-stabilized carbanion to cyclohexenone. See: (a) Cohen, T.; Yu, L.-C. *J. Org. Chem.* **1985**, *50*, 3266. (b) Cohen, T.; Myers, M. *J. Org. Chem.* **1988**, *53*, 457.

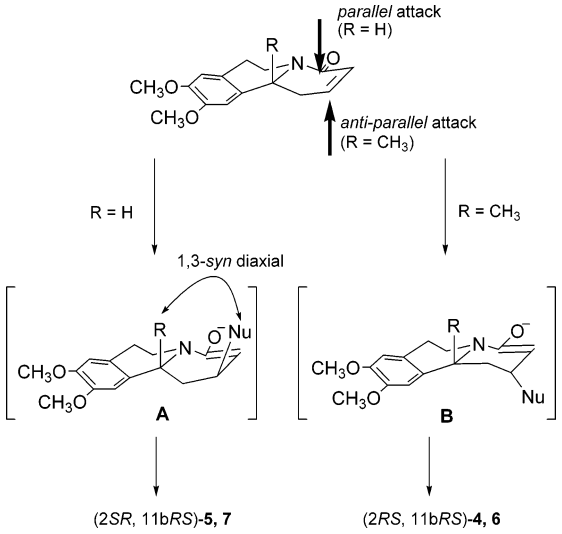


FIGURE 3. Stereochemical outcome of the conjugate addition.

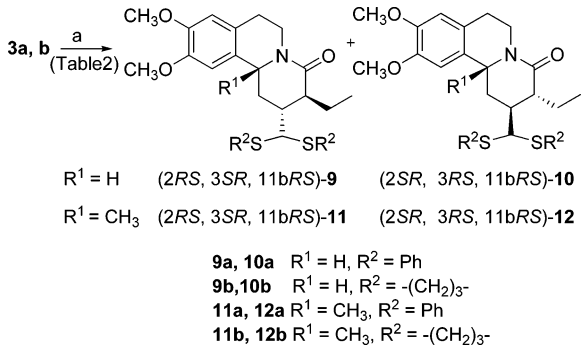
when the C-11b substituted lactam **3b** was used as substrate. As shown in Table 1, the trans adducts **6a** and **6b** were the major compounds formed when **3b** was treated with both bis(phenylthio)methyllithium and 2-lithio-1,3-dithiane, with reasonable diastereoselectivities (entries 4−6). Shorter reaction times did not significantly effect the diastereoselectivity (entry 6).

Thus, benzo[*a*]quinolizinones **3a** and **3b** undergo conjugate addition of sulfur-stabilized anions with opposite facial selectivity. These results are in agreement with those obtained by Amat and Bosch,[23] who have studied the factors governing the facial stereoselectivity observed in the conjugate addition of several types of nucleophiles to phenylglycinol-derived unsaturated bicyclic δ-lactams. Similar effects have also been described by Allin[24] for the conjugate addition reactions on indolo[2,3-*a*]quinolizine systems. It should be noted that, in the cases described by these authors, the angular substituent α to the nitrogen atom is always a hydrogen atom, and we have studied the effect of a methyl substituent at this position. Thus, in our case, when R = H, attack of the nucleophile to these conformationally rigid lactams occurs under stereoelectronic control, parallel with respect to the axial hydrogen in C-11b (exo attack).[25] This leads to a 1,3-syn disposition of both substituents in the resulting intermediate **A** (Figure 3). However, when the axial hydrogen is replaced by a methyl group, this 1,3-syn diaxial interaction in the resulting intermediate or in the transition state leading to it would favor an antiparallel attack leading to the more stable trans diastereomer through an intermediate such as **B**.

We next studied the feasibility of performing a tandem conjugate addition−electrophile trap reaction on these substrates. For this purpose, we chose ethyl iodide as the electrophile. As shown before, the addition of both sulfur-stabilized anions to **3a** was completely syn selective, obtaining the adducts **10a** and **10b** (Scheme 3, Table 2, entries 1 and 2). However, enolate alkylation was not completely stereoselective in the case of the addition of bis(phenylthio)methyllithium, as the product was isolated as an epimeric mixture of **10a** and **10a′** in a 4:1 ratio (Figure 4). On the other hand, the tandem addition−ethyl iodide trap on **3b** yielded the corresponding trans products **11a** and **11b** as the major compounds (entries 3 and 4). These results could be explained by assuming that in the enolates derived from **3a** both the hydrogen on C-11b and the dithioacetal group are in pseudoaxial disposition. Consequently, steric factors associated with the size of the substituents may bock the parallel approach of the electrophile. In the alkylation of the enolates derived from **3b**, with a pseudoaxial methyl group on C-11b and a pseudoequatorial dithioacetal on C-2, approach of the electrophile always takes place opposite to the dithioacetal group.

NOESY and COSY experiments confirmed the stereochemistry of all the benzoquinolizinone derivatives. The most significant results obtained with diastereomeric benzoquinolizinone (2*RS*,11b*RS*)-**6a** and (2*SR*,11b*RS*)-**7a** are shown in Figure 5. Thus, for (2*RS*,11b*RS*)-**6a**, the *J* values of the ABX system

SCHEME 3[a]



[a] Reagents: (a) $(R^2S)_2CHLi$, −78 °C, 1 h, → rt, 5 h; EtI, rt, 12 h.

TABLE 2. Conjugate Addition−Electrophile Trap Reactions of 3a,b

Entry	RLi	R^1	R^2	Prod	Yield (%)	*dr trans/cis*
1		H	Ph	**10a**	62[a]	<5:>95
2		H	-$(CH_2)_3$-	**10b**	75	<5:>95
3		CH_3	Ph	**11a:12a**	67	85:15
4		CH_3	-$(CH_2)_3$-	**11b**	50[b]	>95:<5

[a] **10a** was isolated as a mixture of C-3 epimers (Figure 4). [b] **6b** was isolated as a byproduct.

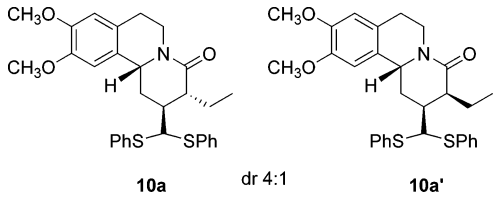


FIGURE 4. Structure of epimeric products **10a** and **10a′**.

(23) (a) Amat, M.; Pérez, M.; Minaglia, A. T.; Casamitjana, N.; Bosch, J. *Org. Lett.* **2005**, *7*, 3653−3656. (b) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681−8693 and references therein.

(24) Allin, S. M.; Khera, J. S.; Thomas, C. I.; Witherington, J.; Doyle, K.; Elsegood, M. R. J.; Edgar, M. *Tetrahedron Lett.* **2006**, *47*, 1961−1964.

(25) See, ref 12a, p 25.

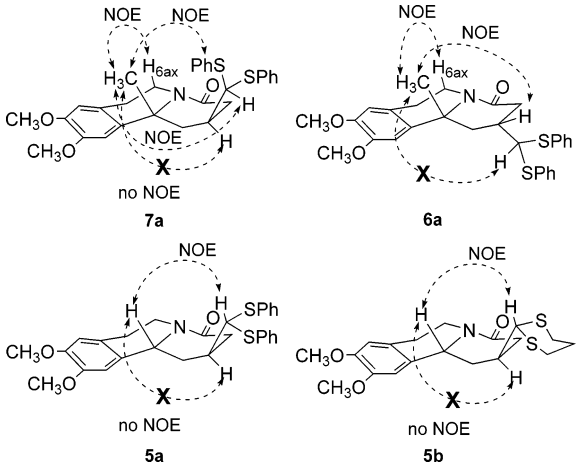


FIGURE 5. Selected NOE enhancements for **5a**, **5b**, **6a**, and **7a**.

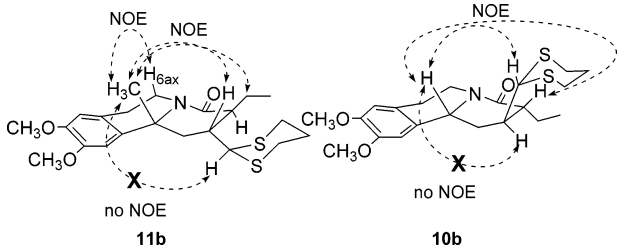


FIGURE 6. Selected NOE enhancements for **10b** and **11b**.

formed by H-2 and H-3 protons indicate that H-2 is in a pseudoaxial position. Additionally, 2D NOE experiments showed an enhancement between the methyl groups on C-11b, H-6_{axial}, and H-2. Besides, no NOE was observed between the methyl group on C-11b and the protons of the $(PhS)_2CH$ group. These data are consistent with the preferred half-chair and half-boat conformation for the quinolizidine system in which the substituents in C-11b and C-2 are in pseudoaxial and pseudoequatorial positions, respectively. Thus, the configuration was assigned as 2*RS*,11b*RS*. On the other hand, for the *cis*-**7a** diastereomer, the *J* values of the ABX system formed by H-2 and H-1 protons indicate that H-2 is also in a pseudoaxial position. In this case, the absence of a NOE enhancement between the methyl protons on C-11b and H-2 and the enhancement observed between these methyl protons and the phenyl protons of the thiophenyl rings confirmed that both substituents are in a cis disposition, resulting from a 2*SR*,11b*RS* configuration. Similar results were observed for benzoquinolizines **5a** and **5b** (see Figure 5). Thus, in both cases, no NOE was observed between H-2 and H-11b, but the signal of the aliphatic methine proton of the $(PhS)_2CH$ group was enhanced when H-11b was irradiated and vice versa.

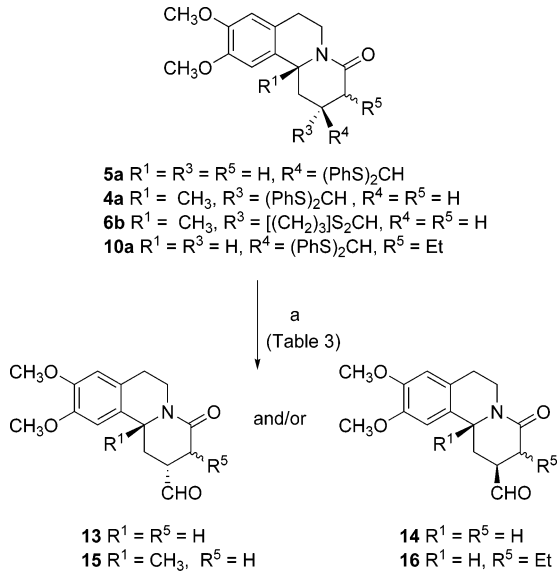
In the same way, the stereochemistry of trisubstituted benzoquinolizidines was determined. As an example, selected NOE enhancements for **11b** and **10b** are shown in Figure 6. Thus, for (2*RS*,3*SR*,11b*RS*)-**11b**, a NOE enhancement between the methyl protons on C-11b, H-2, and the ethyl group was observed. On the other hand, the (2*SR*,3*RS*,11b*RS*)-**10b** diastereomer showed a NOE enhancement between the H-11b atom and the substituent at C-2 and H-3, whereas no NOE was observed between the H-11b atom and the ethyl group (see Figure 5). The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry in each case.

TABLE 3. Deprotection of Thioacetals

Entry	Substrate	Product	Yield (%)
1	**5a**	**13** + **14**	70[a]
2	**5a**	**14**[b]	80
2	**6a**	**15**[b]	80
3	**6b**	**15**[b]	80
4	**10a**[c]	**16**[b,c]	70

[a] Diastereomeric ratio **13**/**14** 2:1. [b] pH was maintained as acidic (pH = 6). [c] 4:1 epimeric mixture at C-3.

SCHEME 4[a]



[a] Reagents: (a) PIDA, TFA, CH_3CN/H_2O, rt.

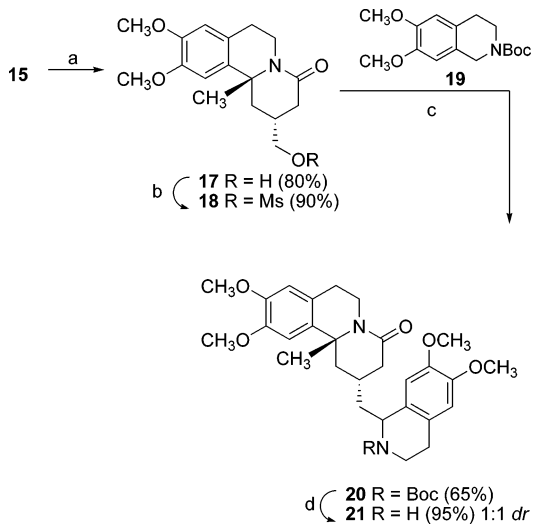
At this point, it was necessary to show that the masked carbonyl groups could be easily deprotected. However, we tried some of the most common deprotecting agents for this transformation,[26] always recovering the unreacted thioacetals. In view of the good results obtained in the oxidation of selenides, we decided to test PIDA as a deprotecting agent.[27] As shown in Table 3 and Scheme 4, selected thioacetals were smoothly deprotected by treatment with PIDA and TFA in CH_3CN/H_2O. Thus, when **5a** was treated with PIDA and the reaction mixture was basified with $NaHCO_3$ during workup, a mixture of aldehydes **13** and **14** was obtained in a 2:1 ratio (entry 1). However, by simply maintaining an acidic medium throughout the workup and purification procedures, this epimerization could be prevented. Under these conditions, aldehydes **15** and **16** were obtained in good yields.

To show the synthetic interest of these reactions, we chose one of the aldehydes to further elaborate the structure toward emetine analogues. Thus, aldehyde **15** was reduced to the

(26) (a) HgO/BF_3: see ref 15. (b) $NaNO_2/AcCl/H_2O$: Khan, A. T.; Mondal, E.; Sahu, P. R. *Synlett* **2003**, 377−381. (c) DMSO, 160 °C: Rao, C. S.; Chandrasekharan, M.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1992**, *33*, 8163−8164. (d) $NaHCO_3/I_2$: Desroy, N.; Le Roux, R.; Phansavath, P.; Chiummiento, L.; Bonini, C.; Gênet, J.-P. *Tetrahedron Lett.* **2003**, *44*, 1763−1766. (e) $NaHCO_3$/MeI: Takai, S.; Sawada, N.; Isobe, M. *J. Org. Chem.* **2003**, *68*, 3225−3231.

(27) Hypervalent iodine compounds such as PIFA [phenyliodine(III) bis(trifluoroacetate)] have been reported to oxidize sulfur-containing compounds. See, for instance: (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287−290. (b) Birk, C.; Voss, J. *Tetrahedron* **1996**, *52*, 12745−12760. (c) Fleming, F. F.; Lee, F.; Altundas, R.; Yung, T. *J. Org. Chem.* **2001**, *66*, 6502−6504. (d) Tohma, H.; Maegawa, T.; Kita, Y. *Arkivoc* **2003**, 62−70.

SCHEME 5[a]



[a] Reagents: (a) $NaBH_4$, EtOH/H_2O, 0 °C, 1 h. (b) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C → rt, 12 h. (c) **19**, *t*-BuLi, −78 °C, 15 min, then **18**, rt. (d) TFA, CH_2Cl_2, rt.

corresponding alcohol **17** in good yield (Scheme 5). This alcohol was mesylated and submitted to nucleophilic displacement with the anion obtained by deprotonation of the isoquinoline **19**, obtaining **20** as a 1:1 mixture of diastereomers. Hydrolysis of the Boc group produced the epimeric emetine analogues **21**.

In conclusion, conjugate addition reactions of sulfur-stabilized nucleophiles to the δ-lactam unit of tetrahydrobenzo[*a*]benzoquinolizines allowed the stereocontrolled formation of carbon−carbon bonds at the C-2 position. The attack of the nucleophile occurred parallel to the hydrogen on C-11b. However, the introduction of a methyl group at the C-11b position caused the reversal of the stereochemical course of the addition. Thus, 2,11b-cis or 2,11b-trans diastereomers could be selectively obtained. The conjugate addition−alkylation tandem reaction also took place in good yields and with high diastereoselectivity. Besides, the polyfunctionalized hexahydrobenzo[*a*]quinolizinone systems obtained could be further elaborated toward emetine-like structures.

Experimental Section

Conjugate Addition Reactions of Lithiodithioacetals to Benzo[*a*]quinolozidones 3a,b. General Procedure. To a solution of bis(thiophenyl)methane or 1,3-dithiane (2 mmol) in dry THF (10 mL) was added *n*-BuLi (2 mmol) at −78 °C. The resulting mixture was stirred at this temperature for 1 h and allowed to warm to room temperature. A solution of benzoquinolizidone **3a** or **3b** (1 mmol) in THF (10 mL) was added, and the resulting solution was stirred for 5 or 16 h. The reaction was quenched by the addition of saturated NH_4Cl (15 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford benzoquinolizidones **4** and/or **5**, which were purified by flash column chromatography.

(2*SR*,11b*RS*)-2-[Bis(thiophenyl)methyl]-9,10-dimethoxy-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (5a). According to the general procedure, **3a** (95 mg, 0.37 mmol) was treated with lithio-bis(thiophenyl)methane, prepared from bis(thiophenyl)-methane (170 mg, 0.73 mmol) and *n*-BuLi (0.60 mL of a 1.2 M solution in hexanes, 0.73 mmol), for 5 h. Flash column chromatography (silica gel, AcOEt) afforded **5a** as a white solid (130 mg, 70%): mp (Et_2O) 149−150 °C; IR (KBr) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) 2.34−2.49 (m, 2H), 2.56−2.72 (m, 3H), 2.80−3.04 (m, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.29 (d, J = 3.6 Hz, 1H), 4.71−4.75 (m, 1H), 4.75−4.79 (m, 1H), 6.63 (s, 1H), 6.79 (s, 1H), 7.23−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) 28.1, 31.1, 34.9, 36.7, 40.9, 54.7, 55.9, 56.1, 65.3, 107.6, 111.8, 127.7, 128.0, 129.1, 129.9, 133.2, 132.6, 133.4, 134.3, 147.5, 147.9, 169.0; MS (EI) *m*/*z* (rel intensity) 492 (M^+ + 1, 3), 491 (M^+, 10), 382 (51), 353 (20), 272 (60), 258 (100), 244 (17), 230 (10), 205 (11), 192 (19). HRMS calcd for $C_{28}H_{29}NO_3S_2$: 491.1589. Found: 491.1607

(2*SR*,11b*RS*)-2-[1,3-Dithian-2-yl]-9,10-dimethoxy-1,2,3,6,7,-11b-hexahydrobenzo[*a*]quinolizin-4-one (5b). According to the general procedure, **3a** (124 mg, 0.47 mmol) was treated with 2-lithio-1,3-dithiane, prepared from 1,3-dithiane (115 mg, 0.95 mmol) and *n*-BuLi (0.80 mL of a 1.2 M solution in hexanes, 0.95 mmol), for 5 h. Flash column chromatography (silica gel, AcOEt) afforded **5b** as a white solid (152 mg, 85%): mp (Et_2O) 158−159 °C; IR (KBr) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) 1.85−1.91 (m, 1H), 2.10−2.40 (m, 5H), 2.59−2.80 (m, 2H), 2.85−3.05 (m, 6H), 3.85 (s, 3H), 3.88 (s, 3H), 4.04 (d, J = 7.5 Hz, 1H), 4.73−4.79 (m, 2H), 6.61 (s, 1H), 6.71 (s, 1H); ^{13}C NMR ($CDCl_3$) 25.6, 27.9, 29.9, 31.1, 34.0, 35.9, 40.7, 50.9, 54.1, 55.7, 55.8, 107.1, 111.6, 127.4, 128.2, 147.3, 147.7, 168.2; MS (EI) *m*/*z* (rel intensity) 380 (M^+ + 1, 15), 379 (M^+, 58), 304 (60), 273 (36), 258 (100), 245 (32), 205 (27), 192 (17), 176 (9). HRMS calcd for $C_{19}H_{25}NO_3S_2$: 379.1276. Found: 379.1271. Anal. Calcd for $C_{19}H_{25}NO_3S_2$: C, 60.13; H, 6.64; N, 3.69. Found: C, 59.95; H, 6.82; N, 3.86.

(2*RS*,11b*RS*)-2-[Bis(thiophenyl)methyl]-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (6a) and (2*SR*,11b*RS*)-2-[Bis(thiophenyl)methyl]-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (7a). According to the general procedure, **3b** (121 mg, 0.44 mmol) was treated with lithio-bis(thiophenyl)methane, prepared from bis-(thiophenyl)methane (210 mg, 0.88 mmol) and *n*-BuLi (0.73 mL of a 1.2 M solution in hexanes, 0.88 mmol), for 16 h. Flash column chromatography (silica gel, AcOEt) afforded a diastereomeric mixture of **6a** and **7a** in a 80:20 diastereomeric ratio (210 mg, 93%). Both diastereomers were separated by chromatography and characterized separately. Major trans diastereomer **6a**, white solid (155 mg, 74%): mp (Et_2O) 130−131 °C; IR (KBr) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) 1.72 (s, 3H), 2.02−2.05 (m, 1H), 2.06−2.11 (m, 1H), 2.46−2.55 (m, 1H), 2.58−2.64 (m, 1H), 2.79 (dd, J = 16.4, 12.0 Hz, 1H), 2.99−3.16 (m, 1H), 3.00 (dd, J = 12.3, 6.7 Hz, 1H), 3.31 (td, J = 12.7, 4.7 Hz, 1H), 3.92 (s, 3H), 3.97 (s, 3H), 4.24 (d, J = 3.6 Hz, 1H), 4.83 (dd, J = 13.0, 6.0 Hz, 1H), 6.60 (s, 1H), 6.90 (s, 1H), 7.19−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) 27.8, 32.8, 34.8, 36.3, 38.0, 38.3, 55.8, 56.1, 59.5, 65.4, 107.1, 112.1, 127.3, 127.9, 128.2, 128.9, 132.5, 132.8, 133.4, 134.3, 147.3, 147.9, 169.5; MS (EI) *m*/*z* (rel intensity) 506 (M^+ + 1, 2), 505 (M^+, 6), 396 (100), 380 (9), 271 (5), 258 (17), 206 (21), 191 (5), 110 (5). HRMS calcd for $C_{29}H_{31}NO_3S_2$: 505.1745. Found: 505.1729. Anal. Calcd for $C_{29}H_{31}NO_3S_2$: C, 68.88; H, 6.18; N, 2.77. Found: C, 68.59; H, 6.15; N, 2.53. Minor cis diastereomer **7a**, colorless oil (50 mg, 18%): IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 1.48 (s, 3H), 1.62−1.81 (m, 1H), 2.55−2.67 (m, 5H), 2.83−2.90 (m, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 4.35 (d, J = 3.6 Hz, 1H), 4.85−4.89 (m, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 7.28−7.48 (m, 10H); ^{13}C NMR ($CDCl_3$) 27.9, 28.6, 33.7, 35.7, 35.8, 39.8, 55.7, 56.2, 58.4, 64.7, 108.4, 111.3, 125.8, 127.9, 128.1, 129.0, 132.5, 133.0, 134.2, 134.3, 147.6, 167.8; MS (EI) *m*/*z* (rel intensity) 505 (M^+, 1), 396 (100), 380 (5), 258 (39), 206 (16), 165 (11), 110 (23). HRMS calcd for $C_{29}H_{31}NO_3S_2$: 505.1745. Found: 505.1760.

(2*RS*,11b*RS*)-2-(1,3-Dithian-2-yl)-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (6b) and (2*SR*,-11b*RS*)-2-(1,3-Dithian-2-yl)-9,10-dimethoxy-11b-methyl-1,2,3,6,7,-11b-hexahydrobenzo[*a*]quinolizin-4-one (7b). According to the general procedure, **3b** (396 mg, 1.45 mmol) was treated with 2-lithio-1,3-dithiane, prepared from 1,3-dithiane (350 mg, 2.9 mmol) and *n*-BuLi (2.23 mL of a 1.3 M solution in hexanes, 2.9 mmol),

for 5 h. Flash column chromatography (silica gel, AcOEt) afforded a diastereomeric mixture of **6b** and **7b** in a 88:12 diastereomeric ratio (430 mg, 75%). Both diastereomers were separated by chromatography and characterized separately. Major trans diastereomer **6b**, white solid (378 mg, 66%): mp (Et_2O) 184−185 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 1.60 (s, 3H), 1.76−1.96 (m, 3H), 2.06−2.13 (m, 1H), 2.38−2.45 (m, 2H), 2.49−0.67 (m, 1H), 2.75−2.89 (m, 4H), 2.96−3.10 (m, 2H), 3.27 (td, J = 12.5, 4.8 Hz, 1H), 3.84 (s, 3H), 3.88 (s, 3H), 3.95 (d, J = 6.2 Hz, 1H), 4.77 (dd, J = 13.1, 6.3 Hz, 1H), 6.55 (s, 1H), 6.72 (s, 1H); ^{13}C NMR ($CDCl_3$) 25.8, 27.5, 29.6, 32.5, 33.7, 35.6, 37.4, 39.3, 51.4, 55.6, 55.8, 59.1, 106.3, 111.9, 126.8, 132.6, 147.1, 147.6, 169.1; MS (EI) *m*/*z* (rel intensity) 394 (M^+ + 1, 4), 393 (M^+, 15), 378 (100), 271 (8), 242 (6), 206 (5). HRMS calcd for $C_{20}H_{27}NO_3S_2$: 393.1432. Found: 393.1432. Anal. Calcd for $C_{20}H_{27}NO_3S_2$: C, 61.04; H, 6.91; N, 3.56. Found: C, 60.64; H, 6.90; N, 3.51. Minor cis diastereomer **7b**, colorless oil (52 mg, 9%): IR (KBr) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) 1.60 (s, 3H), 1.61−1.79 (m, 1H), 1.82−1.97 (m, 1H), 2.09−2.18 (m, 1H), 2.33−2.56 (m, 2H), 2.58 (d, J = 11.9 Hz, 1H), 2.55−2.64 (m, 1H), 2.84−2.87 (m, 1H), 2.88−3.00 (m, 6H), 3.85 (s, 3H), 3.88 (s, 3H), 4.03 (d, J = 5.5 Hz, 1H), 4.85−4.93 (m, 1H), 6.56 (s, 1H), 6.62 (s, 1H); ^{13}C NMR ($CDCl_3$) 25.9, 28.0, 28.8, 30.4, 33.8, 35.8, 41.1, 52.5, 55.8, 56.3, 58.4, 108.5, 111.4, 125.9, 134.4, 147.7, 167.8; MS (EI) *m*/*z* (rel intensity) 394 (M + 1, 16), 393 (M^+, 9), 378 (100), 271 (11), 258 (13), 242 (15), 206 (10), 119 (24), 91 (7). HRMS calcd for $C_{20}H_{27}NO_3S_2$: 393.1432. Found: 393.1437.

(2*SR*,3*RS*,11b*RS*)-9,10-Dimethoxy-2,3-phenylthiomethano-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (8). According to the general procedure, **3a** (115 mg, 0.45 mmol) was treated with lithio-bis(thiophenyl)methane, prepared from bis(thiophenyl)-methane (213 mg, 0.89 mmol) and *n*-BuLi (0.60 mL of a 1.5 M solution in hexanes, 0.89 mmol), for 16 h. Flash column chromatography (silica gel, AcOEt) afforded **5a** (11 mg, 5%) and the cyclopropane derivative **8** as a white solid (120 mg, 68%): mp (Et_2O) 169−170 °C; IR (KBr) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) 1.81−1.98 (m, 1H), 1.98−2.05 (m, 1H), 2.20 (dd, J = 8.3, 3.6 Hz, 1H), 2.57−2.67 (m, 1H), 2.68−2.72 (m, 1H), 2.74−2.79 (m, 2H), 299 (t, J = 3.6 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.45 (dd, J = 11.9, 4.4 Hz, 1H), 4.85−4.91 (m, 1H), 6.59 (s, 1H), 6.60 (s, 1H), 7.17−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) 20.5, 22.5, 27.9, 28.4, 30.4, 38.7, 51.6, 55.7, 55.9, 108.3, 111.4, 125.8, 127.0, 127.3, 128.9, 136.3, 147.6, 147.7, 167.6; MS (EI) *m*/*z* (rel intensity) 382 (M^+ + 1, 10), 381 (M^+, 37), 272 (100), 258 (25), 245 (56), 230 (14), 206 (80), 192 (58), 176 (34), 147 (10), 91 (11), 77 (12). HRMS calcd for $C_{22}H_{23}NO_3S$: 381.1399. Found: 381.1404.

Tandem Conjugate Addition Reactions of Lithio Dithioacetals−EtI Trap. General Procedure. To a solution of bis(thiophenyl)methane or 1,3-dithiane (2 mmol) in dry THF (10 mL) was added *n*-BuLi (2 mmol) at −78 °C. The resulting mixture was stirred at this temperature for 1 h and allowed to warm to room temperature. A solution of **3a** or **3b** (1 mmol) in THF (10 mL) was added, and the resulting solution was stirred for 5 or 16 h. EtI (2 mmol) was added, and the reaction mixture was further stirred for 6 h. The reaction was quenched by the addition of saturated NH_4Cl (15 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford benzoquinolizidones **9**−**12**, which were purified by flash column chromatography.

(2*SR*,3*RS*,11b*RS*)-2-[Bis(thiophenyl)methyl]-3-ethyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (10a) and (2*SR*,3*SR*,11b*RS*)-2-[Bis(thiophenyl)methyl]-3-ethyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (10a′). According to the general procedure, **3a** (381 mg, 1.47 mmol) was treated with lithio-bis(thiophenyl)methane, prepared from bis(thiophenyl)methane (684 mg, 2.9 mmol) and *n*-BuLi (2.45 mL of a 1.2 M solution in hexanes, 2.9 mmol), for 5 h, and EtI (0.38 mL, 4.8 mmol). Flash column chromatography (silica gel, AcOEt) afforded a diastereomeric mixture of **10a** and **10a′** in a 4:1 diastereomeric ratio that could not be separated (500 mg, 65%): mp (Et_2O) 149−150 °C; IR (KBr) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) 0.55 (t, J = 7.4 Hz, 3H major diast.), 1.03 (t, J = 7.4 Hz, 3H minor diast.), 1.46−1.57 (m, 1H minor diast. + 1H both diast.), 1.71−1.81 (m, 1H major diast. + 1H both diast.), 2.05−2.10 (m, 1H minor diast.), 2.15−2.26 (m, 1H both diast.), 2.30−2.93 (m, 2H major diast. + 3H both diast.), 3.63−3.72 (m, 1H minor diast.), 3.87 (s, 3H both diast.), 3.91 (s, 3H both diast.), 4.16 (d, J = 5.9 Hz, 1H minor diast.), 4.43 (d, J = 4.8 Hz, 1H major diast.), 4.73−4.79 (m, 2H both diast.), 6.59 (s, 1H minor diast.), 6.62 (s, 1H major diast.), 6.83 (s, 1H both diast.), 6.97−7.5 (m, 10H both diast.); ^{13}C NMR ($CDCl_3$) 10.0 (major diast.), 11.9 (minor diast.), 21.7 (major diast.), 22.8 (minor diast.), 28.3 (major diast.), 28.7 (minor diast.), 29.6 (major diast.), 34.8 (minor diast.), 37.0 (major diast.), 37.2 (major diast.), 38.6 (minor diast.), 40.7 (major diast.), 44.6 (major diast.), 45.7 (minor diast.), 53.7 (major diast.), 55.7 (minor diast.), 55.9, 56.0 (both diast.), 58.9 (major diast.), 64.4 (minor diast.), 107.8 (major diast.), 108.6 (minor diast.), 110.8 (major diast.), 111.6 (minor diast.), 125.9, 126.1, 127.9, 127.9, 128.2, 128.3, 128.6, 128.8, 128.9, 129.8, 132.5, 133.5, 133.6, 135.1 (both diast.), 147.4 (major diast.), 147.7 (major diast.), 147.8 (minor diast.), 148.2 (minor diast.), 170.9 (major diast.), 171.2 (minor diast.); MS (EI) *m*/*z* (rel intensity) 520 (M^+ + 1, 7), 519 (M^+, 15), 410 (52), 381 (24), 300 (62), 286 (100), 272 (34), 230 (16), 205 (16), 192 (11), 135 (7), 109 (8), 91 (4).

(2*SR*,3*RS*,11b*RS*)-2-[1,3-Dithian-2-yl]-3-ethyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (10b). According to the general procedure, **3a** (259 mg, 0.99 mmol) was treated with 2-lithio-1,3-dithiane, prepared from 1,3-dithiane (240 mg, 1.98 mmol) and *n*-BuLi (1.98 mL of a 1.0 M solution in hexanes, 1.98 mmol), for 5 h, and EtI (0.15 mL, 1.98 mmol). Flash column chromatography (silica gel, AcOEt) afforded **10b** as a single diastereomer (322 mg, 80%): mp (Et_2O) 167−168 °C; IR (KBr) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) 0.84 (t, J = 7.3 Hz, 3H), 1.47−1.59 (m, 1H), 1.75−1.97 (m, 2H), 2.00−2.03 (m, 1H), 2.04−2.09 (m, 2H), 2.48−2.69 (m, 2H), 2.71−2.76 (m, 2H), 2.77−288 (m, 5H), 3.76 (s, 3H), 3.79 (s, 3H), 4.09 (d, J = 8.3 Hz, 1H), 4.62−4.69 (m, 1H), 4.70−4.79 (m, 1H), 6.52 (s, 1H), 6.61 (s, 1H); ^{13}C NMR ($CDCl_3$) 11.4, 24.0, 25.7, 28.2, 28.7, 29.9, 36.7, 39.8, 44.5, 49.9, 52.6, 55.5, 55.8, 107.5, 111.2, 126.9, 128.8, 147.3, 147.4, 170.5; MS (EI) *m*/*z* (rel intensity) 408 (M^+ + 1, 12), 407 (M^+, 43), 378 (10), 332 (39), 301 (13), 286 (100), 270 (20), 258 (25), 230 (10), 205 (43), 192 (10), 119 (37). HRMS calcd for $C_{21}H_{29}NO_3S_2$: 407.1589. Found: 407.1589.

(2*RS*,3*SR*,11b*RS*)-2-[Bis(thiophenyl)methyl]-3-ethyl-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (11a). According to the general procedure, **3b** (295 mg, 1.08 mmol) was treated with lithio-bis(thiophenyl)methane, prepared from bis(thiophenyl)methane (513 mg, 2.16 mmol) and *n*-BuLi (2.27 mL of a 0.95 M solution in hexanes, 2.16 mmol), for 16 h, and EtI (0.17 mL, 2.16 mmol). Flash column chromatography (silica gel, 70% hexane/AcOEt) afforded a diastereomeric mixture of **11a** and **12a** in an 85:15 ratio (385 mg, 67%). Only the major compound **11a** could be separated and fully characterized: mp (Et_2O) 149−150 °C; IR (KBr) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) 0.13 (t, J = 7.2 Hz, 3H), 1.16−1.27 (m, 1H), 1.66 (s, 3H), 1.93−1.96 (m, 1H), 1.97−2.00 (m, 1H), 2.00−2.10 (m, 1H), 2.54 (dd, J = 16.3, 3.7 Hz, 1H), 2.77−2.84 (m, 1H), 2.85 (td, J = 16.3, 5.7 Hz, 1H), 3.14−3.18 (m, 1H), 3.25 (td, J = 13.2, 4.5 Hz, 1H), 3.88 (s, 3H), 3.96 (s, 3H), 4.28 (d, J = 1.6 Hz, 1H), 4.80 (dd, J = 13.2, 5.7 Hz, 1H), 6.57 (s, 1H), 6.96 (s, 1H), 6.97−7.5 (m, 10H); ^{13}C NMR ($CDCl_3$) 8.0, 19.6, 28.7, 32.9, 35.5, 36.4, 37.1, 45.1, 55.9, 56.1, 58.9, 64.3, 107.6, 112.1, 127.4, 128.0, 128.5, 129.1, 132.6, 132.9, 133.7, 134.1, 134.4, 147.3, 147.8, 171.5; MS (EI) *m*/*z* (rel intensity) 533 (M^+, 3), 518 (2), 424 (100), 314 (4), 286 (18), 206 (7), 123 (5). HRMS calcd for $C_{31}H_{35}NO_3S_2$: 533.2058. Found: 533.2054

(2*RS*,3*SR*,11b*RS*)-2-[1,3-Dithian-2-yl]-3-ethyl-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (11b).

According to the general procedure, **3b** (335 mg, 1.20 mmol) was treated with 2-lithio-1,3-dithiane, prepared from 1,3-dithiane (295 mg, 1.60 mmol) and *n*-BuLi (2.45 mL of a 1.0 M solution in hexanes, 1.98 mmol), for 5 h, and EtI (0.38 mL, 4.8 mmol). Flash column chromatography (silica gel, AcOEt) afforded **11b** as a single diastereomer (258 mg, 50%): mp (Et_2O) 176−177 °C; IR (KBr) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) 0.62 (t, J = 7.1 Hz, 3H), 1.25−1.48 (m, 1H), 1.56 (s, 3H), 1.72−2.03 (m, 3H), 2.13−2.30 (m, 2H), 2.55 (dd, J = 16.4, 4.5 Hz, 1H), 2.61−2.67 (m, 1H), 2.78−3.04 (m, 6H), 3.26 (td, J = 12.7, 4.6 Hz, 1H), 3.82 (s, 3H), 3.88 (s, 3H), 4.26 (d, J = 2.4 Hz, 1H), 4.79 (dd, J = 13.4, 6.7 Hz, 1H), 6.53 (s, 1H), 6.73 (s, 1H); ^{13}C NMR ($CDCl_3$) 9.3, 19.9, 26.3, 28.3, 30.7, 31.3, 32.8, 35.7, 36.7, 37.3, 44.7, 50.9, 55.7, 55.9, 58.7, 106.5, 111.9, 126.9, 132.9, 147.3, 147.6, 171.5; MS (EI) *m*/*z* (rel intensity) 421 (M^+, 11), 406 (100), 298 (11), 270 (12), 258 (25), 204 (4), 119 (12). HRMS calcd for $C_{22}H_{31}NO_3S_2$: 421.1745. Found: 421.1741.

Deprotection of Thioacetals. General Procedure. A solution of the benzoquinolizidones **5a**, **6a**, **6b**, or **10a** (1 mmol) in CH_3CN/H_2O (2:1, 15 mL) was treated with TFA (10 mmol) at room temperature. PIDA (1.3 mmol) was added in portions, and the resulting mixture was stirred for 1.5 h. The reaction mixture was extracted with hexane (3 × 20 mL). The combined organic extracts were treated with saturated $NaHCO_3$, maintaining an acidic media (pH ≈ 6). The aqueous phase was extracted with $CHCl_3$ (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel) afforded the 2-formylbenzoquinolizidones **14**, **15**, or **16**.

(2*SR*,11b*RS*)-2-Formyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (14). According to the general procedure, benzoquinolizidone **5a** (102 mg, 0.20 mmol) was treated with TFA (0.2 mL, 2.0 mmol) and PIDA (86 mg, 0.26 mmol). Flash column chromatography (silica gel, 20% AcOEt/NH_3) afforded **14** as a colorless oil (48 mg, 80%): IR (KBr) 1719, 1636 cm^{-1}; ^1H NMR ($CDCl_3$), 1.94−2.06 (m, 1H), 2.64−2.71 (m, 2H), 2.72−2.90 (m, 5H), 3.86 (s, 3H), 3.93 (s, 3H), 4.58 (dd, J = 10.3, 4.6 Hz, 1H), 4.75−4.82 (m, 1H), 6.60 (s, 1H), 6.65 (s, 1H), 9.82 (s, 1H); ^{13}C NMR ($CDCl_3$) 28.2, 29.4, 31.3, 39.5, 44.0, 53.4, 55.0, 56.0, 107.9, 111.5, 127.1, 127.8, 147.8, 147.9, 167.0, 200.4; MS (EI) *m*/*z* (rel intensity) 290 (M^+ + 1, 11), 289 (M^+, 50), 261 (32), 245 (95), 232 (19), 205 (35), 192 (100), 176 (33), 164 (8), 146 (9), 115 (8), 77 (10). HRMS calcd for $C_{16}H_{19}NO_4$: 289.1314. Found: 289.1344.

(2*RS*,11b*RS*)-2-Formyl-9,10-dimethoxy-11b-methyl-1,2,3,6,7,-11b-hexahydrobenzo[*a*]quinolizin-4-one (15). According to the general procedure, benzoquinolizidone **6a** (166 mg, 0.33 mmol) was treated with TFA (0.3 mL, 3.3 mmol) and PIDA (138 mg, 0.43 mmol). Flash column chromatography (silica gel, 20% AcOEt/NH_3) afforded **15** as a white solid (80 mg, 80%): IR (KBr) 1675, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) 1.52−1.68 (m, 1H), 1.61 (s, 3H), 2.41−2.50 (m, 1H), 2.53−2.84 (m, 5H), 2.90−2.97 (m, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 4.81−4.89 (m, 1H), 6.53 (s, 1H), 6.60 (s, 1H), 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$) 27.6, 28.7, 30.6, 35.8, 36.9, 41.5, 55.7, 56.0, 58.2, 108.0, 111.3, 125.9, 133.4, 147.7, 166.5, 200.6; MS (EI) *m*/*z* (rel intensity) 304 (M^+ + 1, 3), 303 (M^+, 10), 288 (100), 272 (2), 260 (6), 246 (3), 206 (4), 190 (3). HRMS calcd for $C_{17}H_{21}NO_4$: 303.1470. Found: 303.1476.

(2*SR*,3*RS*,11b*RS*)-3-Ethyl-2-formyl-9,10-dimethoxy-1,2,3,6,7,-11b-hexahydrobenzo[*a*]quinolizin-4-one (16). According to the general procedure, benzoquinolizidone **10a** (274 mg, 0.52 mmol, 4:1 epimeric mixture in C-3) was treated with TFA (0.5 mL, 5.2 mmol) and PIDA (220 mg, 0.69 mmol). Flash column chromatography (silica gel, 20% AcOEt/NH_3) afforded **16** as a colorless oil, as a 4:1 epimeric mixture in C-3. Data of the mixture are given (117 mg, 70%): IR (KBr) 1720, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) 0.89−1.03 (m, 3H both diast.), 1.40−1.50 (m, 1H minor diast.), 1.50−2.03 (m, 3H both diast. + 1H major diast.), 2.58−2.91 (m, 3H both diast. + 1H major diast.), 2.41−2.50 (m, 1H both diast.), 2.97−3.03 (m, 1H minor diast.), 3.85 (s, 3H both diast.), 3.88 (s, 3H both diast.), 4.55−4.63 (m, 1H both diast.), 4.77−4.83 (m, 1H both diast.), 6.60 (s, 1H major diast.), 6.62 (s, 1H minor diast.), 6.66 (s, 1H major diast.), 6.80 (s, 1H minor diast.), 9.71 (s, 1H, minor diast.), 9.83 (s, 1H, major diast.); ^{13}C NMR ($CDCl_3$) 11.9 (major diast.), 12.9 (minor diast.), 22.6 (minor diast.), 24.8 (major diast.), 27.1 (minor diast.), 27.2 (major diast.), 28.5 (both diast.), 39.6 (minor diast.), 39.8 (major diast.), 41.1 (major diast.), 41.6 (minor diast.), 46.3 (major diast.), 47.8 (minor diast.), 53.1 (major diast.), 54.9 (minor diast.), 55.8 (both diast.), 56.1 (both diast.), 108.0, 111.5 (both diast.), 126.9 (minor diast.), 127.1 (major diast.), 128.1 (minor diast.), 128.2 (major diast.), 147.8, 148.0 (both diast.), 170.1 (major diast.), 170.3 (minor diast.), 201.2 (minor diast.), 202.1 (major diast.); MS (EI) *m*/*z* (rel intensity) 317 (M^+, 37), 289 (50), 274 (53), 258 (33), 246 (100), 218 (29), 205 (73), 191 (88), 176 (38), 146 (14), 130 (18), 115 (11), 77 (13). HRMS calcd for $C_{18}H_{23}NO_4$: 317.1627. Found: 317.1617.

(2*RS*,11b*RS*)-2-Hydroxymethyl-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (17). $NaBH_4$ (50 mg, 1.3 mmol) was added in portions to a solution of aldehyde **15** (100 mg, 0.33 mmol) in 2:1 EtOH/H_2O (10 mL) at 0 °C, keeping pH = 7 by addition of saturated NH_4Cl. The resulting solution was stirred for 1 h. H_2O was added (10 mL), and the mixture was extracted with AcOEt (3 × 15 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, AcOEt) afforded the 2-hydroxymethylbenzoquinolizidone **17** as a colorless oil (80 mg, 80%): IR (KBr) 3384, 1609 cm^{-1}; ^1H NMR ($CDCl_3$) 1.45−1.55 (m, 1H), 1.61 (s, 3H), 1.90 (broad s, 1H), 2.07 (dd, J = 17.0, 11.9 Hz, 1H), 2.26−2.63 (m, 4H), 2.77−2.94 (m, 2H), 3.46−3.65 (m, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.84−4.95 (m, 1H), 6.58 (s, 1H), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$) 28.1, 28.9, 31.2, 34.6, 35.8, 40.6, 55.8, 56.2, 58.6, 66.4, 108.4, 111.3, 125.9, 134.7, 147.6, 147.7, 168.6; MS (EI) *m*/*z* (rel intensity) 305 (M^+, 5), 290 (100), 274 (6), 206 (13), 190 (6), 165 (4), 145 (3), 115 (7). HRMS. Calcd for $C_{17}H_{23}NO_4$: 305.1627. Found: 305.1617.

(2*RS*,11b*RS*)-2-Methanesulfonyloxymethyl-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (18). $MeSO_2Cl$ (0.06 mL, 0.73 mmol) and NEt_3 (0.1 mL, 0.73 mmol) were added to a solution of alcohol **17** (193 mg, 0.61 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. The solvent was concentrated in vacuo. Flash column chromatography (silica gel, AcOEt) afforded the mesylate **18** as a yellow oil (215 mg, 90%): IR (KBr) 1621, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03−1.08 (m, 1H), 1.09−1.32 (m, 1H), 1.23 (s, 3H), 1.47−1.61 (m, 1H), 1.62 (s, 3H), 1.88 (td, J = 8.7, 3.6 Hz, 1H), 2.12 (dd, J = 13.9, 3.9 Hz, 1H), 2.44−2.72 (m, 3H), 2.78−2.90 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.78−4.91 (m, 1H), 6.50 (s, 1H), 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$) 12.8, 14.0, 16.3, 28.6, 29.6, 31.3, 34.8, 36.1, 55.7, 56.1, 57.9, 108.7, 111.1, 125.4, 136.9, 147.4, 147.6, 170.9; MS (EI) *m*/*z* (rel intensity) 287 (6), 272 (100), 256 (6), 115 (2), 91 (2), 77 (2). HRMS calcd for $C_{18}H_{25}NO_6S$: 383.1403. Found: 387.1393.

(1′*RS*,2*RS*,11b*RS*)- and (1′*SR*,2*RS*,11b*RS*)-2-(6′,7′-Dimethoxy-1′,2′,3′,4′-tetrahydroisoquinolin-1-ylmethyl)-9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (21). *t*-BuLi (0.8 mL of a 1.1 M solution, 0.88 mmol) was added to a solution of isoquinoline **19**[28] (260 mg, 0.88 mmol) in THF (7 mL) at −78 °C. After 15 min, a solution of mesylate **13** (85 mg, 0.22 mmol) in THF (2 mL) was added, and the resulting solution was stirred for 5 min. The reaction mixture was allowed to warm to 0 °C and stirred at this temperature for 3 h. H_2O was added (10 mL), and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford **20**, which was deprotected without further purification. Thus, crude **20** was treated

(28) Boc-protected isoquinoline **19** was prepared by treatment of commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with di-*tert*-butyl dicarbonate. See: Coppola, G. M. *J. Heterocycl. Chem.* **1991**, *28*, 1769−1772.

with TFA (0.23 mL, 3 mmol) in CH_2Cl_2 (10 mL) at room temperature for 1 h. Saturated $NaHCO_3$ (10 mL) was added, and the organic phase was washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, AcOEt) afforded **21** as 1:1 mixture of C-1′ epimers (50 mg, 45% overall two steps): IR (KBr) 3314, 1639 cm^{-1}; ^1H NMR ($CDCl_3$) 1.97 (broad s, 1H both diast.), 2.50−3.05 (m, 8H both diast.), 3.26 (s, 3H one diast.), 3.21−3.48 (m, 3H, both diast.), 3.67 (s, 3H, other diast.), 3.80 (s, 6H, both diast.), 3.84 (s, 18H both diast.), 3.70−3.85 (m, 1H both diast.), 4.36−4.41 (m, 1H both diast.), 4.58−5.05 (m, 3H both diast.), 6.21 (s, 1H one diast.), 6.45 (s, 1H other diast.), 6.55−6.61 (m, 3H both diast.); ^{13}C NMR ($CDCl_3$) 25.6 (both diast.), 27.8 (one diast.), 28.4 (other diast.), 28.6 (both diast.), 40.6, 42.4, 42.6, 43.5, 44.6, 54.9, 55.8, 55.9 (one and/or other diast.), 58.5 (one diast.), 60.9 (other diast.), 108.1, 108.9, 109.3, 109.8, 111.7, 112.7, 124.4, 124.9, 125.8, 126.6, 126.9, 127.1, 147.4, 147.6, 147.7, 147.8, 147.9, 148.1 (one and/or other diast.), 171.1 (one diast.), 171.7 (other diast.); MS (EI) *m*/*z* (rel intensity) 234 (1), 221 (1), 192 (100), 176 (6), 164 (1), 148 (3), 131 (2), 105 (1), 91 (1).

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Supporting Information Available: Experimental procedures and full characterization data for compounds **1**−**3**. Copies of ^1H and ^{13}C NMR spectra of compounds described and selected 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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