C-10b Functionalized 5,6-dihydropyrrolo[2,1-*a*]isoquinolines as intermediates in the synthesis of erythrinane systems. Intra- *vs.* intermolecular conjugate addition based strategies

Iñaki Osante, Media N. Abdullah, 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 Prof. Joan Bosch on occasion of his 60th birthday

---

Abstract

C-10b Functionalized 5,6-dihydropyrrolo[2,1-*a*]isoquinolines have been prepared *via* Parham cyclization and α-amidoalkylation reactions, using functionalized organolithium reagents. Their utility as intermediates in the synthesis of erythrinanes *via* intra or intermolecular conjugate addition reactions has been studied. Thus, a protocol for preparing the erythrinane skeleton through a Parham cyclization–intermolecular α-amidoalkylation–intermolecular conjugate addition–ring-closing metathesis process has been described.

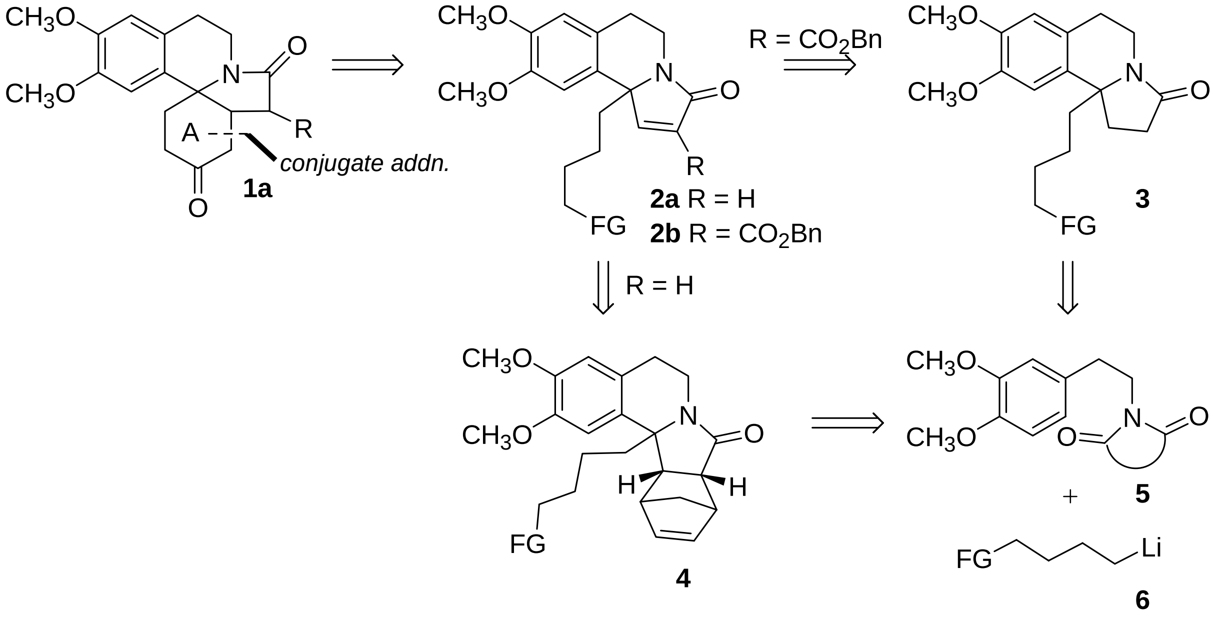
Keywords: Pyrroloisoquinolines, erythrinanes, functionalized organolithium compounds, conjugate addition, ring-closing metathesis

---

Introduction

The erythrinanes represent a significant class of alkaloids of broad pharmacological activity. Besides the curare–like and hypnotic action, they are known to display sedative, hypotensive, neuromuscular blocking, and CNS activity. This activity is attributed to antagonistic action of the nicotinic acetylcholine receptors in the brain.[1] Because of their unique spiro amine structure and physiological activities, these alkaloids have been a target of synthesis for a long time.[2]

Over the last years we have developed[3] new procedures for the synthesis of tetrahydro- and dihydropyrroloisoquinolones based on organolithium[4] and *N*-acyliminium chemistry.[5] These approaches proved to be an effective and expeditious method for the synthesis of these heterocycles in enantiomerically pure form.[6] A notable characteristic of these processes is that products are armed with a readily functionalized substituent at C-10b, and that they posses the α,β-unsaturated lactam unit, which is suitable for conjugate addition reactions. This feature offered a potentially facile route for erythrinane skeleton assembly, by closing ring A in the final step. We describe the reduction of this plan to practice.[7] The retrosynthetic analysis for our first approach to erythrinanes of general structure **1** is described in Scheme 1.



Scheme 1

We anticipated that the spiroamine unit could be assembled through an intramolecular conjugate addition reaction of a dihydropyrroloisoquinoline **2**, which incorporates a functionalized four-carbon atom substituent in C-10b. Compared with some other classes of conjugate acceptors, α,β–unsaturated amides and lactams are usually less reactive.[8] Thus, success of the conjugate addition reaction might require the presence of an activating group attached to the unsaturated system. Therefore, two types of 5,6-dihydropyrroloisoquinolones **2a** (R = H) and **2b** (R = CO_2Bn) would be compared for efficiency. These key intermediates **2** would be derived from pyrroloisoquinolines **3** or **4**, which would be obtained by addition of a functionalized organolithium reagent **6** to known imides **5**, followed by intramolecular α-amidoalkylation reaction.

Results and Discussion

Synthesis of precursors **2a,b** is depicted in Schemes 2 and 3. The first task was the choice of the organolithium **6**, which would behave as a 1,4-dianion equivalent. In this context, we had previously reported that 2-(3-lithiopropyl)-2-trimethylsilyl-1,3-dithiane **6c** (Figure 1) may be used in this addition–α-amidoalkylation sequence for the synthesis of functionalized dihydropyrroloisoquinolines of general structure **2a**.[3d] However, desilylation was problematic, and subsequent attempts of intramolecular conjugate addition were unsuccessful.[9] Therefore, we decided to test other possible 1,4-dianion equivalents, and selected protected β-carbonylorganolithiums, as 2-(2-lithioethyl)-2-methyl-[1,3]dioxolane **6a** and 2-(2-lithioethyl)-2-methyl-[1,3] dithiane **6b** (Figure 1).

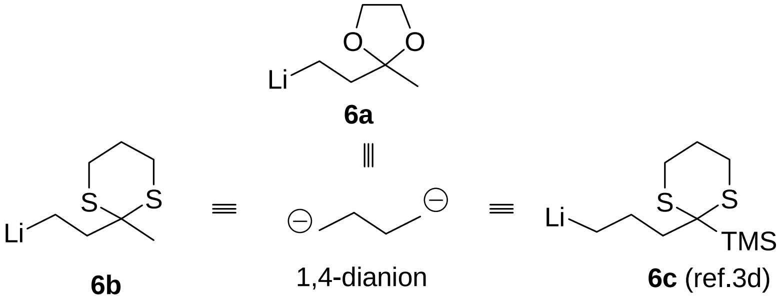
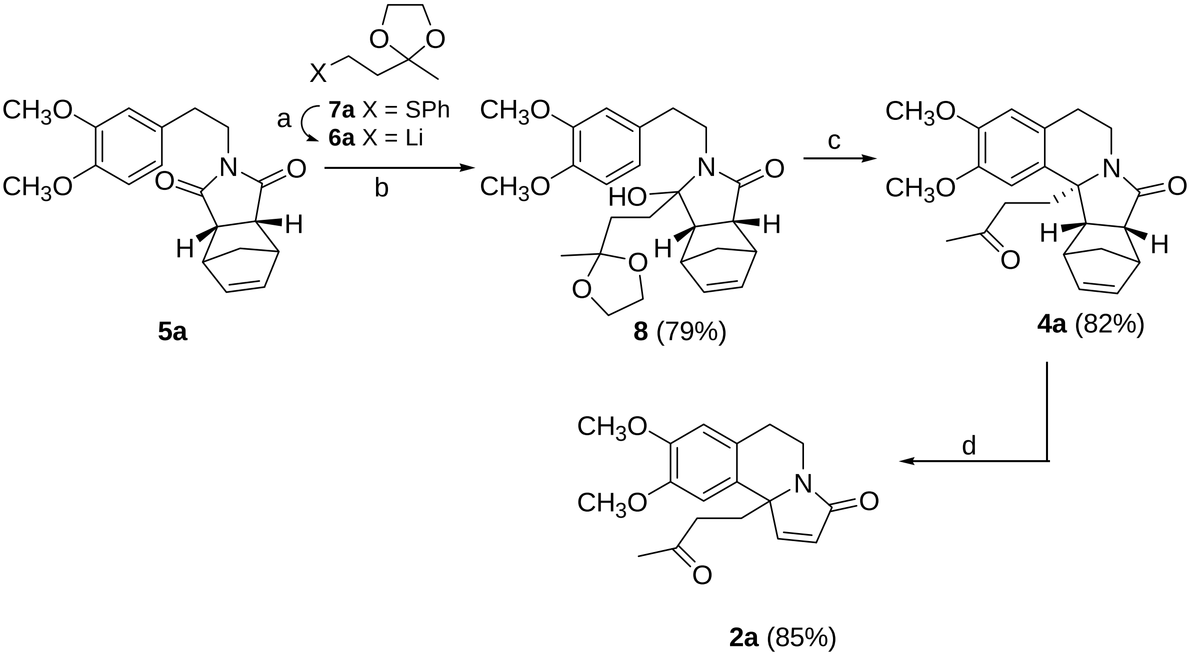


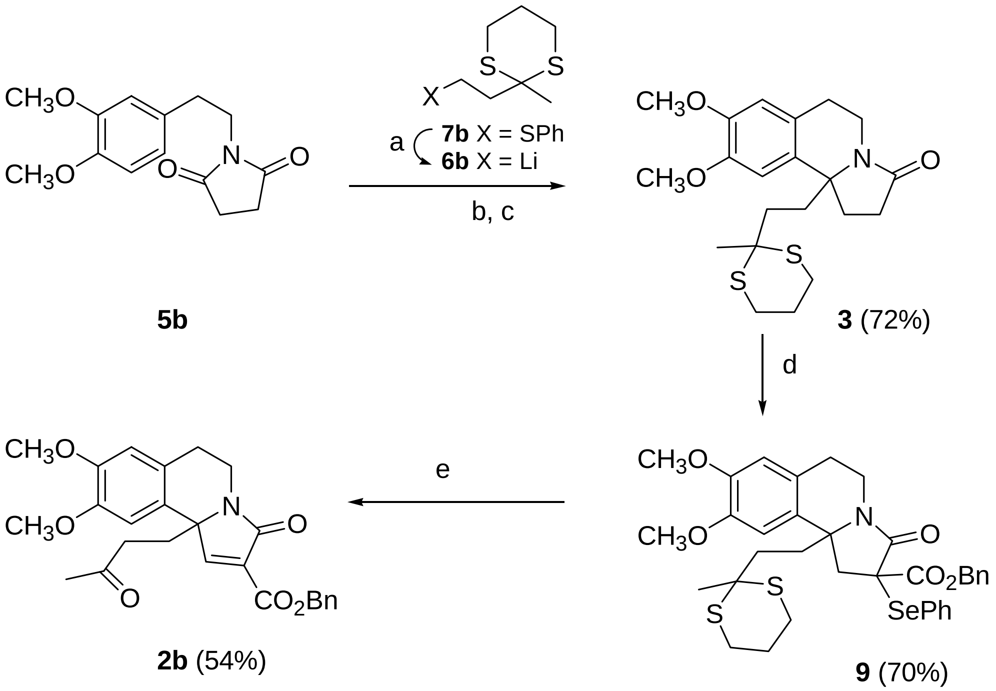
Figure 1

Thus, organolithium **6a** was generated *in situ* from phenylsulfanyl derivative **7a** by reductive lithiation[10] with Li/DBB (4,4'-di-*tert*-butylbiphenyl), and reacted with imide **5a** to afford hydroxylactam **8**. Cyclization and simultaneous hydrolysis of the acetal were accomplished upon treatment with TFA. The α-amidoalkylation reaction proceeded stereoselectively, affording isoindoloisoquinoline **4a** as a single diastereomer. Finally, thermal retro Diels-Alder reaction gave functionalized 5,6-dihydroisoquinoline **2a** in high overall yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) Li/DBB, – 78°C. (b) **5a**, – 78°C. (c) TFA, CH_2Cl_2, rt. (d) *o*-dichlorobenzene, reflux.

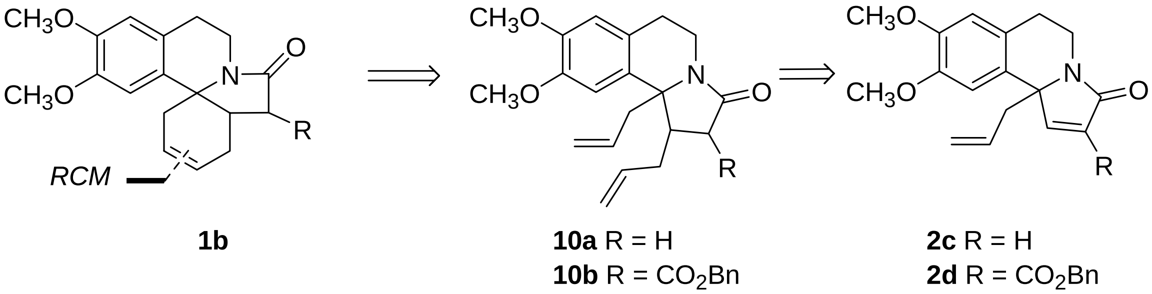
An analogous addition–α-amidoalkylation sequence was applied for the synthesis of **2b**. In this case, organolithium **6b** was generated from phenylsulfanyl derivative **7b**, and reacted with imide **5b**. Without purification, the crude reaction mixture was treated with TFA in refluxing CH_2Cl_2 to afford 10b substituted tetrahydropyrroloisoquinoline **3** in high overall yield. Unsaturation was then introduced by a two step procedure.[11] Thus, LDA deprotonation and sequential treatment with $ClCO_2Bn$ and PhSeBr afforded pyrroloisoquinoline **9**. Oxidative β-elimination of phenylselenyl group and hydrolysis of dithiane was accomplished in a single step using PIFA [Bis(trifluoroacetoxy)iodobenzene].[12]



Scheme 3. *Reagents and conditions*: (a) Li/DBB, – 78°C. (b) **5b**, – 78°C. (c) TFA, CH_2Cl_2, reflux. (d) LDA, $ClCO_2Bn$, PhSeBr, THF, – 78°C. (e) TFA, PIFA, CH_3CNC/H_2O, rt.

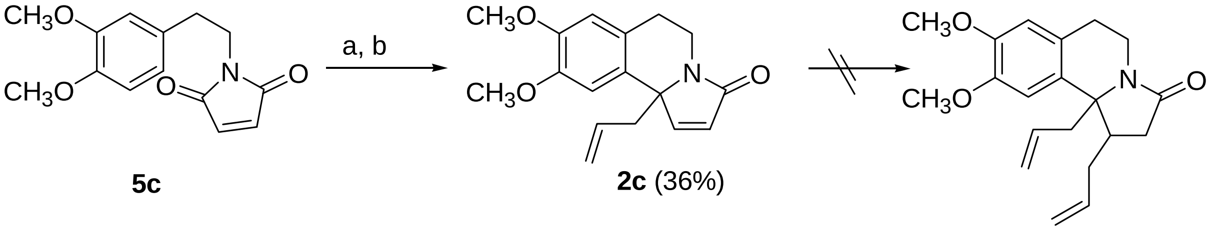
Once the dihydropyrroloisoquinolines **2a,b** had been prepared, we studied the intramolecular conjugate addition reaction. Thus, the kinetic control enolate was generated by treatment of **2a,b** with LDA at –78 °C, but no cyclization was observed under any of the experimental conditions tested. The use of other bases (LiHMDS) or additives (HMPA) did not improve the results. In all cases, no reaction was observed with **2a**, recovering starting material, while **2b** led to a mixture of products. To check that the enolate was being efficiently formed, we carried out the deprotonation with LDA at –78 °C, and quenched the reaction with TMSCl, obtaining the corresponding enol ethers that could be characterized by ^1H NMR. Without purification, these enol ethers were treated with $SnCl_4$ or $TiCl_4$ under Michael-Mukaiyama conditions. However, no cyclization product was obtained under the conditions tested, recovering the corresponding pyrroloisoquinolines **2a,b.** Therefore, although functionalized dihydropyrroloisoquinolines **2a,b** have been prepared through organolithium addition–α-amidoalkylation sequences, the α,β-unsaturated lactam unit is unreactive towards the intramolecular conjugate addition of enolates or enol ethers, under the conditions tested.

In view of these results, we thought of an alternate route that would involve an intermolecular conjugate addition. Thus, ring A of the erythrinane system could be assembled through the ring-closing metathesis (RCM) reaction of pyrroloisoquinolones **10**. The allyl group on C-1 could be introduced by conjugate addition on the dihydro derivatives **2c,d**. These key intermediates **2** would be derived from the known imides **5**, *via* *N*-acyliminium or Parham cyclizations.[13] (Scheme 4).



Scheme 4

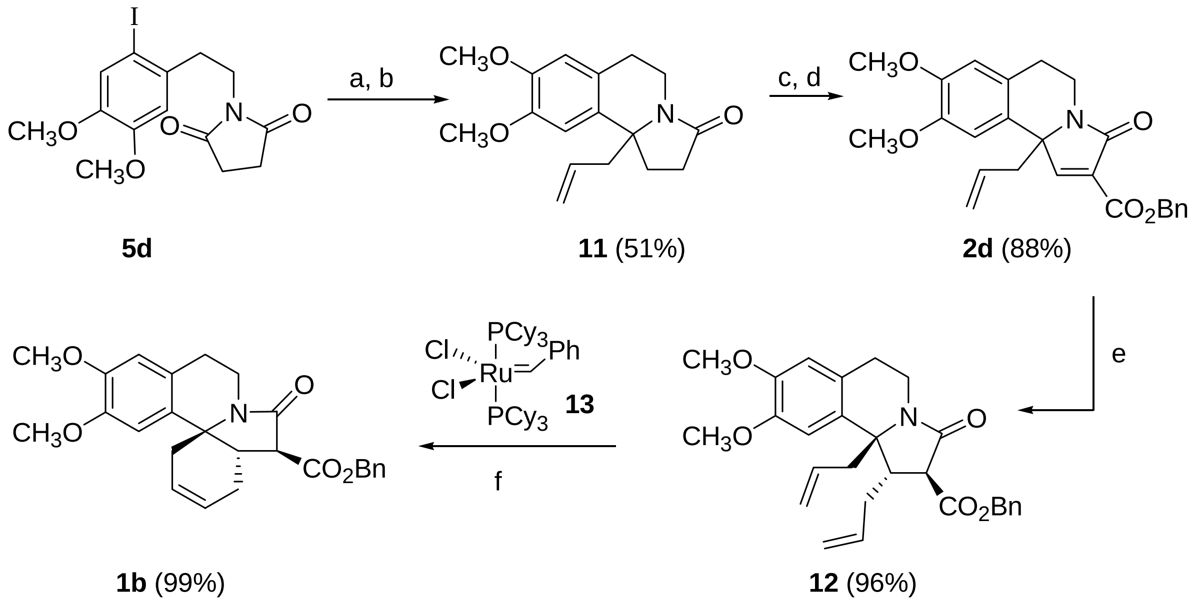
The first goal of our synthetic sequence was to elaborate the dihydropyrroloisoquinolones that would install the allyl group at the C-10b position. As depicted on Scheme 5, unactivated pyrroloisoquinoline **2c** was obtained from maleimide **5c** by allylmagnesium chloride addition and *N*-acyliminium cyclization (36% overall yield).



Scheme 5. *Reagents and conditions:* (a) allylmagnesium chloride, THF, –78°C. (b) TFA, CH_2Cl_2, reflux.

It then remained to introduce the allyl group by conjugate addition. First, we studied the addition of Gilman's allylcuprate to lactam **2c**. The cuprate could be efficiently prepared by addition of two equivalents of allylmagnesium chloride to a suspension of CuI in THF at –78°C. Several reaction conditions were tested, but no reaction was observed if the lactam **2c** was added at this temperature, and the reaction mixture was allowed to warm up to temperatures ranging from –40 °C to 20 °C. The use of other solvents or additives such as TMSCl did not improve these results. Therefore, we decided to test the Sakurai reaction using allyltrimethylsilane and TBAF in DMF.[14] When the reaction was carried out at room temperature, starting material was recovered and operating under reflux lead to an intractable mixture of products.

Therefore, we focussed our attention on the conjugate addition to α,β–unsaturated lactam **2d** with an activating benzyloxycarbonyl group at the α position of the lactam carbonyl group. Thus, as depicted on Scheme 6, succinimide **5d** was cyclized under Parham reaction conditions to afford an α-hydroxylactam, which, without purification, was subjected to intermolecular α-amidoalkylation with allyltrimethylsilane in the presence of $TiCl_4$ providing **11**.[15] Subsequent sequential treatment with LDA, benzyl chloroformate, and phenylselenyl bromide, followed by β-elimination with H_2O_2 provided the dihydropyrroloisoquinoline **2d** (Scheme 6). After extensive screening of conditions, it was found that conducting the reaction with Gilman's allylcuprate (prepared as described above) with TMSCl as additive provided diastereoselectively the *trans* isomer **13** in high yield (96%),[16] thereby setting the stage for the key RCM reaction. The stereochemical outcome of the conjugate addition might be explained as a result of the attack of the nucleophile from the opposite side of the allyl group in C-10b, which would be in a *pseudo*-axial conformation. Protonation of the resulting enolate would lead to the more stable *trans* isomer. To test the RCM protocol[17] for the construction of the erythrinane framework, we chose the first generation Grubbs catalyst **13**. Thus, RCM was carried out on the tetrahydropyrroloisoquinolone **12**, which cyclized smoothly to give **1b** as a single diastereomer in quantitative yield.



Scheme 6. *Reagents and conditions*: (a) *t*-Buli, THF, –78°C. (b) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, –78°C. (c) LDA, $ClCO_2Bn$, PhSeBr, THF, –78°C. (d) H_2O_2, pyridine, CH_2Cl_2, 0 °C to

rt. (e) (allyl)$_2$CuMgI, TMSCl, THF, –78°C to 0 °C. (f) Grubbs catalyst **13** (20% mol), CH_2Cl_2, reflux.

In summary, a stereoselective approach to erythrinanes using Parham cyclization, α-amidoalkylation, conjugate addition, and ring-closing metathesis reactions as key steps has been developed. The strategy we have implemented is convergent, efficient, and flexible, and could compete with previously reported strategies.[2] Besides, it allows modifications mainly at ring A just by changing the nucleophile in the conjugate addition step. Further applications of this protocol to alkaloid synthesis are the subject of current investigations, the results of which will be disclosed in due course.

Experimental Section

4-[2-(3,4-Dimethoxyphenyl)ethyl]-5-hydroxy-5-[2-(2-methyl-[1,3]dioxolan-2-yl)-ethyl]-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (8). A solution of **7a** (3.64 g, 16.2 mmol) in dry THF (20 mL) was added dropwise over a suspension of lithium powder (0.62 g, 89.3 mmol) and 4,4’-di-*tert*-butylbiphenyl (DBB) (0.68 g, 2.56 mmol) in dry THF (20 mL) at –78 °C, and the mixture was stirred for 1 h 30 min. Imide **5a**[3d] (2.1 g, 6.41 mmol) was added , and the reaction mixture was further stirred for 5 h at –78 °C. The reaction was quenched by addition of water (20 mL). 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 brine (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silicagel, ethyl acetate) afforded hydroxylactam **8** as an oil (2.25 g, 79%): IR (KBr) 3323, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.29 (s, 3H), 1.38 (d, J = 8.3 Hz, 1H), 1.55 (d, J = 8.3 Hz, 1H), 1.61-1.87 (m, 4H), 2.41 (s, 1H), 2.73-2.82 (m, 3H), 2.99 (broad s, 1H), 3.04-3.10 (m, 2H), 3.26 (broad s, 1H), 3.41-3.52 (m, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 3.89-3.94 (m, 4H), 6.03 (broad s, 1H), 6.12 (broad s, 1H), 6.79 (broad s, 3H); ^{13}C NMR ($CDCl_3$) 23.9, 32.7, 34.1, 34.3, 40.8, 45.1, 45.6, 47.5, 49.1, 51.2, 55.6, 55.7, 64.5, 64.6, 90.7, 109.2, 110.2, 111.8, 120.6, 131.7, 133.6, 135.6, 147.2, 148.5, 173.7; MS (EI) *m/z* (rel intensity) 444 (M^++1, 2), 443 (M^+, 5), 363 (2), 323 (2), 262 (2), 230 (3), 166 (2), 165 (24), 164 (100), 153 (3), 152 (2), 151 (2), 149 (3), 135 (2), 88 (2), 87 (57), 73 (2). HRMS Calcd for $C_{25}H_{31}NO_6$ (M^+-2H): 441.2151. Found: 441.2156.

(8a*RS*, 9*SR*, 12*RS*, 12a*SR*, 12b*SR*)-2,3-Dimethoxy-12b-(3-oxobutyl)-5,6,8a,12,12a-hexahydro-9,12-methaneisoindolin[2,3-*a*]isoquinolin-8-one (4a). TFA (3.6 mL, 46.7 mmol) was added over a solution of hydroxylactam **8** (0.51 g, 1.14 mmol) in dry CH_2Cl_2 (25 mL) at 0 ºC. The reaction mixture was allowed to reach rt, and stirred for one day. Water (10 mL) was added, and the mixture was neutralised with saturated $NaHCO_3$. 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 brine (2 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (silicagel, 96% ethyl acetate/triethylamine) afforded isoindoloisoquinoline **4a** (0.36 g, 82%): mp (Et_2O/pentane) 125-127 ºC; IR (KBr) 1713, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) 1.39 (d, *J* = 8.2 Hz, 1H), 1.60 (d, *J* = 8.2 Hz, 1H), 1.90-2.02 (m, 4H), 2.13-2.19 (m, 1H), 2.34-2.41 (m, 2H), 2.44-2.53 (m, 1H), 2.85-2.96 (m, 1H), 2.98-3.13 (m, 3H) 3.19 (broad s, 1H), 3.24 (broad s, 1H), 3.79 (s, 3H), 3.85 (s, 3H), 4.09-4.17 (m, 1H), 6.16-6.17 (m, 2H), 6.48 (s, 1H), 6.60 (s, 1H); ^{13}C NMR ($CDCl_3$) 26.1, 29.9, 31.6, 34.7, 40.0, 44.3, 45.7, 48.7, 49.0, 52.1, 55.6, 56.1, 63.2, 108.5, 111.8, 126.2, 132.7, 134.1, 135.3, 146.7, 147.7, 175.2, 206.9; MS (EI) *m/z* (rel intensity) 381 (M^+, 4), 311 (11), 310 (51), 245 (17), 244 (100), 200 (3), 83 (2). Anal. Calcd. for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.12; N, 3.67; Found C, 71.92; H, 7.26; N, 3.53.

8,9-Dimethoxy-10b-(3-oxobutyl)-6,10b-dihydro-5*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (2a). A solution of **4a** (0.57 g, 1.49 mmol) in *o*-DCB (30 mL) was refluxed for 2 days. The solvent was evaporated under vacuum, and the resulting oil was purified by column chromatography (silicagel, 96% ethyl acetate/triethylamine) to afford pyrroloisoquinline **2a** (0.40 g, 85%) as a colorless oil: IR (KBr) 1682 cm^{-1}; ^1H NMR ($CDCl_3$) 2.06 (s, 3H), 2.11-2.33 (m, 3H), 2.35-2.45 (m, 1H), 2.62 (dd, *J* = 5.9, 3.7 Hz, 1H), 2.81-2.95 (m, 1H), 3.08 (td, *J* = 12.5, 4.4 Hz, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 4.33 (dd, *J* = 13.1, 6.0 Hz, 1H), 6.10 (d, *J* = 6.0 Hz, 1H), 6.57 (s, 1H), 6.71 (s, 1H), 7.17 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) 28.8, 30.2, 31.0, 34.6, 36.8, 55.7, 56.0, 65.7, 108.9, 111.8, 124.9, 126.1, 128.6, 147.6, 148.1, 151.8, 170.9, 207.5; MS (EI) m/z (rel intensity) 315 (M^+, 5), 258 (2), 246 (3), 245 (17), 244 (100), 229 (2), 228 (2), 200 (6), 91 (3), 85 (2), 83 (4), 69 (2). HRMS Calcd. for $C_{18}H_{21}NO_4$: 315.1470; Found: 315.1461.

8,9-Dimethoxy-10b-[2-(2-methyl-[1,3]dithian-2-yl)-ethyl]-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (3). A solution of **7b** (2.54 g, 9.37 mmol) in dry THF (20 mL) was added dropwise over a suspension of lithium powder (0.36 g, 52.5 mmol) and 4,4'-di-*tert*-butylbiphenyl (DBB) (0.4 g, 1.5 mmol) in dry THF (20 mL) at –78 °C, and the mixture was stirred for 1 h 30 min. Imide **5b**[3c] (0.99 g, 3.75 mmol) was added , and the reaction mixture was further stirred for 5 h at –78 °C. The reaction was quenched by addition of water (20 mL). 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 brine (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The so-obtained hydroxylactam was treated with TFA (1.5 mL, 18.7 mmol) in dry CH_2Cl_2 (25 mL) at 0 ºC. The reaction mixture was refluxed for 10 h. Saturated $NaHCO_3$ (10 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 washed with brine (2 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (silicagel, ethyl acetate) afforded isoindoloisoquinline **3** as an oil (0.90 g, 72%): IR (KBr) 1683 cm^{-1}; ^1H NMR ($CDCl_3$) 1.53 (s, 3H), 1.87-1.93 (m, 4H), 1.97-2.23 (m, 3H), 2.35-2.46 (m, 2H), 2.54-2.80 (m, 6H), 2.88 (td, *J* = 16.0, 6.4 Hz, 1H), 3.09 (td, *J* = 12.3, 4.7 Hz, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 4.32 (dd, *J* = 12.6, 6.0 Hz, 1H), 6.55 (s, 1H), 6.56 (s, 1H); ^{13}C NMR ($CDCl_3$) 24.9, 26.2, 26.3, 27.6, 27.7, 31.0. 32.3, 34.7, 35.5, 36.6, 48.5, 55.6, 55.9, 63.4, 107.6, 111.3, 124.6, 134.0, 147.6, 147.7, 173.2; MS (EI) *m/z* (rel intensity) 248 (2), 247 (18), 246 (100), 231 (2), 230 (3), 202 (2). Anal. Calcd. for $C_{21}H_{29}NO_3S_2$: C, 61.88; H, 7.17; N, 3.44; Found C, 61.42; H, 6.87; N, 3.23.

2-Benzyloxycarbonyl-8,9-dimethoxy-10b-(3-oxobutyl)-6,10b-dihydro-5*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (2b). A solution of **3** (204 mg, 0.5 mmol) in THF (7 mL) was added drop wise over a solution of LDA [1.1 mmol, prepared from *i*-Pr_2NH (0.15 mL, 1.1 mmol) and *n*-BuLi (0.89 mL of a 1.2 M solution in hexanes, 1.1 mmol)] in THF (5 mL), at — 78ºC. After 1 h, benzyl chloroformate (0.07 mL, 0.5 mmol) was added and the solution was stirred for 30 min. A solution of PhSeBr (0.19 g, 0.7 mmol) in THF (1 mL) was added dropwise, and the reaction mixture was stirred at — 78 ºC for 1 h 30 min. The reaction was quenched by addition of 1 M HCl (10 mL). The organic phase was separated, and the resulting aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (silica gel, 30% hexane/AcOEt) afforded a mixture of selenides **9** (0.24 g, 70%), that were not separated. A solution of the diastereomeric mixture of selenides **9** in CH_3CN/H_2O (2:1, 30mL) was treated with TFA (0.27 mL, 3.5 mmol) at rt. PIFA (614 mg, 1.4 mmol) was added in two portions, and the resulting mixture was stirred for 2 h. The reaction mixture was extracted with hexane (3 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (silica gel, AcOEt) afforded dihydropyrroloisquinoline **2b** (85 mg, 54%; overall yield from **3**, 38%) as a colorless oil: IR (KBr) 1744, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.05 (s, 3H), 2.11-2.30 (m, 3H), 2.35-2.49 (m, 1H), 2.60-2.67 (m, 1H), 2.86-3.00 (m, 1H), 3.05-3.16 (m, 1H), 3.83 (s, 3H), 3.89 (s, 3H), 4.41 (dd, *J* = 13.0, 5.8 Hz, 1H), 5.29 (s, 2H), 6.59 (s, 1H), 6.72 (s, 1H), 7.28-7.45 (m, 5H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$) 28.6, 30.1, 31.3, 34.9, 36.7, 55.7, 56.0, 65.4, 66.6, 108.9, 112.0, 125.3, 126.9, 128.1, 128.4, 128.9, 135.2, 147.6, 148.3, 158.1, 161.0, 165.8, 207.0; MS (EI) *m/z* (rel intensity) 449 (M$^+$, 3), 380 (4), 379 (24), 378 (100), 341 (3), 284 (3), 272 (2), 245 (2), 244 (14), 91 (12). HRMS Calcd. for $C_{26}H_{27}NO_6$: 449.1838; Found 449.1817.

10b-Allyl-8,9-dimethoxy-6,10b-dihydro-5*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (2c). To a solution of imide **5c** (0.31g, 1.19 mmol) in dry THF (20 mL), allylmagnesium chloride (1.48 mL of a 2.0 M solution, 2.97 mmol) was added at –78 ºC and the resulting mixture was stirred at this temperature for 6 h. The reaction was quenched by the addition of H_2O (15 mL) and the mixture was allowed to reach rt. 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*. A solution of the crude reaction mixture in dry CH_2Cl_2 (20 mL) was treated with TFA (2 mL, 26 mmol), and the reaction mixture was refluxed for 6 h. The reaction was quenched by the addition of $NaHCO_3$ (sat) (15 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 (silicagel, AcOEt) afforded pyrroloisoquinolone **2c** as a colorless oil (122 mg, 36%): IR (KBr) 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.61-2.69 (m, 3H), 2.84-2.98 (m, 1H), 3.21 (td, *J* = 12.5, 4.5 Hz, 1H), 3.82 (s, 3H), 3.87 (s, 3H), 4.40 (dd, *J* = 13.2, 6.4 Hz, 1H), 5.01-5.07 (m, 2H), 5.38-5.57 (m, 1H), 6.12 (d, *J* = 5.5 Hz, 1H), 6.59 (s, 1H), 6.69 (s, 1H), 7.25 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 28.7, 34.5, 43.0, 55.6, 55.9, 67.8, 108.8, 111.8, 118.9, 125.2, 126.0, 128.2, 131.0, 147.3, 147.9, 151.3, 170.4. MS (EI) *m/z* (rel intensity) 285 (M^+, 1), 258 (2), 246 (2), 245 (15), 244 (100), 228 (2), 200 (7), 183 (2), 85 (4), 83 (8). HRMS Calcd for $C_{17}H_{19}NO_3$: 285.1365. Found: 285.1371.

10b-Allyl-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (11). To a solution of the iodinated imide **5d** (0.57 g, 1.46 mmol) in dry THF (40 mL), *t*-BuLi (2.93 mL of a 1.0 M solution in hexanes, 2.93 mmol) was added at –78 ºC and the resulting mixture was stirred at this temperature for 6 h. The reaction was quenched by the addition of H_2O (15 mL) and the mixture was allowed to reach rt. Et_2O (15 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*. Over a solution of the so-obtained hydroxylactam, without further purfication, in dry CH_2Cl_2 (15 mL) at –78 ºC were sequentially added allyltrimethylsilane (0.93 mL, 5.86 mmol) and $TiCl_4$ (0.32 mL, 2.93 mmol). The reaction mixture was stirred at this temperature for 2 h, and 20 h at room temperature. The reaction was quenched by the addition of $NaHCO_3$ (sat) (15 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 (silicagel, AcOEt) afforded pyrroloisoquinolone **11** as a colorless oil (215 mg, 51%): IR (KBr) 1677 cm^{-1}; ^1H NMR ($CDCl_3$) 2.03-2.18 (m, 1H), 2.30-2.70 (m, 6H), 2.82-2.96 (m, 1H), 3.14 (td, J = 12.5, 4.9 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.27-4.34 (m, 1H), 5.11-5.18 (m, 2H), 5.65-5.81 (m, 1H), 6.54 (s, 1H), 6.55 (s, 1H); ^{13}C NMR ($CDCl_3$) 27.5, 30.9, 31.6, 34.0, 45.4, 55.6, 55.8, 63.4, 107.6, 111.1, 119.3, 124.4, 132.2, 133.8, 147.5, 172.9. MS (EI) *m/z* (rel intensity) 248 (2), 247 (15), 246 (100), 232 (4), 231 (4), 230 (7), 202 (4), 185 (2), 83 (2). HRMS Calcd for $C_{17}H_{21}NO_3$: 287.1521. Found: 287.1445.

10b-Allyl-2-benzyloxycarbonyl-8,9-dimethoxy-6,10b-dihydro-5H-pyrrolo[2,1-*a*] isoquinolin-3-one (2d). A solution of pyrrolisoquinoline **11** (120.4 mg, 0.42 mmol) in dry THF (6 mL) was added over a solution of LDA [obtained from $^iPr_2NH$ (0.13 mL, 0.92 mmol) and *n*-BuLi (1.15 mL of a 0.8 M solution, 0.92 mmol)] in THF (3 mL) at –78 °C. The reaction mixture was stirred for 1 h and benzyl chloroformiate (0.06 mL, 0.42 mmol) was added. After stirring the mixture for 45 min, a solution of phenylselenyl bromide (154.6 mg, 0.67 mmol) in THF (1 mL) was added, and the reaction was stirred at –78 °C for 2 h 30 min. The reaction was quenched by addition of HCl (1M, 10 mL) and allowed to reach rt. The organic layer was separated, and the aqueous phase was extracted with AcOEt (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silicagel, 30 % hexane/AcOEt) afforded a diastereomeric mixture of selenides (147 mg, 61%). To carry out the oxidative elimination, pyridine (0.051 mL, 0.64 mmol) and 30% H_2O_2 were added sequentially to a solution of this diastereomeric mixture in dry CH_2Cl_2 (25 mL) at 0 ºC. The reaction mixture was allowed to reach rt, and stirred for 12h. The reaction was quenched by addition of HCl (5% aq., 15 mL), the organic layer was separated, and washed with HCl (5% aq.) (2 ×15 mL) and brine (2 ×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silicagel, AcOEt) afforded pyrrolisoquinoline **2d** (92 mg, 88%): IR (KBr) 1693, 1738, cm^{-1}; ^1H NMR ($CDCl_3$) 2.62-2.75 (m, 3H), 2.88-3.02 (m, 1H), 3.17-3.30 (m, 1H), 3.84 (s, 3H), 3.89 (s, 3H), 4.47 (dd, *J* = 13.4, 6.4 Hz, 1H), 5.05-5.17 (m, 2H), 5.29 (s, 2H), 5.42-5.58 (m, 1H), 6.61 (s, 1H), 6.69 (s, 1H), 7.31-7.44 (m, 5H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$) 28.7, 35.0, 43.2, 55.8, 56.1, 65.6, 66.6, 108.9, 112.1, 119.8, 125.7, 126.5, 128.1, 128.4, 129.1, 130.4, 135.4, 147.6, 148.4, 158.7, 161.2, 165.5. MS (EI) *m/z* (rel intensity) 419 (M^+, 11), 378 (100), 311 (3), 286 (2), 285 (12), 284 (47), 268 (3), 256 (2), 245 (4), 244 (17), 242 (2), 240 (49), 212 (2), 108 (5), 107 (2), 92 (2), 91 (18), 79 (4), 77 (2), 71 (3), 69 (2), 57 (3). HRMS Calcd for $C_{25}H_{25}NO_5$: 419.1733. Found: 419.1722.

(1*SR*,2*SR*,10b*RS*)-1,10b-Diallyl-2-benzyloxycarbonyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-pyrrolo[2,1-a]isoquinolin-3-one (**12**). Allylmagnesium chloride (1.95 mL of a 2.0 M solution, 3.9 mmol) was added dropwise over a suspension of CuI (372 mg, 1.95 mmol) in dry THF (5 mL) at –20 °C. After 15 min, the mixture was cooled to – 78 ºC, and a solution of **2d** (81 mg, 0.19 mmol) and TMSCl (0.05 mL, 0.38 mmol) in THF (5 mL) were sequentially added. The reaction mixture was stirred for 2h, allowed to warm up to 0 ºC, and stirred at this temperature for 12 h. The reaction was quenched by sequential addition of NH_3 (12% aq.) (20 mL) and NH_4Cl (sat.) (10 mL) at 0 °C. After allowing the mixture to warm up to rt, 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 (silicagel, 20 % hexane/AcOEt) afforded pyrroloisoquinolone **12** as a colorless oil (86 mg, 96%): IR ($CHCl_3$) 1691, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.34-1.48 (m, 1H), 1.99-2.17 (m, 1H), 2.50-2.75 (m, 4H), 2.79-2.92 (m, 1H), 3.15 (td, *J* = 12.6, 4.5 Hz, 1H), 3.40 (d, *J* = 0.8 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 4.34 (dd, *J* = 12.9, 4.6 Hz, 1H), 4.79-5.10 (m, 4H), 5.22 (d, *J* = 12.3 Hz, 1H), 5.32 (d, *J* = 12.3 Hz, 1H), 5.38-5.61 (m, 2H), 6.54 (s, 1H), 6.58 (s, 1H), 7.28-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) 28.7, 35.7, 36.6, 46.0, 48.1, 53.4, 55.6, 56.1, 66.7, 67.2, 109.3, 111.4, 118.6, 119.0, 127.1, 127.2, 128.2, 128.3, 128.5, 133.2, 134.2, 135.3, 147.6, 147.7, 167.1, 169.9. MS (EI) *m/z* (rel intensity) 420 (M^+-41, 100), 380 (2), 335 (5), 312 (7), 285 (17), 284 (9), 271 (2), 270 (2), 245 (5), 244 (21), 200 (3), 92 (3), 91 (42).

(5*RS*,6*SR*,7*SR*)-7-Benzyloxycarbonyl-15,16-dimethoxy-8-oxo-erythrinan-2-ene (1b). Grubbs catalyst **13** (10% mol) was added over a solution of pyrroloisoquinoline **12** (53 mg, 0.11 mmol) in dry CH_2Cl_2 at rt. The reaction mixture was heated under reflux for 8 h, and another load of catalyst **13** (10% mol) was added. The mixture was refluxed for 16 h, and allowed to reach rt. The solvent was evaporated under reduced pressure, and the crude reaction mixture was chromatographed (silicagel, 40 % hexane / AcOEt), to obtain erythrinane **1b** (50 mg, 99%): IR ($CHCl_3$) 1697, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.46-2.57 (m, 5H), 2.85-2.95 (m, 2H), 3.00-3.33 (m, 2H), 3.74 (s, 3H), 3.80 (s, 3H), 4.00-4.20 (m, 1H), 5.22 (s, 2H), 5.91 (broad s, 1H), 6.00-6.10 (m, 1H), 6.53 (s, 1H), 7.03 (s, 1H), 7.31-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 25.8, 26.4, 36.8, 40.1, 44.8, 51.4, 55.6, 55.8, 59.4, 67.0, 109.8, 112.1, 127.5, 127.7, 128.0, 128.1, 128.5, 130.2, 135.4, 146.6, 147.9, 169.0, 172.7. MS (EI) *m/z* (rel intensity) 433 (M^+, 22), 380 (3), 379 (9), 343 (10), 342 (44), 325 (5), 324 (26), 298 (2), 297 (2), 296 (10), 282 (3), 246 (5), 245 (35), 244 (100), 206 (2), 200 (6), 164 (3), 92 (2), 91 (29). HRMS Calcd for $C_{26}H_{27}NO_5$: 433.1889. Found: 433.1878.

Acknowledgements

Financial support from MCYT (BQU2003-03239), and Universidad del País Vasco/Euskal Herriko Unibertsitatea is gratefully acknowledged. I. O. is grateful to Gobierno Vasco for a grant and M. N. A to Gobierno Vasco, Fundación Kawa, and Universidad del País Vasco for their financial support.

References and Footnotes

1. Tsuda, Y.; Sano, T. In *The Alkaloids: Chemistry and Pharmacology*, Vol. 48; Cordell, G. A., Ed.; Academic Press: San Diego, 1996; Chap. 4, p 249. (b) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444, and references cited therein.
2. For a review, see reference 1a. For some recent examples, see: (a) Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235. (b) Parsons, A. F.; Williams, D. A. J. *Tetrahedron* **2000**, *56*, 7217. (c) Hosoi, S.; Nagao, M.; Tsuda, Y.; Isobe, K.; Sano, T.; Ohta, T. *J. Chem. Soc. Perkin 1* **2000**, 1505. (d) Jousse-Karinthi, C.; Riche, C.; Chiaroni, A.; Desmaele, D. *Eur. J. Org. Chem.* **2001**, 3631. (e) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464. (f) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 1135. (g) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312. (h) Gill, C.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron Lett.* **2003**, *44*, 7803. (i) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619. (o) Reimann, E.; Ettmayr, C. *Mon. Chem.* **2004**, *135*, 1143. (j) Blake, A. J.; Gill, C.; Greenhalgh, D. A.; Simpkins, S.; Zhang, F. *Synthesis* **2005**, 3287. (k) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; JIang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373.
3. Manteca, I.; Sotomayor, N.; Lete, E. *Tetrahedron Lett*. **1996**, *33*, 7841. (b) Collado, M. I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *Tetrahedron Lett.* **1996**, *37*, 6193. (c) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *J. Org. Chem*. **1997**, *62*, 2080. (d) Manteca, I.; Etxarri, B.; Ardeo, A.; Arrasate, S.; Osante, I.; Sotomayor, N.; Lete, E. *Tetrahedron* **1998**, *54*, 12361.
4. For reviews on organolithium compounds, see: (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; 2nd Edn., Pergamon: New York, 1990. (b) Clayden, J. *Organolithiums: Sectivity for Synthesis*, Pergamon: New York, 2002. (c) Hodgson, D. M., Ed., *Organolithiums in Enantioselective Synthesis, Topics in Organometallic Chemistry*; Springer: Berlin, 2003; Vol. 5. (e) Rappoport, Z.; Marek, I., Eds. *The Chemistry of Organolithium Compounds*; *Patai Series: The Chemistry of Functional Groups*, Rappoport, Z.; Ed., Wiley: Chichester, 2004.
5. For reviews on *N*-acyliminium ion cyclizations, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. in *The Alkaloids*; Academic Press, New York, 1988; Vol. 32, p 271. (c) Hiemstra, H.; Speckamp, W. N. In

Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I. Eds., Pergamon: Oxford, 1991; Vol. 2, p 1047. (d) de Koning, H.; Speckamp, W. N. In *Stereoselective Synthesis [Houben-Weyl]*, Helmchen, G.; Hoffmann, R. W.; Muzler, J.; Schaumann, E. Eds.; Thieme: Stuttgart, 1996, Workbench Ed. E21, Vol. 3, p 1952. (e) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (f) Marson, C. M. *Arkivoc* **2001**, 1. (g) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (h) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (i) Dobbs, A. P.; Rossiter, S. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. 3, p 419.

6. García, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2001**, *42*, 1511. (b) González-Temprano, I.; Sotomayor, N.; Lete, E. *Synlett* **2002**, 593. (c) González, I; Osante, I.; Sotomayor, N.; Lete, E *J. Org. Chem.* **2004**, *69*, 3875. (d) García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *J. Org. Chem*. **2005**, *70*, 10368.
7. For a preliminary communication, see: Osante, I.; Sotomayor, N.; Lete, E *Lett. Org. Chem.* **2004**, *1*, 148.
8. For reviews, see: Perlmutter, P. *Conjugate addition reactions in organic synthesis* Pergamon: Oxford, **1992**; p 283. (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, p 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, p 21.
9. Only small ammounts of the desired erythrinane (<4%) were obtained. Manteca, I. Ph. D. Dissertation, Universidad del País Vasco, Bilbao (Spain), 1997.
10. Recent reviews: (a) Yus, M. *Synlett* **2001**, 1197. (b) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867. (c) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667. (d) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *56*, 3139.
11. See, for instance: Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miratvilles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074.
12. Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem*. **2001**, *66*, 6502.
13. For reviews on Parham cyclization, see: (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. (b) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 11; p 66. (c) Ardeo, A.; Collado, M. I.; Osante, I.; Ruiz, J.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems*, Atanassi, O.; Spinelli, D. Eds.; Italian Society of Chemistry: Roma, 2001, Vol. 5, p 393. (d) Mealy, M. M.; Bailey, W. F. *J. Organomet. Chem*. **2002**, 649, 59. (e) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, 7, 275. (f) Arrasate, S.; Sotomayor , N.; Lete, E. In *New Methods for the Asymmetric Synthesis of*

Nitrogen Heterocycles , Vicario, J. L.; Badía, D.; Carrillo, L.; Eds., Research Signpost: India, 2005, p 223.

14. Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett*. **1978**, *33*, 3043. (b) Majetich, G.; Casares,. A. M.; Chapman, D.; Behnke, M.*J. Org. Chem*. **1986**, *51*, 1745. (c) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem*. **1998**, *63*, 5517. (d) Groaning, M. D.; Meyers, A. I. *Tetrahedron Lett***. 1999**, *40*, 8071.
15. Pyrroloisoquinoline **11** has been previously prepared by allyl-lithium addition followed by *N*-acyliminium cylization with TFA (see ref 3c). However, as stated there, by this route it is difficult to obtain the product in pure form due to contamination with the stannane residue of the precursor of the allyllithium. Besides, allylmagnesium chloride addition followed by α-amidoalkylation with TFA, $BF_3.OEt_2$ or $TiCl_4$ did not give **11**. In this case, allyl group is not stable under these conditions, and isomerization of the double bond occurs.
16. Nuclear Overhauser effect difference spectroscopy and ^{1}H-^{1}H decoupling experiments confirmed the stereochemistry of **12**. For instance, an enhancement of the H-2 signals was observed upon irradiation on one of the methylene hydrogens of the allyl group in C-1 and *vice versa*. This fact, together with the absence of NOE between both allyl groups confirms they are in a *trans* disposition. The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry.
17. For selected reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Schrock, R. R *Tetrahedron* **1999**, *55*, 8141. (c) Phillips, A. J.; Abell, A. D.; *Aldrichimica Acta* **1999**, *32*, 75. (d) Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3012. (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (f) Grubbs, R. H. *Handbook of Metathesis*, Wiley: New York, 2003. (g) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (h) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (i) Deiters, A.; Martin, S. F. **2004**, *Chem. Rev.104*, 2199.