



Article

Subscriber access provided by UNIVERSITY OF THE SUNSHINE COAST

Unified Total Synthesis of Pyrroloazocine Indole Alkaloids Sheds Light on Their Biosynthetic Relationship

Fedor M. Miloserdov, Mariia S. Kirillova, Michael E. Muratore, and Antonio M. Echavarren

J. Am. Chem. Soc., Just Accepted Manuscript • DOI: 10.1021/jacs.7b13484 • Publication Date (Web): 12 Feb 2018

Downloaded from http://pubs.acs.org on February 12, 2018

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036 Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

7

8 9

10 11 12

13

14

15 16

17

18

19

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

Unified Total Synthesis of Pyrroloazocine Indole Alkaloids Sheds Light on Their Biosynthetic Relationship

Fedor M. Miloserdov,[†] Mariia S. Kirillova,[†] Michael E. Muratore,[†] and Antonio M. Echavarren^{†,‡}*

[†] Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science and Technology, Av. Països Catalans 16, 43007 Tarragona (Spain).

[‡] Departament de Química Orgànica i Analítica, Universitat Rovira i Virgili, C/ Marcel·lí Domingo s/n, 43007 Tarragona (Spain). Supporting Information Placeholder

ABSTRACT: The total synthesis of seven members of the lapidilectine and grandilodine family of alkaloids has been accomplished in racemic and enantiopure form without protection / deprotection of functional groups. The two key steps, an 8-endo-dig hydroarylation and a 6-exo-trig photoredox cyclization, were catalyzed using gold. A rationale for the formation of the cyclopropane ring of the lundurines is also provided.

INTRODUCTION

Lapidilectines and grandilodines are indole alkaloids, isolated from peninsular Malaysia species *Kopsia grandifolia* D. J. Middleton, that feature lactone (**1**, **2**) or diester motifs (**3–7**) (Figure 1).^{1,2} Together with tenuisines and the cyclopropane-containing lundurines isolated from *Kopsia tenuis* species,³ they represent a family of sixteen indole alkaloids containing the common pyrroloazocine core. Preliminary studies on the biological activity of lapidilectines and grandilodines demonstrated their ability to reverse multidrug resistance in vincristine-resistant cancer cells.²



Figure 1. Pyrroloazocine Indole Alkaloids.

The first total synthesis of (±)-lapidilectine B (1) was achieved by Pearson in 25 steps.⁴ Only very recently, the total syntheses of (+)-lapidilectine B (1)/(+)-grandilodine C (2),⁵ and racemic grandilodine B (7)⁶ have been devel-

oped. However, a synthetic approach to lapidilectine Atype natural compounds **3-5** has not yet been disclosed. Our interest in *Kopsia* indole alkaloids launched with the discovery of a gold-catalyzed hydroarylation of alkynes that allows a fast access to the pyrroloazocine indole core of these natural compounds.⁷ Based on this strategy, we developed a concise total synthesis of lundurines A–C.⁸

Besides the synthetic challenge the pyrroloazocine indole alkaloids pose,^{9,10} we were intrigued by the biosynthetic relationships among the main classes of this family of alkaloids, and in particular, fascinated by the origin of the cyclopropane ring of the lundurines. Here we report a unified total synthesis of seven members 1-7 of the lapidilectine/grandilodine family streamlined by the use of two gold-catalyzed reactions for the key cyclization steps. With ready access to the main members of this natural product family, we have examined their chemical interconversions, uncovering that the cyclopropane ring can arise from the photochemical decarboxylation of a lactone. This photochemical origin differs from an early biosynthetic hypothesis¹¹ and is unprecedented among the many pathways that have been elucidated for the biosynthesis of cyclopropane-containing natural products.¹²

RESULTS AND DISCUSSION

We considered that compounds 1,2 and 3,4 might be biosynthetically connected through an oxidative decarboxylation¹³ via carbocation **A**, which could become a key intermediate for the synthesis of lactone **8**, or be treated with a carbon nucleophile to construct the quaternary stereocenter in **9** *en route* to diesters **3-7** (Scheme 1). The diastereoselectivity of the latter transformation would be controlled by the CO_2Me moiety, which shields one face of carbocation **A** from nucleophilic attack. Intermediate **A** could be readily accessed from alkene **10**, whose synthesis was envisioned through a radical photoredox-catalyzed cyclization of **11**. This process was expected to favor the formation of the product with an *endo*-methoxycarbonyl group. Precursor **11** could ultimately be obtained from aldehyde **12**, whose 5-OMe-analogue was an intermediate in our synthesis of the lundurines.⁸

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16 17

18

19 20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56 57 58

59

60

Scheme 1. Bioinspired Unified Retrosynthesis of Lapidilectine/Grandilodine Family of Alkaloids



Unified total synthesis. The synthesis of advanced pyrroloazocine compound 12 was realized in both enantiopure and racemic form in 5 steps, on gram scale, from commercially available tryptamine (Scheme 2). The first step in our synthetic sequence, a condensation/lactamization/Claisen rearrangement cascade of oxoesters 13a,b with tryptamine occurred with high yield (83%) and for (+)-13b with a good level of chirality transfer from the allylic fragment to the C20 stereocenter (>99% *ee* for 13b to 70% *ee* for (-)-14b).^{8,14} Aldehydes 14a,b underwent a Seyferth-Gilbert homologation to give alkynes 15a,b.

The Au-catalyzed cyclization of 15 was found to be more challenging than that of its 5-OMe derivative.⁸ In the presence of the standard AuCl-based catalytic system, the reaction stopped at an unsatisfactory ca. 60% conversion, due to catalyst decomposition. With ligand-stabilized cationic gold complex [IPrAu(NCCH₂)]SbF₆ (2 mol%), (±)-15a undergoes the gold-catalyzed cyclization with a satisfactory ca. 20:1 8-endo/7-exo selectivity. After subsequent reaction with methyl chloroformate and crystallization (removing traces of 7-exo product), (±)-17a was obtained in 65% yield over two steps.14 Alternatively, in the presence of acetic acid, the AuCl catalyst was found to be more stable,15 and full conversion could be achieved with 5+2 mol% catalyst loading (Scheme 2). The reaction proceeds with excellent 8-endo selectivity (>50:1 endo/exo), and with high yield (16a,b, 76-82%). After introducing the methylcarbamate, the exocyclic double bond of 17a,b was cleaved by a one-pot $OsO_4/NaIO_4$ protocol to give aldehyde 12 in racemic and enantioenriched form. For the latter, the enantiomeric excess was enhanced from 70% to >99% by crystallization from acetone, and its absolute configuration was confirmed by high-resolution single crystal X-ray diffraction.¹⁶

Scheme 2. Synthesis of Enantiopure Aldehyde Intermediate 12



^{*a*} see Supporting Information for the synthesis of **13b**. ^{*b*} Initial 5 mol% of AuCl catalyst employed, then additional 2 mol% added after 0.5-1 hours to reach full conversion.¹⁴

At this point the synthetic route diverges from the one previously developed for the lundurines.8 Hydrogenation of the double bond in 12 required carefully controlled conditions¹⁴ in order to prevent over-reduction of the indole into indoline. This was achieved with 10 wt% Pd/C catalyst in EtOAc/CH₂Cl₂ to give 18 in 65-77% and 92% brsm yields (Scheme 3). With aldehyde 18 in hand, we focused on the development of an approach to an estercontaining precursor for the radical cyclization. Current methods to access α -halo esters by aldehyde homologation are essentially limited to cyanohydrin synthesis, requiring several steps and harsh conditions. Thus, seeking an alternative, our attention turned to the work of Denmark *et al.*, where α -hydroxy methyl esters were synthesized from aldehydes and *t*-BuNC, in a Passerini-type reaction, with an exceptional functional group tolerance.¹⁷ To apply this transformation to compound 18, we had to account for the presence of several Lewis-basic centers in the molecule, increasing the amount of $SiCl_4$ (4.35 equiv instead of 1.1 equiv) and raising the reaction temperature (from -74 °C to -40 °C).¹⁴ The α -hydroxy ester 19 was obtained in an excellent 88% yield, while the relatively labile methylcarbamate remained intact (Scheme 3). Finally, bromide 11 was obtained in ca. 90% yield through an Appel-type reaction using a modified protocol.¹⁴

Scheme 3. Synthesis of α-Bromo Ester 11

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60



The photoredox process to build the rigid azabicyclic [4.2.2] skeleton was expected to be challenging, as it consists of a rare 6-exo-trig radical spirocyclization onto an indole through a transition state that cannot adopt a chair-like conformation.^{18,19} Nevertheless, our initial study employing [Ru(bpy),]Cl²⁰ showed that 11 indeed underwent cyclization to the key synthetic intermediate 10 with excellent endo-diastereoselectivity, which most likely originates from the CO₂Me-group adopting an equatorial position in a twist-boat-like transition state (Scheme 4). However, the reaction did not reach full conversion because of catalyst decomposition, and several other evaluated catalytic systems did not provide a significant improvement.14 Remarkably, the digold photoredox catalyst [(dppmAuCl)₂] introduced by Barriault,²¹ showed an outstanding efficiency leading to 10 in 91% yield (Scheme 4).

The main challenge of the photoredox transformation presumably arises from the lack of driving force for the cyclization of the relatively stable α -CO₂Me radical R1 into strained benzyl radicals R2a (endo-CO₂Me) and R2b (exo-CO₂Me). DFT calculations²² provided ΔG^{\ddagger} values of 20.2 and 23.2 kcal/mol for the cyclization of R1 into R2a and R2b, respectively, which is in accord with the observed high endo-selectivity (Scheme 4). In addition, these barriers indicate that the radical cyclization is a relatively slow process, four to six orders of magnitude slower than a standard 6-exo-trig cyclization of 6-hepten-1-yl radical.¹⁴ Furthermore, from a thermodynamic point of view, the open form of radical R1 was found to be even more stable than the cyclized radical intermediates (ΔG° = 1.7 kcal/mol for R2a and 7.5 kcal/mol for R2b). This suggests that the oxidation of benzylic radicals R2 is the main driving force of the transformation that shifts the equilibrium between R1 and R2. Both kinetic and thermodynamic data of the radical cyclization imply that R1 may accumulate in the reaction medium, causing sidereactions and catalyst decomposition. For example, the undesired reduction of R1 leads to 11H, which was isolated and identified as the main byproduct in both Au- and Ru-catalyzed photoredox processes.¹⁴ This reduction into 11H naturally results in the oxidation of the photoredox catalyst, and ultimately leads to the deactivation of the catalytic system.²³ For [Ru(bpy)₃]Cl₂ catalyst, such deactivation product, deep-purple trans-[Ru(bpy)₂Br₂]Br, was isolated and structurally characterized.¹⁴





^{*a*} Values for *exo*-CO₂Me isomer (**R2b**).

Alkene 10 was used as a precursor of benzylic carbocation A, a common intermediate in the synthesis of both lactones 1,2 and diesters 3-7 (Schemes 1 and 5). Under strong acidic conditions (50% aqueous H₂SO₄), the styrene moiety underwent protonation. The subsequent hydrolysis of the ester, presumably involving cyclized cation A' (see below), led to the desired lactone 8 (Scheme 5). Forging the quaternary carbon center bearing the benzylic CO₂Me group proved to be challenging. Besides the obvious increase in molecular strain, this transformation goes in the opposite direction to that of the proposed natural biosynthetic scheme, in which the benzylic C-C bond is cleaved, not constructed. Our scouting experiments suggested that carbocation A undergoes proton elimination providing alkene 10 or lactonization into 8 faster than it reacts with carbon nucleophiles (t-BuNC, TMSCN, anisole, or 1,3-dimethoxybenzene).14

We found that benzylic alcohol 20, accessible from 10 via Mukaiyama hydration,²⁴ can partake in a Hosomi-Sakurai-type allylation with allylTMS,²⁵ providing the desired product 9. Although promising, this result was not suitable for application in the total synthesis because 9 was formed together with alkene 10 as an inseparable mixture in ca. 1:2 ratio. Other allylic nucleophiles were tested (Scheme 5), and allylSnBu₃²⁶ demonstrated outstanding efficiency (ca. 30:1 ratio of 9:10). Allylated product **9** was obtained in 72% yield over two steps as a single diastereomer (Scheme 6), confirming that the ester moiety provides sufficient steric hindrance to favor the exclusive attack of the nucleophile on one face of carbocation A. Our attempts to perform a one-pot radical cyclization / benzylic C-C bond construction were unsuccessful.^{14,27} The [(dppmAuCl),]-catalyzed photoredox cyclization of 11 in the presence of nucleophiles such as TMSCN and allyITMS led to elimination product 10. Employing allylSnBu₃ (10 equiv) as nucleophile, this one-pot procedure provided a mixture of 9 and 10 in an unsatisfactory 1:2 ratio.²⁸

1

2

3

4

5 6

7

8

9

10

11 12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58

59

60

Scheme 5. Lactonization of 10 and Benzylic Allylation of 20



Two-carbon degradations of allyl moieties to aldehydes are typically performed through double-bond migration/ozonolysis sequence.²⁹ However, low conversion and difficult separation of isomeric alkenes made this strategy impractical in our case. To circumvent this issue, we envisioned to first cleave the double bond in 9 with $OsO_4/NaIO_4$ to aldehyde 21, which could be further converted to an enamine, that could undergo a second oxidative cleavage (Scheme 6).30 Treating aldehyde 21 with pyrrolidine afforded enamine 22 quantitatively (¹H NMR), which was then fragmented to aldehyde 23, under similar oxidative conditions. A base (Na₂CO₃) was utilized in the second C=C cleavage to efficiently generate the enamine intermediate and suppress the retro-Stork enamine alkylation reaction, which results in the formation of alkene 10 and/or alcohol 20 byproducts.¹⁴ As both events involved $OsO_4/NaIO_4$, we combined them, thereby developing a novel one-pot degradation of an allyl group to the twocarbon lower aldehyde homolog. With this strategy, 9 was converted into 23 in 72% yield.31 The oxidation of aldehyde 23 to carboxylic acid 24 was hampered by the steric hindrance of the substrate and the oxidative decarboxylation of the carboxylic acid product (see below). The oxidation under Pinnick conditions³² was found to be less selective, than that with KMnO₄. Excess of oxidants $(KMnO_4 \text{ and } NaIO_4)$ was employed to minimize the side decarboxylation, presumably mediated by reduced manganese species. Finally, carboxylic acid 24, was converted

into methyl ester **25** by treatment with TMSdiazomethane (80% yield over two steps).

Scheme 6. Introduction of Benzylic CO_2Me -group. X-ray Structures of (\pm) -20 and (\pm) -24



Seven pyrroloazocine indole alkaloids were accessed from lactone 8 and diester 25 utilizing a unified end-game strategy (Scheme 7). The introduction of a double bond in (+)-8 and (-)-25 following Magnus' thioamide sequence^{8,33} provided (+)-grandilodine C (2) and (-)-lapidilectam (4), respectively. These results allowed us to revise the sign of the optical rotation for lapidilectam (4) from the previously reported^{1^b} (+) to (-).¹⁴ Treatment of diester 4 under basic conditions led to a ca. 3.5:1 mixture of 4 and 7, which could be separated, affording (+)-grandilodine B (7). The final reduction of amides 2, 4 and 7 with $Me_2OBF_4/NaBH_4$ led to (-)-lapidilectine A (3), (+)lapidilectine B (1) and (+)-isolapidilectine A (6),¹⁴ whilst (-)-grandilodine А (5) and unnatural (+)dihydrolapidilectine B (26) were synthesized by direct reduction of (-)-25 and (+)-8 with borane.

On the biosynthesis of pyrroloazocine indole alkaloids. With the natural products and synthetic intermediates in hand, we studied the biosynthetic relationships

2

3

4

5

6

7

8

9

18

19

20

21

22

23

24

25

26

27

28 29

30

31 32

33

34

35

36

37

38

39 40

41

42

43

44

45 46

47

48 49 50

51

52

53

54

59

60

of pyrroloazocine indole alkaloids. The initial proposal contains a rare oxidative decarboxylation of a methyl ester in lapidilectine A-type diesters, followed by a heterolytic decarboxylation of the lactone, furnishing the cyclopropane of the lundurines (Scheme 8).^{11,14} However, to date, there is still no experimental support for this hypothesis. To probe the first decarboxylation event we attempted to transform diester 25 into alcohol 20, alkene 10, or directly into lactone 8. However, 25 was unreactive to SET oxidation agents (CAN), and no oxidation peak was observed (up to +2.0 V) by cyclic voltammetry. In 10 contrast, the sodium salt of carboxylic acid 24 (oxidative 11 potential peak of +0.9 V) underwent the desired oxidative 12 decarboxylation with CAN in the presence of MeOH.³⁴ 13 Under these conditions, a ca. 1:1 mixture of alkene 10 and 14 the methyl ether of 20 (20Me) was formed. Treatment of 15 this mixture with 50% aqueous sulfuric acid afforded 16 lactone 8 in 62% NMR yield (Scheme 8). 17

Next, the hypothesis of heterolytic cleavage of lactones to cyclopropanes was tested. When lactone 8 was treated with KCl in wet DMSO at 85 °C for 17 h,³⁵ no cyclopropane product was observed. This led us to consider an alternative mechanism for the generation of the cyclopropane via homolytic photochemical decarboxylation of the ylactone.³⁶ To our delight, irradiation of lactone 8 with UVb light (300 nm) or UVc light (254 nm) gave the corresponding cyclopropane 27 in moderate NMR yield, with UVb wavelength being more selective and efficient (Scheme 8).

Finally, it was noticed that despite their lower stability in comparison with the corresponding pyrrolones,¹⁴ 3pyrrolines (lundurine B, lapidilectines A,B, isolapidilectine A, tenuisine A) were isolated in significantly greater amounts,^{1a,2} suggesting that the pyrrolones (lundurine A, grandilodines B,C, lapidilectam, tenuisine C) could arise from an autoxidation process. Indeed, synthetic lundurine B^8 spontaneously converted (> 50%) into lundurine A upon storage under air for 16 months.

We suggest an alternative biosynthetic scheme, which features carboxylic acids 28 as key intermediates and homolytic mechanism for decarboxylation of lactone into cyclopropane. The new proposal is summarized on Scheme 8. It is in line with the experimentally observed reactivity and additional DFT studies (see below).

The new biosynthetic hypothesis starts with the hydrolysis of kopsijasminilam-type precursors to pyrrolinecontaining carboxylic acids 28 (Scheme 8). The close proximity between C20 and amide N atom in known kopsijasminilam-type structures³⁷ suggests that lactam hydrolysis might involve *N*-acyl ammonium cations **29** as key intermediates.^{38,39} Indeed, the DFT optimization²² of kopsijasminilam-type structures with planar amide and the carbocation at C20 led to more stable cations 29 that have short C20-N distances (ca. 1.62 Å), non-planar nitrogen atoms and elongated amide C21-N bonds (ca. 1.52 Å).¹⁴ This geometry resembles the one previously reported for N-alkylated twisted amides, which are prone to hydrolysis of N-CO bond.40

Scheme 7. Endgame: Diversification of Intermediates (+)-8 and (-)-25 into Seven Natural Products of the Lapidilectine/Grandilodine Family. X-ray Structures of (±)-1, (±)-3, (±)-4, (±)-5, (±)-7



Scheme 8. Cyclopropane Formation by Stepwise Decarboxylation of Acid 24 and Lactone 8. Original and New Proposal for the Origin of the Cyclopropane of Lundurines



 a Simplified version. For the full scheme see Supporting Information and ref. 11.

via radical pathway

Carboxylic acids **28** can be further converted into methyl esters lapidilectine A and isolapidilectine A. These compounds were previously proposed as precursors to lactones. Our experimental results suggest that this scenario is unlikely, but carboxylic acids **28** might undergo an oxidative decarboxylation/lactonization leading to the formation of lactones lapidilectine B and tenuisine A. The proximity of the lactone carbonyl group and the pyrroline nitrogen atom in lapidilectine B (2.5 Å, X-ray structure, Scheme 7) suggests a possible intramolecular assistance of the latter in the lactonization process. While we were not able to obtain amino-acid **28** or its 14,15-dihydro analogue to test this hypothesis experimentally, our DFT calcula-

Lundurine B

Lundurine A

tions²² support this possibility. On one hand, open benzylic carbocation **A** is more stable than closed carbocation **A**' by 5.3 kcal/mol (Scheme 9). This suggests that the lactonization of lactam derivatives is hampered by this unfavorable equilibrium. Experimentally, we indeed observed that this transformation only takes place efficiently in a strongly acidic medium, and that under milder conditions the major pathway observed is towards elimination product **10**. On the other hand, pyrroline-containing cation **B**' benefits from additional stabilization by the nitrogen and, in this scenario, is more stable than open benzylic cation **B** by 5.6 kcal/mol.⁴¹ This, in turn, suggests

Grandilodine C

Tenuisine C

Lapidilectine B

Ťenuisine A

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58

59

60

that the lactonization of pyrroline derivatives should be a favorable natural process.

The subsequent decarboxylation into cyclopropane may be a light-induced process, as was demonstrated experimentally for **8**. Tenuisine A, after a photochemical decarboxylation, would give lundurine B, featuring a 3pyrroline fragment. This transformation presumably proceeds with the initial excitation of the arene system (absorption band at 290 nm in **1**, **2** and **8**), that results in the homolytic cleavage of the benzylic C–O bond, which is perpendicular to the aromatic system. Irradiation of a thin film of neat **8** between two quartz plates with sunlight over 10 days also showed formation of **27**, suggesting the relevance of the photochemical decarboxylation in the biosynthetic scheme and the sufficiency of UVb light to trigger this transformation.⁴²

Finally, pyrrolines might undergo allylic oxidation, producing pyrrolones. As the decarboxylation of lactone and allylic oxidation do not require any specific enzyme, the corresponding compounds could have been formed after collection of the plant material, and be even artefacts of the isolation process.

Scheme 9. Relative Stability of Cation Intermediates A, A' and B, B'.



CONCLUSIONS

In summary, we have developed concise total syntheses (11-19 steps) of enantiomerically pure (+)-lapidilectine B (1), (+)-grandilodine C (2), (-)-lapidilectine A (3), (-)-lapidilectam (4), (-)-grandilodine A (5), (+)-isolapidilectine A (6), (+)-grandilodine B (7), and unnatural (+)-dihydrolapidilectine B (26) by means of two highly efficient gold-catalyzed cyclization processes. The skeleton of grandilodines/lapidilectines (10) was assembled in only 9 steps and 16% overall yield from tryptamine. We also propose a new hypothesis of biosynthetic relationship among *Kopsia* pyrroloazocine indole alkaloids by means of two decarboxylation events: the elimination of a carboxylic acid to form a lactone and a photo-induced

conversion into the cyclopropane present in the lundurines.

ASSOCIATED CONTENT

Supporting Information

Additional details, theoretical calculations, experimental procedures, characterization data (PDF). Crystallographic data (CIF).

AUTHOR INFORMATION

Corresponding Author

aechavarren@iciq.es

ORCID

Fedor M. Miloserdov: 0000-0002-7906-4650 Mariia S. Kirillova: 0000-0003-1628-4186 Michael E. Muratore: 0000-0002-3298-9381 Antonio M. Echavarren: 0000-0001-6808-3007

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Agencia Estatal de Investigación (CTQ2016-75960-P MINECO/AEI/FEDER, UE), AEI-Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-0319), the European Research Council (Advanced Grant No. 321066), the AGAUR (2014 SGR 818 and predoctoral fellowship to M.S.K.), and CERCA Program / Generalitat de Catalunya for financial support. M.E.M. acknowledges the receipt of a COFUND postdoctoral fellowship (Marie Skłodowska-Curie actions). We also thank the ICIQ X-ray diffraction unit for the crystallographic studies.

REFERENCES

(1) (a) Awang, K.; Sévenet, T.; Hadi, A. H. A.; David, B.; Païs, M. *Tetrahedron Lett.* **1992**, *33*, 2493–2496. (b) Awang, K.; Sévenet, T.; Païs, M.; Hadi, A. H. A. *J. Nat. Prod.* **1993**, *56*, 1134–1139.

(2) Yap, W.-S.; Gan, C.-Y.; Low, Y.-Y.; Choo, Y.-M.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. J. Nat. Prod. 2011, 74, 1309–1312.

(3) Kam, T.-S.; Lim, K.-H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739–10745.

(4) (a) Pearson, W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. J. Am. Chem. Soc. 2001, 123, 6724-6725. (b) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. J. Org. Chem. 2004, 69, 9109-9122.

(5) Nakajima, M.; Arai, S.; Nishida, A. Angew. Chem. Int. Ed. 2016, 55, 3473-3476.

(6) Wang, C.; Wang, Z.; Xie, X.; Yao, X.; Li, G.; Zu, L. *Org. Lett.* **2017**, *19*, 1828–1830.

(7) (a) Ferrer, C.; Echavarren, A. M. Angew. Chem. Int. Ed. **2006**, 45, 1105–1109. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. Chem. Eur. J. **2007**, 13, 1358–1373. (c) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. Tetrahedron **2009**, 65, 9015–9020. (d) Muratore, M. E.; Echavarren, A. M. Gold-Catalyzed Hydroarylation of Alkynes. In The Chemistry of Organogold Compounds; Rappoport, Z.; Liebman, J. F.; Marek, I., Ed.; John Wiley & Sons, Ltd: Chichester, UK, 2015, 805–900.

(8) Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. J. Am. Chem. Soc. **2016**, *13*8, 3671-3674.

(9) Schultz, E. E.; Pujanauski, B. G.; Sarpong, R. Org. Lett. 2012, 14, 648–651.

(10) (a) Kirillova, M. S.; Miloserdov, F. M.; Echavarren, A. M. *Org. Chem. Front.* **2018**, 5, 273–287. (b) Arai, S.; Nakajima, M.; Nishida, A. Total Synthesis of Lundurine and Related Alkaloids: Synthetic Approaches and Strategies. In *The Alkaloids: Chemistry and Biology*; Knölker, H.-J., Ed.; Academic Press: Cambridge, MA, 2017; 78, 167–204.

(11) Kam, T.-S.; Lim, K.-H. Alkaloids of Kopsia. In *The alkaloids chemistry and biology*; Cordell, G. A., Ed.; Academic Press: London, 2008; 66, 1–111.

(12) Wessjohann, L. A.; Brandt, W.; Thiemann, T.; *Chem. Rev.* **2003**, *1*03, 1625–1647.

(13) Li, T.; Huo, L.; Pulley, C.; Liu, A. *Bioorg. Chem.* **2012**, *4*3, 2–14.

(14) See Supporting Information for details.

2 3 4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58

59

60

(15) For a discussion about Brønsted acid effect in Aucatalyzed alkyne hydroarylation with indole see: Zhang, L.; Wang, Y.; Yao, Z.-J.; Wang, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2015**, 137, 13290–13300.

(16) Escudero-Adán, E. C.; Benet-Buchholz, J.; Ballester, P. Acta Crystallogr. 2014, B70, 660–668.

(17) (a) Denmark, S. E.; Fan, Y. J. Am. Chem. Soc. 2003, 125, 7825–7827. (b) Denmark, S. E.; Fan, Y. J. Org. Chem. 2005, 70, 9667–9676.

(18) Bar, G.; Parsons, A. F. Chem. Soc. Rev. 2003, 32, 251-263.

(19) To the best of our knowledge there are only two other examples of 6-exo-trig radical spirocyclization on indole, which occurred in 43%^{19a} and 10-13%^{19b} yield: (a) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* 2003, 44, 1795–1798.
(b) Bremner, J. B.; Sengpracha, W. *Tetrahedron* 2005, 61, 5489–5498.

(20) (a) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104–3107. (b) Erdenebileg, U.; Demissie, T. B.; Hansen, J. H. *Synlett* **2017**, *28*, 907–912.

(21) (a) Revol, G.; McCallum, T.; Morin, M.; Gagosz, F.; Barriault, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 13342–13345. (b) Kaldas S. J.; Cannillo, A.; McCallum, T.; Barriault, L. *Org. Lett.* **2015**, *17*, 2864–2866.

(22) DFT calculations were carried out using the Gaussiano9 program package at PCM(acetonitrile or water)-B3LYP/6-311+G(2d,2p)//B3LYP/6-31+G(d,p) level of theory.¹⁴

(23) (a) Devery III, J. J.; Douglas, J. J.; Nguyen, J. D.; Cole, K. P.;
Flowers II, R. A.; Stephenson, C. R. J. *Chem. Sci.* 2015, *6*, 537–541.
(b) Xie, J.; Li, J.; Weingland, V.; Rudolph, M.; Hashmi, A. S. K. *Chem. Eur. J.* 2016, 22, 12646–12650.

(24) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, *18*, 1071-1074. (b) Sugimori, T.; Horike, S.-i.; Tsumura, S.; Handa, M.; Kasuga, K. *Inorg. Chim. Acta* **1998**, *283*, 275–278. (c) Magnus, P.; Payne, A. H.; Waring, M. J.; Scott, D. A.; Lynch, V. *Tetrahedron Lett.* **2000**, *41*, 9725–9730.

(25) (a) Hosomi, A.; Sakurai, H.; *Tetrahedron Lett.* **1976**, *16*, 1295–1298. (b) Cela, J. A. J. Org. Chem. **1982**, *47*, 2125–2130.

(26) (a) Hosomi, A.; Iguchi, H.; Endo, M.; Sakurai, H. *Chem. Lett.* **1979**, 977–980. (b) Kim, H.; Lee, D. *Synlett* **2015**, *26*, 2583–2587.

(27) For an example of one-pot radical indole functionalization / benzylic C–C bond construction see: Alpers, D.; Hoffmann, F.; Brasholz, M. Synlett 2017, 28, 919–923.

(28) For examples of one-pot radical addition / allylSnR₃ trapping see: (a) Keck, G. E.; Kordik, C. P. *Tetrahedron Lett.* **1993**, *34*, 6875–6876. (b) Sibi, M. P.; Chen, J. J. Am. Chem. Soc. **2001**, *123*, 9472–9473. (c) Murai, K.; Katoh, S.-I.; Urabe, D.; Inoue, M. *Chem. Sci.* **2013**, *4*, 2364–2368. (d) Hashimoto, S.; Katoh, S.-I.; Kato, T.; Urabe, D.; Inoue, M. J. Am. Chem. Soc. **2017**, *139*, 16420–16429.

(29) Sunazuka, T.; Yoshida, K.; Kojima, N.; Shirahata, T.; Hirose, T.; Handa, M.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Õmura, S. *Tetrahedron Lett.* **2005**, *46*, 1459–1461.

(30) The direct one-carbon cleavage of aldehyde 21 was not successful. For conditions see: Belotti, D.; Andreatta, G.; Pra-daux, F.; BouzBouz, S.; Cossy J. *Tetrahedron Lett.* 2003, 44, 3613–3615.

(31) For an alternative two step approach for allyl group twocarbon degradation *via* ene reaction with DEAD see: Mason, J. D.; Weinreb, S. M. *Angew. Chem. Int. Ed.* **2017**, *32*, 493.

(32) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, 37, 2091–2096.

(33) Magnus, P.; Pappalardo, P. A. J. Am. Chem. Soc. 1986, 108, 212–217.

(34) Boscá, F.; Martínez-Mánez, R.; Miranda, M. A.; Primo, J.; Soto, J.; Vaño, L. *J. Pharm. Sci.* **1992**, *81*, 479–482.

(35) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331-3334-

(36) (a) Givens, R. S.; Oettle, W. F. J. Org. Chem. 1972, 37, 4325-4334. (b) Greene, A. E.; Muller, J.-C.; Ourisson, G. Tetrahedron Lett. 1971, 12, 4147-4149.

(37) For the X-ray structures of kopsijasminilam-type compounds see: Magnus, P.; Hobson, L. A.; Westlund, N.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 993–997.

(38) Similar activation of the amide *via* electrophilic attack at the nitrogen atom was suggested to explain the high yield of the Friedel-Crafts cyclization step in the Ziegler's classic synthesis of quebrachamine: (a) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342–2346. (b) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. J. Org. Chem. **2007**, *72*, 4431–4439.

(39) (a) *N*-acyl ammonium cations **29** might be also generated in the course of the fragmentation of lahadinine-³⁷ and kopsidasine-type^{39b,c} natural compounds.¹⁴ (b) Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. *Tetrahedron* **2002**, *58*, 3423–3443. (c) Kuehne, M. E.; Li, Y.-L.; Wei, C.-Q. J. Org. Chem. **2000**, *65*, 6434–6440.

(40) Hu, F.; Lalancette, R.; Szostak, M. Angew. Chem. Int. Ed. 2016, 55, 5062–5066.

(41) Similarly, the pyrrolidine-containing analogues of **B** and **B**' (14,15-dihydro; **C** and **C**') were calculated, and analogously, the cyclized form **C**' was found to be 6.9 kcal/mol more stable than open form **C**.¹⁴

(42) The photochemical decarboxylation of lactone 8 to cyclopropane provides a biomimetic entry to the lundurines, although our previously developed synthetic scheme⁸ is superior in terms of number of steps and overall efficiency.

8

Table of Contents graphic:

photoredox cyclization

hν

- CO₂

ĺ

X = O, H2

0

CO₂Me

MeO₂C

CO₂Me

CO₂Me

CO₂Me

(–)-Lapidilectam, (–)-Lapidilectine A (–)-Grandilodine A, (+)-Grandilodine B (+)-Isolapidilectine A

X

CO₂Me



57 58