

Cite this: *RSC Adv.*, 2017, 7, 28298

Efficient total synthesis of neocryptolepine and synthetic access to 6-methylquinindoline from a common intermediate†

María V. Méndez, , Daniel A. Heredia, , ‡ Enrique L. Larghi, , Andrea B. J. Bracca and Teodoro S. Kaufman *

A convenient approach toward the indoloquinolines neocryptolepine and 6-methylquinindoline from a common intermediate, is reported. Both sequences, designed for maximum use of accessible reagents and robust conditions, are straightforward and efficient. They involved the amidation of 2-aminobenzaldehyde (prepared by iron-mediated reduction of 2-nitrobenzaldehyde) with 2-nitrophenylacetic acid, followed by a K_2CO_3 -assisted cyclization to form a 3-(2-nitrophenyl)quinolin-2-one as the common precursor. Me_2CO_3 -mediated *N*-methylation of the lactam, reduction of the nitro moiety and final cyclization resulted in 55% overall yield of neocryptolepine, whereas cyclocondensation and *N*-methylation afforded 79% overall yield of 6-methyl quinindoline. Thus, the sequences toward the targets entailed two $POCl_3$ -promoted C–N bond forming reactions, two Fe-mediated nitro group reductions and two base-promoted transformations.

Received 11th May 2017

Accepted 23rd May 2017

DOI: 10.1039/c7ra05349e

rsc.li/rsc-advances

Introduction

Cryptolepis sanguinolenta (Lindl.) Schlachter (Periplocaceae) is a climbing vine, which grows in West and Central Africa, where it is locally known as nibima, kadze or gangamau, and has served Ghanaian traditional healers as a folk medicine since ancestral times. The decoction of the roots of this plant have been used in the therapy against various fevers, including malaria, but also as treatment for hypertension, hepatitis, jaundice and inflammation.¹

The systematic phytochemical examination of *C. sanguinolenta* demonstrated that it is a rich source of indoloquinolines. The latter are a small and unique family of alkaloids, which feature two differently fused ring systems, an indole and a quinoline.²

Some of its monomeric members are neocryptolepine (1),^{3a} cryptolepine (2),^{3b,c} quindoline (3),^{3d} quindolinone (4),^{3e} cryptosanguinolentine (5),^{4a} 11-isopropylcryptolepine (6),^{4b,c} cryptolepinone (7),^{4d} and quinindoline (8), as shown in Fig. 1.^{5a} Several dimeric alkaloids are also known, including biscryptolepine (9),^{5b} cryptoquindoline,^{4d} cryptolepicarboline,^{6a} cryptospirolepine,^{6b} quindolinocryptotackieine,^{6c} and cryptomisrine.^{6d}

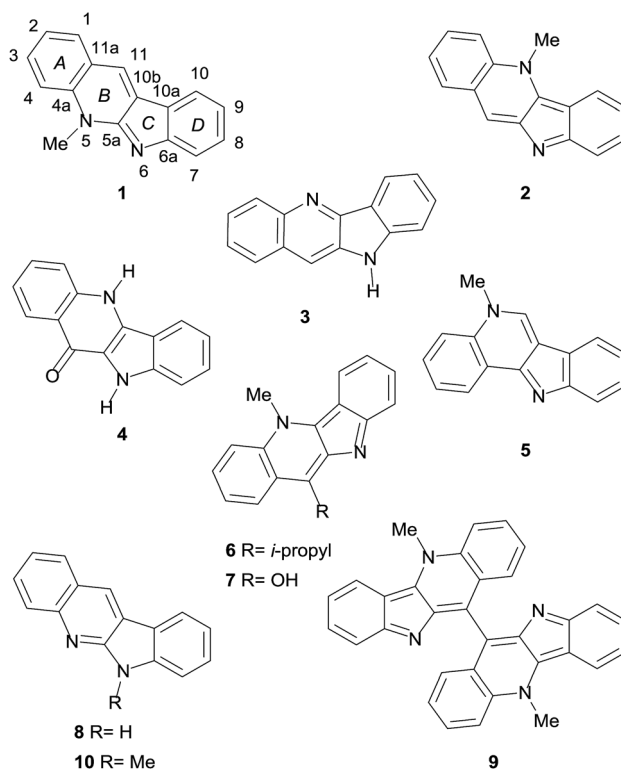


Fig. 1 Chemical structures of representative examples of the indoloquinoline alkaloids. Neocryptolepine (cryptotackieine, 1), cryptolepine (2), quindoline (3), quindolinone (4), cryptosanguinolentine (5), 11-isopropylcryptolepine (6), cryptolepinone (7), quinindoline (8), biscryptolepine (9) and the unnatural 6-methylquinindoline (10).

Instituto de Química Rosario (CONICET-UNR), Suipacha 531, S2002LRK, Rosario, SF, Argentina. E-mail: kaufman@iquir-conicet.gov.ar; Fax: +54-341-4370477 ext. 105; Tel: +54-341-4370477 ext. 105

† Electronic supplementary information (ESI) available: Selected spectra of intermediates and final product. See DOI: 10.1039/c7ra05349e

‡ Present address: Departamento de Química, Universidad Nacional de Río Cuarto, Agencia Postal No. 3, X5804BYA, Río Cuarto, Argentina.

Although most of the indoloquinolines have been isolated from this shrub, there are some scattered reports disclosing additional sources of these heterocycles, including *Cryptolepis triangularis* N. E. Br., *Sida acuta* Burm. (Malvaceae), *Microphilis guyanensis* (A. DC) Pierre (Sapotaceae), *Justicia betonica* (Acanthaceae) and *Genipa americana* L. (Rubiaceae).⁷

The isolation of neocryptolepine (**1**) from the bark of the roots of *C. sanguinolenta* was reported independently and almost simultaneously in 1996, by the groups of Schiff, who termed the new alkaloid cryptotakieine,^{3a} and Pieters.^{5b} Curiously, this is not the only case of dual naming of the same alkaloid isolated from this plant.^{6c}

In both instances, the structure of the natural product was elucidated through extensive NMR spectroscopic analyses, including 2D experiments,^{5b} which conclusively proved that it is an isomer of cryptolepine and isocryptolepine,^{4a} and unambiguously defined the site of *N*-methylation.

Interestingly enough, the structure of **1** concealed great interest and its synthesis was already described long before its isolation from natural sources.^{8a-d} Furthermore, the natural product, whose skeleton bears key common features with those of the communesins,^{8e-g} demonstrated to display cytotoxic and antimalarial activity, also acting as a DNA intercalator.

We have recently reviewed both, the synthesis and the biological activities of neocryptolepine,⁹ and classified the total syntheses of **1** in three groups, according to the compounds employed as key starting materials for their syntheses; these included those derived from indoles,¹⁰ quinolines¹¹ and benzenoids.¹²

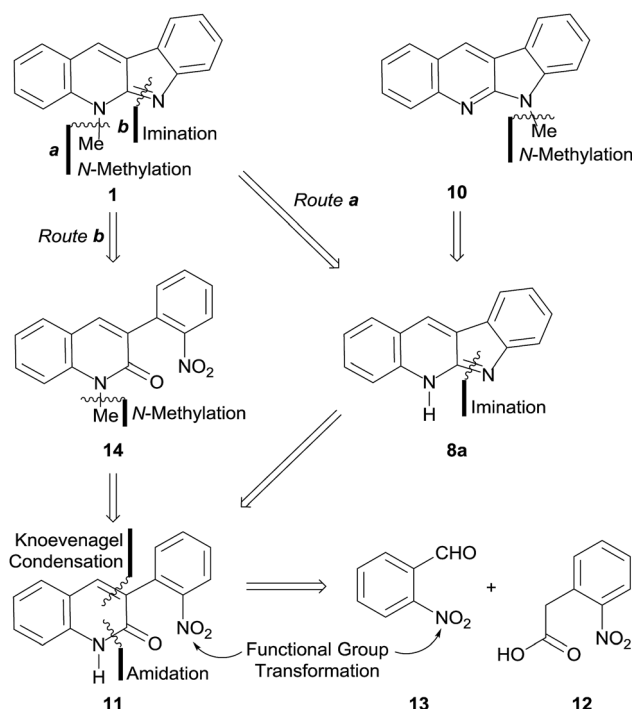
In this way, we found out that after its isolation the natural product has also attracted an unusually great amount of attention from the organic synthetic community, to the extent that approximately 15 total syntheses and 8 formal total syntheses¹³ of it have been reported to date; further, most of them have used quinindoline (**8**) as key intermediate.^{10a-c,11a,12a-f,13b-h} However, in spite of the exceptionally important number of published total syntheses of **1**, neither of them has been designed to take into account the care for the environment.

The development of efficient and versatile synthetic sequences toward complex molecules has become one of the most relevant goals of modern organic chemistry. Therefore, herein we wish to report a short total synthesis of neocryptolepine (**1**), which involves a new strategic approach for building the tetracycle and contains environmentally benign stages.

In addition, a synthesis of the isomeric 6-methylquinindoline (**10**) is also disclosed, employing a common synthetic intermediate and the same operational principles for both targets. Interestingly, there are only four previous records on the preparation of the non-natural compound **10**.¹⁴

Results and discussion

Our approach toward **1** relied on the retrosynthetic analysis shown in Scheme 1. The initial rational disconnection was made on the *N*-5 substituent (Route a), assuming that it could



Scheme 1 Retrosynthetic analyses of neocryptolepine (**1**) and 6-methyl quinindoline (**10**).

be accessed by *N*-methylation under eco-conscious conditions, instead of using the more conventional but less safe Me_2SO_4 or MeI as alkylating agents, as in all previous syntheses. This revealed the synthetic need of **8a**, the tautomer of quinindoline (**8**), which was conjectured as accessible through an intramolecular imination of the lactam **11**.

In turn, the key intermediate **11** was structurally simplified by performing two successive strategic disconnections of its heterocyclic ring, which uncovered an amide precursor and further revealed 2-nitrophenylacetic acid (**12**) and 2-nitrobenzaldehyde (**13**), as the most logical starting materials.

On the other hand, a second set of disconnections was also deemed possible, by merely reversing the order of the initial disconnections. This strategy, which already proved fruitful in our hands,¹⁵ conveniently furnished an alternative path (Route b) toward the target.

In this case, the first disconnection was performed on the $\text{C}=\text{N}$ bond of the five-membered ring, unearthing **14**, which was subjected to the retrosynthetic fission of the *N*-methyl bond, exhibiting the precursor lactam **11** as the common intermediate of both retrosynthetically proposed routes.

In both cases, it was foreseen that functional group transformations would be required in order to accommodate the readily available nitro-derivatives proposed as starting materials to the needs of the synthetic sequences. However, this would be rewarded by completely avoiding the need of protective groups.

In this analysis, it was also hypothesized that **8a** could also become a suitable precursor of **10**, provided appropriately selective *N*-methylation conditions could be found.

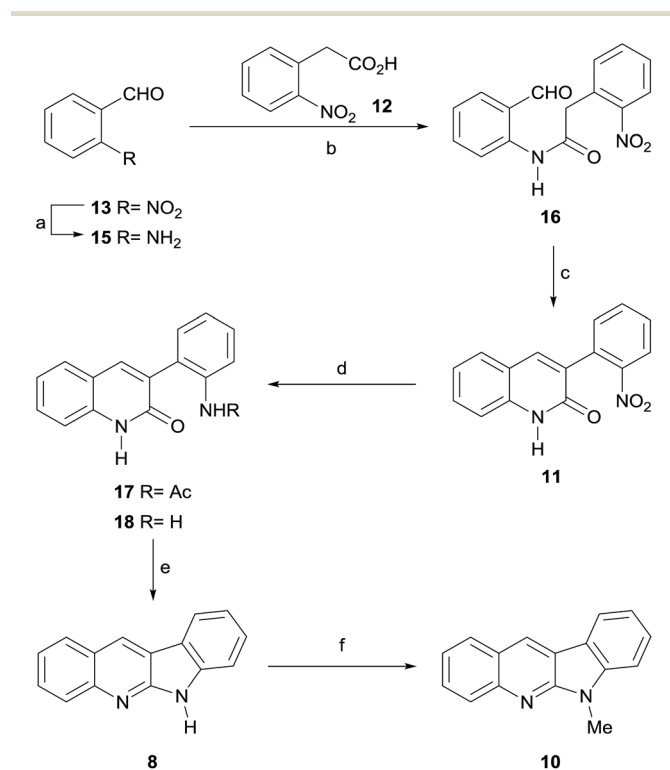


The Route a, which pivoted on an A \rightarrow AD \rightarrow ABD \rightarrow ABCD ring forming sequence, was initially explored. To that end, despite the required 2-aminobenzaldehyde **15** is commercially available, its elevated cost and reportedly high instability¹⁶ prompted for its synthesis *in situ*, which was undertaken as the first task.

Among the various protocols which were examined, the most successful one proved to be that which uses metallic iron in a refluxing hydro-alcoholic (10 : 90 v/v) medium, in the presence of a mild acid catalyst such as NH₄Cl.¹⁷ Under these conditions, 96% of **15** was easily obtained, with no sensitive drop in yields when the reduction was performed on a gram scale (Scheme 2).

However, it was found that special care had to be placed in removing even the smallest traces of iron and its salts, as any of both promoted self-condensation of the product during concentration of the solutions containing the *ortho*-amino-aldehyde, through Schiff base formation.

After securing the supply of **15**, its amidation with acid **12** was scrutinized, in a task that proved to be non-trivial. The use of carbodiimide coupling agents (DCC, EDCI) afforded only moderate yields of **16**, partly due to self-condensation of **12**,^{18a} but also because of its rather poor solubility. On the other hand, the use of a mixed carboxylic anhydride strategy in THF (Table 1), with (Boc)₂O as activating agent and Et₃N (entry 1) or pyridine (entries 2–4) as bases,^{18b} produced at best 26% of the expected amide **16**.



Scheme 2 Reagents and conditions: (a) Fe, NH₄Cl, EtOH–H₂O (9 : 1, v/v), reflux, 2 h (96%); (b) POCl₃, pyridine, DMF (cat.), **12**, PhCF₃, r.t., 3 h (97%); (c) K₂CO₃, DMF, 100 °C, 1 h (99%); (d) Fe, AcOH, reflux, overnight (**17**, 99%) or Fe, NH₄Cl, EtOH–H₂O (9 : 1, v/v), reflux, 2 h (**18**, 99%); (e) Py·HCl, 240 °C, 10 min (70% from **17**; 93% from **18**) or POCl₃, MeCN, 90 °C (94% from **18**); (f) DMC, MgO, MW (170 °C), 30 min (89%).

The outcomes of these reactions were similar when carried out either in two stages (activation and condensation) or in a single stage (mixing all the reactants together at once). No substantially better performance was achieved with Ac₂O in toluene (entry 5).^{23a}

In the pharmaceutical industry, acid chlorides are by far the most common acylating agents for the preparation of drug candidate molecules,^{18c} with oxalyl chloride and SOCl₂ being preferred based on criteria of wide utility, scalability and greenness.^{18d} However, attempts at formation of the acid chloride with oxalyl chloride in toluene,^{18e} and its further condensation with aniline **15** afforded at most 34% yield of **16**, when pyridine was used as base (entry 6).

This result was substantially improved when SOCl₂ (entries 7 and 8) was used, and yields as high as 50% could be obtained with pyridine as base. Surprisingly, however, no better yields were initially obtained when the less volatile POCl₃ was employed as activating agent either in two-stage (entry 9) or single-stage (entry 10) setups.^{18f}

An in-tube NMR monitoring experiment revealed that the first stage required catalytic amounts of DMF to speed up the formation of the acid chloride (ArCH₂COCl as a singlet at δ_{H} = 4.54 ppm). The reaction resulted in H₃PO₄ as the only by-product (δ_{31P} = 0.00 vs. δ_{31P} = 3.19 ppm for POCl₃) after complete conversion of the acid **12** was achieved; however, other phosphorus-containing reaction intermediates were also observed.¹⁹

Interestingly, the success of this experiment also confirmed that POCl₃ afforded a transformation with better atom economy than SOCl₂, minimizing reagent utilization and byproduct generation, and that the low solubility of **12** in toluene adversely affected the reaction performance.

It was also observed that addition of the base (Et₃N or pyridine) all at once to the preformed acid chloride caused an almost immediate destruction of the latter, whereas dropwise or partial addition promoted self-condensation of the amino-aldehyde **15**, compromising product yields.

The effects of overcoming the solubility problem on the yields was tested in a small-scale experiment run in CH₂Cl₂, where we were pleased to discover that this modification afforded 93% of the amide **16** (entry 11).

An eco-acceptable solution was implemented using benzo-trifluoride as solvent replacement, which furnished 97% of the expected product (entry 12).²⁰ The optimally accessed amide **16** was then submitted to an intramolecular Knoevenagel-type cyclization under K₂CO₃ promotion,²¹ to afford 99% of the desired 3-arylquinolone **11**.

An attempt to reach the key intermediate **8** through a one pot reduction of the nitro moiety and subsequent *in situ* cyclization of the resulting product, was next made. Hence, **11** was exposed to iron powder in refluxing AcOH. However, this resulted in the generation of acetanilide derivative **17**, which could not be cyclized with POCl₃,^{11b,22} but afforded 70% of the expected product **8** upon exposure to molten pyridinium hydrochloride (Py·HCl).²³

An effort to improve the performance of the synthesis was made, under the hypothesis that the free aniline should be a more suitable substrate for the cyclocondensation. Therefore,



Table 1 Optimization of the amidation of acid **12** with aniline **15**

Entry no.	Solvent	Coupling reagents (equivalents), temperature, time		Yield ^a (%)
		Step 1	Step 2	
1	THF	(Boc) ₂ O, MgCl ₂ , r.t., 1.2 h	Et ₃ N, reflux, 15 h	14
2	THF	(Boc) ₂ O, MgCl ₂ , r.t., 1.2 h	Pyridine (2.0), reflux, 15 h	26
3	THF	(Boc) ₂ O, MgCl ₂ , r.t. 1.2 h	Pyridine (2.5) reflux, 15 h	13
4	THF	(Boc) ₂ O, MgCl ₂ , pyridine (2.5), reflux, 15 h		20
5	PhMe	Ac ₂ O, Et ₃ N, 90 °C, 48 h		28
6	PhMe	(COCl) ₂ (2.0), DMF (cat.), 0 °C to r.t.	Pyridine (3.0), 40 °C, 2.5 h	34
7	PhMe	SOCl ₂ (1.85), DMF (cat.), 50 °C, 5 h	Et ₃ N (3.0), 50 °C, 28 h	36
8	PhMe	SOCl ₂ (1.85), DMF (cat.), 50 °C, 5 h	Pyridine (3.0), r.t., 1.5 h	50
9	PhMe	POCl ₃ (0.7), DMF (cat.), r.t., 1.5 h	Pyridine (3.0), r.t., 20 h	27
10	PhMe	POCl ₃ (0.7), DMF (cat.), pyridine (3.0), r.t., 48 h		35
11	CH ₂ Cl ₂	POCl ₃ (0.7), DMF (cat.), pyridine (3.0), r.t., 15 h		93
12	PhCF ₃	POCl ₃ (0.7), DMF (cat.), pyridine (3.0), r.t., 3 h		97

^a Isolated yields of the product.

compound **11** was reduced with iron powder in EtOH–H₂O, as for the synthesis of **15**, providing to our delight the required intermediate aniline **18** in essentially quantitative yield.

Based on the previous experience, the use of the high temperature ionic liquid Py·HCl was deemed the most suitable approach toward cyclization of **18**, which cleanly afforded the thermodynamic (more stable) amidine isomer **8** in 93% yield. The latter is a natural product, isolated from coal tar pitch and from *Justicia betonica*,^{5a,24} which has been repeatedly synthesized.²⁵ However, quite a similar result (94% yield of **8**) was obtained employing POCl₃ as cyclization agent, under milder conditions.

Next, the final *N*-methylation stage was approached, with the use of a MgO-catalyzed methylation with dimethyl carbonate (DMC).²⁶ The latter is a versatile and safe replacement of more hazardous alkylating agents, such as MeI, Me₂SO₄ and MeOTf, which have been widely used in the field of indoloquinoline chemistry; further, it does not produce harmful reaction waste.

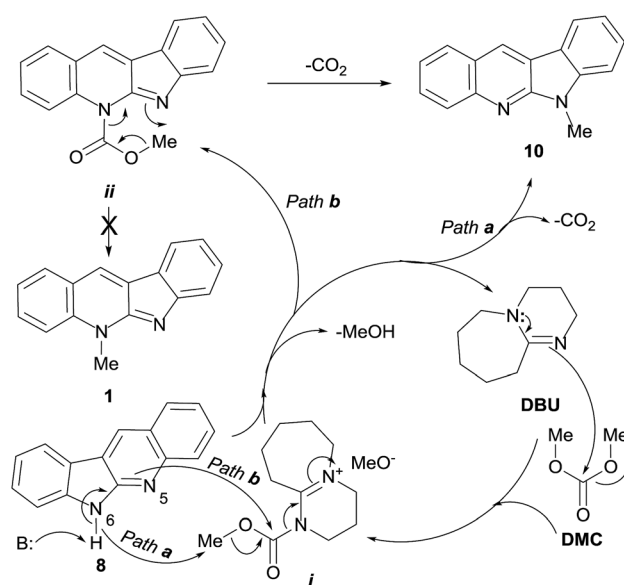
However, and not without surprise, we were able to observe the smooth generation of a single less polar compound, in 89% yield, which turned out to be 6-methyl quinindoline (**10**), the unnatural isomer of **1** and one of our synthetic targets. Other alternatives were explored, including the use of DBU as catalyst; however, all of them met with the same result.²⁷

The formation of **10** as the sole reaction product was unequivocally assessed by exhaustive examination of the ¹H and ¹³C NMR spectra of the product, and their comparison with authentic spectra and literature data of both, **1** and **10**.

The diagnostic ¹H NMR resonance of the methyl moiety of **10** in CDCl₃ was seen at δ 4.02 ppm, in agreement with the literature [δ 3.99,^{14b} 3.97 (ref. 14b) and 3.82 (ref. 14a) ppm], whereas the 5-methyl group of the natural product was reported to

resonate as a singlet in the narrow range of δ 4.34 ± 0.03 ppm. Interestingly, this analysis also revealed that at least once, these subtle spectral differences between **1** and **10** resulted in a case of incorrect assignment of product identity.^{14b}

Although the intimate details of the mechanism of this unique transformation remain unknown, an operating mechanistic picture for the DBU-mediated transformation like that shown in Scheme 3 can be drawn, based on various literature precedents.



Scheme 3 Proposed pathways for the DMC-mediated methylation of quinindoline (**8**), under DBU promotion, resulting exclusively in 6-methylquinindoline (**10**).



Accordingly, it is reasonable to assume that the catalytic cycle is initiated by the nucleophilic attack of DBU to DMC, a recognized ambident electrophile.²⁸ As previously proposed, at the reaction temperature (90 °C) this could generate the ion pair intermediate *i*.²⁷ In turn, this highly activated species could act as methyl (Path a) or methoxycarbonyl (Path b) transferring agent.²⁹

Quinindoline (**8**) is also an ambident nucleophile, which offers two possible sites of alkylation (*N*-5 and *N*-6). It can be postulated that in the presence of DBU as base, due to the relative basicities of both heteroatoms of the amidino moiety, *N*-6 may become the preferred position for the reaction (Path a), resulting in the methylated tetracycle **10**, with concomitant loss of CO₂ and MeOH, and regeneration of the catalyst.

Factors controlling analogous processes in other amidines have been discussed, and seem to be in agreement with the above findings.³⁰ Further, there is ample precedent in the chemistry of indoloquinolines indicating that in unsubstituted derivatives, selective methylation of the pyridine ring takes place by reaction with MeI and Me₂SO₄ alone, whereas in the presence of bases, alkylation of the pyrrole ring becomes predominant or exclusive.³¹

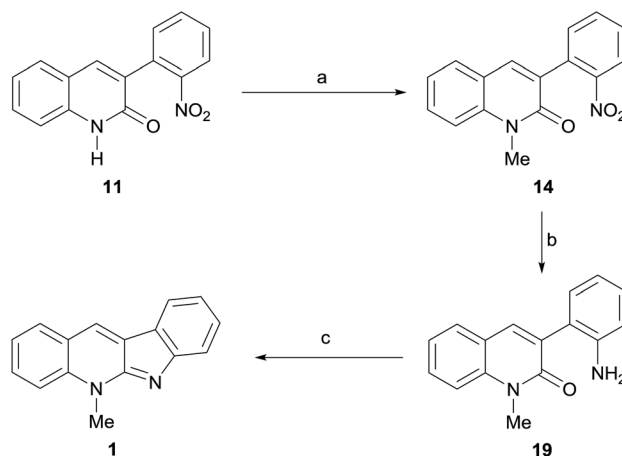
Alternatively, it can be conjectured that the highly activated species *i* could act as a methoxycarbonyl transferring agent (Path b).²⁹ Therefore, in the presence of quinindoline (**8**), this should result in the carbamate intermediate *ii*, formed under assistance of *N*-6 of the heterocycle **8**, with concomitant loss of MeOH and regeneration of the catalyst.

It has been shown that methylcarbamates cannot be converted into the related *N*-methyl derivatives by mere heating. This would preclude the direct access of **1** from *ii*. However, intermediate *ii* could undergo an intramolecular thermally-assisted extrusion of CO₂ that would result in the observed compound **10**. Analogous mechanisms have been proposed for the organic base-mediated alkylation of other functional groups bearing acidic protons.³² On the other hand, the intermediacy of carbamates in these reactions has some precedents, and mixtures of carbamates and *N*-methyl derivatives have been obtained in many occasions.³³

The exquisite and unusual selectivity of this *N*-6 methylation along Path b could also find an explanation based on the hard-soft acid-base theory. In this context, the formation of intermediate *ii* could be understood as the typical result of the attack of a hard nucleophile (*N*-5) to the hard carbonyl centre. This would bring about the production of a soft nucleophile and presumably lower the p*K*_a of *N*-6, turning it capable of becoming involved in an intramolecular attack on the soft methyl group, to afford **10**, with concomitant release of CO₂.

Regardless the fine details of the mechanism, the reactivity of the nitrogen atoms of quinindoline is quite special and it has been shown that it can be modified by minor structural variations on the rings.^{34a,b} Accordingly, the work of Mastalarz and coworkers is illustrative of the different outcomes of *N*-methylations of a substituted indoloquinoline with Me₂SO₄, MeI and DMC,^{34c} and in agreement with our findings.

Ultimately, compound **10** was one of the projected synthetic targets and the reaction of **8** with DMC demonstrated to provide



Scheme 4 Reagents and conditions: (a) DMC, DMF, DBU, 90 °C, overnight (95%); (b) Fe, NH₄Cl, EtOH–H₂O (9 : 1, v/v), reflux, 3 h (96%); (c) 1. POCl₃, MeCN, 90 °C, overnight; 2. DIPEA, 120 °C, overnight (63%).

the suitably selective *N*-methylation conditions looked for in the planning stage. Therefore, focusing back on **1**, the unexpected outcome of the DMC-mediated methylation of **8** prompted us to explore the Route b. Here, it became clear that efforts should be placed on transforming the lactam **11** into the natural product, with a view of simplifying the proposed synthesis.

Toward this end, the lactam was suspended in DMC to which a small amount of DMF was added in order to favor its solubility, and exposed to methylation under DBU catalysis. Delightfully, 95% of the more soluble *N*-methyl lactam **14** was obtained after heating overnight at 90 °C (Scheme 4). In turn, the second iron-mediated reduction of a nitro moiety was put in practice under the previously used conditions, affording 96% of the known aniline derivative **19**.^{11b} Finally, exposure of **19** to POCl₃ in MeCN, to form a reactive 2-chloroquinolinium intermediate, followed by treatment of the latter with DIPEA, gave the expected tetracycle **1** in 63% yield. Its spectroscopic data were in full agreement with those of the literature for neocryptolepine.

An original aspect is that the syntheses feature the environmentally benign DMC as methylating agent which, acting in two different scenarios, provides two different outcomes. Further, to the best of our knowledge, this is the first total synthesis of **1** which employs this alkylating agent; previous sequences relied on methylation steps with MeI or Me₂SO₄, which severely compromised their eco-friendliness.

Conclusions

We have developed very simple and efficient 5-step strategies for the total synthesis of the natural indoloisoquinoline alkaloid neocryptolepine (55% overall yield) and its non-natural isomer 6-methylquinindoline (79% overall yield) from 2-nitro phenylacetic acid and 2-aminobenzaldehyde, employing a 3-aryl quinolin-2-one common precursor.

The syntheses were designed from the onset to be as straightforward and reagent-economic as possible, while



complying with an original key retrosynthetic disconnection (C-11–C-10b). This is the first synthetic solution toward both targets featuring this strategy. Further, both targets were synthesized employing essentially the same reagents but inverting the order of some reaction steps, and unlike most previous approaches, the syntheses employed readily available starting materials and reagents.

The synthesis of neocryptolepine involved a couple of convenient iron-mediated reductions of aromatic nitro moieties to their corresponding anilines and two POCl₃-assisted C–N bond forming reactions. A base-assisted cyclization and a base-promoted *N*-methylation with dimethyl carbonate (DMC) completed the set of reactions.

The strategy toward both heterocycles, which did not resort to the use of protecting groups, employed robust reactions and maximized the use of comparatively benign solvents. Being modular, differently substituted *o*-amino benzaldehydes and *o*-nitrophenylacetic acids could be used to prepare analogs. Hence, this contribution should pave the way for the elaboration of more complex analogs of the natural product and its congeners.

Experimental section

General information

All the reactions were carried out under dry nitrogen or argon atmospheres, employing oven-dried glassware. Anhydrous THF and Et₂O were obtained from a M. Braun solvent purification and dispenser system; anhydrous DMF was obtained by heating the PA grade product over BaO for 4 h, followed by distillation under reduced pressure; anhydrous pyridine was prepared by sequential storage of the product for 7 days on NaOH pellets and atmospheric pressure distillation; anhydrous Et₃N was prepared by distillation of the commercial product from CaH₂; anhydrous solvents were stored in dry Young ampoules. EtOH refers to the 96° product. All other reagents were used as received.

Flash column chromatographies were carried out with Merck's silica gel 60 H. The elutions were carried out with hexane/EtOAc or EtOAc/EtOH mixtures, under positive pressure and employing gradient of solvent polarity techniques. All new compounds gave single spots on TLC plates (silica gel 60 GF₂₅₄) run in different hexane/EtOAc and EtOAc/EtOH solvent systems.

The chromatographic spots were detected by exposure to 254 nm UV light, followed by spraying with Dragendorff reagent (Munier and Macheboeuf modification),³⁵ or with ethanolic *p*-anisaldehyde/sulfuric acid reagent and final careful heating of the plates for improving selectivity.

Apparatus

The melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are reported uncorrected. The IR spectra were recorded with a Shimadzu Prestige 21 spectrophotometer, as solid dispersions in KBr disks or as thin films held between NaCl cells. The NMR spectra were acquired at 300.13 (¹H), 121.5 MHz (³¹P) or 75.48 (¹³C) MHz on a Bruker Avance spectrometer in CDCl₃, unless stated otherwise. The

peak for CHCl₃ in CDCl₃ (δ_{H} = 7.26 ppm), H₃PO₄ (δ_{P} = 0.00 ppm) and the signal of CDCl₃ (δ_{C} = 77.0 ppm) were used as the corresponding internal standards. Chemical shifts are reported in parts per million on the δ scale and *J*-values are given in Hertz. In special cases, ³¹P NMR, DEPT and 2D-NMR experiments (COSY, HMBC and HMQC) were also employed. Pairs of signals marked with asterisk (*) indicate that their assignments may be exchanged. The high-resolution mass spectra were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA). Detection of the ions was performed in electrospray ionization, positive ion mode. Microwave-assisted reactions were performed in a CEM Discover microwave oven.

2-Aminobenzaldehyde (15)^{17c}

2-Nitrobenzaldehyde (**13**, 500 mg, 3.3 mmol) was added to a refluxing mixture of clean iron powder (1020 mg, 18.3 mmol) and NH₄Cl (120 mg, 2.2 mmol) in EtOH : H₂O (9 : 1, v/v, 50 mL). The reaction mixture was stirred at reflux for 2 h under an argon atmosphere; then it was allowed to cool to room temperature, filtered and the residue was washed with EtOH. The filtrate was concentrated under reduced pressure and the resulting oily residue was redissolved in EtOAc (50 mL) and washed with saturated NaHCO₃ solution (5 mL). The organic layer was dried (MgSO₄) and concentrated to afford **15** (385 mg, 96%), as a stinky yellow oil, which slowly crystallized on standing to give a solid with a low melting point. IR (film, ν): 3459, 3443, 3418, 3333, 3321, 3282, 3100, 2916, 2848, 2700, 2357, 1643, 1591, 1557, 1479, 1454, 1396, 1317, 1205, 1155, 1026, 883, 748, 665 and 627 cm⁻¹. ¹H NMR: δ 6.11 (br s, $w_{1/2}$ = 29.2, 2H, NH₂), 6.64 (d, 1H, *J* = 8.4, H-3), 6.75 (ddd, *J* = 7.8, 7.2 and 1.0, 1H, H-5), 7.31 (ddd, *J* = 8.4, 7.2 and 1.6, 1H, H-4), 7.48 (dd, *J* = 7.8 and 1.6, 1H, H-6) and 9.87 (s, 1H, CHO). ¹³C NMR: δ 116.0 (C-3), 116.3 (C-5), 118.8 (C-1), 135.2 (C-4), 135.7 (C-6), 149.9 (C-2) and 194.0 (CHO).

N-(2-Formylphenyl)-2-(2-nitrophenyl)acetamide (16)

A solution of 2-nitrophenylacetic acid (**12**, 561 mg, 3.1 mmol), pyridine (0.67 mL, 8.36 mmol) and DMF (0.071 mL, 0.93 mmol) in PhCF₃ (20 mL) was stirred 1 h at room temperature. Then, a solution of 2-aminobenzaldehyde (376 mg, 3.1 mmol) in PhCF₃ (10 mL) was added to the mixture, which was successively treated dropwise at 0 °C with POCl₃ (0.20 mL, 2.17 mmol). The mixture was stirred 3 h at room temperature, most of the solvent was recovered under reduced pressure, saturated Na₂CO₃ (10 mL) was added, and the mixture was stirred for additional 30 min. The organic products were extracted with EtOAc (4 × 15 mL), and the combined organic phases were washed with brine (10 mL), dried (MgSO₄), and concentrated under reduced pressure. Chromatography of the residue furnished **16** (854 mg, 97%) as a yellow solid, mp 142–144 °C. IR (KBr, ν): 3285, 3100, 3050, 2930, 2850, 2700, 1813, 1740, 1607, 1490, 1450, 1369, 1240, 1215, 1059, 1043, 1030, 968, 885, 835, 797, 758 and 698 cm⁻¹. ¹H NMR: δ 4.18 (s, 2H, NHCOCH₂), 7.22 (dt, *J* = 7.5 and 0.9, 1H, H-4), 7.49 (dd, *J* = 7.6 and 1.4, 1H, H-6'), 7.54 (dt, *J* = 7.8 and 1.7, 1H, H-4'), 7.57 (dt, *J* = 7.8 and 1.8, 1H, H-5), 7.65 (dd, *J* = 7.6 and 1.7, 1H, H-3), 7.67 (dt, *J* = 7.6 and 1.4, 1H, H-5'), 8.17 (dd, *J* = 8.1 and 1.2, 1H, H-3'), 8.69 (d, *J* = 8.4, 1H, H-6), 9.85 (s,



1H, CHO) and 11.21 (br s, $w_{1/2} = 9.3$, 1H, NHCOCH_2). ^{13}C NMR: δ 43.1 (NHCOCH_2), 120.0 (C-6), 121.7 (C-2), 123.1 (C-4), 125.5 (C-3'), 128.9 (C-4'), 129.5 (C-1'), 133.8 (C-5'), 133.8 (C-6'), 135.9 (C-3), 136.2 (C-5), 140.7 (C-1), 149.0 (C-2'), 168.5 (NHCOCH_2) and 195.5 (COH). HRMS m/z calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_4$ 285.0870 [$\text{M} + \text{H}$] $^+$; found: 285.0861.

3-(2-Nitrophenyl)quinolin-2(1H)-one (11)

A stirred solution of carboxamidobenzaldehyde **16** (197 mg, 0.69 mmol) in anhydrous DMF (7 mL) was treated with K_2CO_3 (447 mg, 3.45 mmol) and the reaction mixture was heated at 100 °C for 1 h under an argon atmosphere. Once warmed to room temperature, the reaction mixture was diluted with EtOAc (50 mL) and successively washed with a saturated solution of NH_4Cl (10 mL) and water (10 mL). The organic phase was concentrated *in vacuo* to give **11** (184 mg, 99%), as an orange-brown solid, mp 320–321 °C (lit.: 317–318 °C).^{20a} IR (KBr, ν): 3220, 2922, 2891, 2851, 1653, 1609, 1564, 1560, 1522, 1431, 1356, 1233, 1150, 955, 928, 785, 754, 710 and 631 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 7.24 (t, $J = 7.6$, 1H, H-6), 7.35 (d, $J = 8.2$, 1H, H-8), 7.55 (t, $J = 8.2$, 1H, H-7), 7.64 (dd, $J = 7.3$ and 1.5, 1H, H-6'), 7.67 (dt, $J = 8.0$ and 1.5, 1H, H-4'), 7.76 (d, $J = 7.6$, 1H, H-5), 7.82 (t, $J = 7.3$, 1H, H-5'), 8.04 (d, $J = 8.0$, 1H, H-3'), 8.15 (s, 1H, H-4) and 11.97 (s, 1H, NH). ^{13}C NMR ($\text{DMSO}-d_6$): δ 115.5 (C-8), 119.9 (C-4a), 122.7 (C-6), 124.4 (C-3'), 128.8 (C-5), 129.9 (C-4'), 131.2 (C-7), 131.4 (C-3), * 131.5 (C-1'), * 132.7 (C-6'), 134.2 (C-5'), 138.1 (C-4), 139.0 (C-8a), 149.4 (C-2') and 160.5 (C-2). HRMS m/z calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_3$ 267.0764 [$\text{M} + \text{H}$] $^+$; found: 267.0768.

Pyridine hydrochloride (Py·HCl)

Concentrated HCl (5.12 mL) was added dropwise to a vigorously stirred solution of pyridine (5 mL) in Et_2O (30 mL) at room temperature. A white precipitate was immediately formed. The slurry thus obtained was filtered and the solid product was washed with Et_2O , recrystallized from $\text{CHCl}_3/\text{EtOAc}$ and further washed with Et_2O . The resulting purified material was dried under vacuum and stored into a desiccator.

6H-Indolo[2,3-b]quinoline (quinindoline, **8**)^{5a}

Method A. Iron powder (70 mg, 0.26 mmol) was added to a solution of **11** (121 mg, 2.16 mmol) in glacial AcOH (2 mL) at 110 °C under an argon atmosphere. After stirring overnight at 110 °C, the solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed to give 3-(2-acetamidophenyl)quinolin-2(1H)-one (**17**, 141 mg, 99%) as a brown solid, mp 236–238 °C; IR (KBr, ν): 3300, 3050, 2953, 2918, 2893, 2851, 2300, 1700, 1670, 1637, 1582, 1541, 1449, 1429, 1369, 1312, 1200, 737, 592 and 569 cm^{-1} . ^1H NMR: δ 2.04 (s, 3H, COMe), 7.27 (t, $J = 7.4$, 1H, H-5'), 7.32 (dd, $J = 8.0$ and 7.7, 1H, H-6), 7.36 (dd, $J = 7.4$ and 1.5, 1H, H-6'), 7.40 (d, $J = 8.3$, 1H, H-8), 7.48 (ddd, $J = 8.2$, 7.4 and 1.5, 1H, H-4'), 7.58 (dt, $J = 7.7$ and 1.3, 1H, H-7), 7.68 (d, $J = 8.0$, 1H, H-5), 7.90 (d, $J = 8.2$, 1H, H-3'), 7.98 (s, 1H, H-4), 9.20 (br s, 1H, NHCOMe), 11.73 (br s, 1H, H-1). ^{13}C NMR: δ 24.4 (COMe), 115.5 (C-8), 120.3 (C-4a), 123.7 (C-6), 125.5 (C-3' and C-5'), 128.4 (C-5), 129.3 (C-4'), 130.0 (C-1'), 131.3 (C-7 and C-6'), 131.8 (C-3), 136.6

(C-2'), 137.7 (C-8a), 142.8 (C-4), 163.2 (C-2), 170.0 (COMe). Without further purification, compound **17** (100 mg, 0.36 mmol) and anhydrous $\text{Py}\cdot\text{HCl}$ (1.0 g) were successively transferred to a reaction vessel, which in turn was placed in a pre-heated sand bath at 240 °C for 10 min. Then, the heating bath was removed and when the system reached room temperature, H_2O was added (10 mL) to dissolve the brownish cake, affording a suspension that was filtered under reduced pressure. The residue was washed with H_2O and dried to afford the tetracycle **8** (55 mg, 70%), as a yellow solid, mp 298–299 °C (lit.: >300 °C).^{10c} IR (KBr, ν): 2918, 2849, 1645, 1500, 1454, 1260, 1100 and 1011 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 7.26 (ddd, $J = 8.1$, 7.7 and 2.1, 1H, H-9), 7.45–7.53 (m, 3H, H-2, H-7 and H-8), 7.73 (ddd, $J = 8.5$, 6.7 and 1.4, 1H, H-3), 7.97 (d, $J = 8.5$, 1H, H-4), 8.10 (d, $J = 7.6$, 1H, H-1), 8.25 (d, $J = 7.7$, 1H, H-10), 9.05 (s, 1H, H-11) and 11.72 (br s, $w_{1/2} = 8.8$, 1H, H-6). ^{13}C NMR ($\text{DMSO}-d_6$): δ 111.4 (C-7), 118.4 (C-10b), 120.2 (C-9), 120.5 (C-10a), 122.1 (C-10), 123.3 (C-2), 123.9 (C-11a), 126.8 (C-4), 128.3 (C-11), 128.7 (C-8), 129.0 (C-1), 129.3 (C-3), 141.7 (C-6a), 146.0 (C-4a) and 152.8 (C-5a). The spectroscopic data of the synthetic compound were in full agreement with those of the literature.

Method B. Compound **11** (50 mg, 0.19 mmol) was added to a refluxing mixture of clean iron powder (58 mg, 1.04 mmol) and NH_4Cl (7 mg, 0.13 mmol) in $\text{EtOH} : \text{H}_2\text{O}$ (10 : 1 v/v, 3 mL) and the reaction mixture was stirred at reflux for 2 h under an argon atmosphere. Then, the solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was redissolved in EtOAc (40 mL) and washed with saturated NaHCO_3 solution (2×4 mL). The organic layer was dried (MgSO_4) and concentrated *in vacuo* to afford **18** (44 mg, 99%) as an orange-brown solid. Mp 224–226 °C. IR (KBr, ν): 3100, 2953, 2918, 2849, 2359, 2150, 1715, 1607, 1574, 1495, 1471, 1429, 1396, 1321, 1258, 1119, 1050, 850, 787 and 743 cm^{-1} . ^1H NMR: δ 4.26 (br s, $w_{1/2} = 31.9$, 2H, NH_2), 6.82 (dd, $J = 8.1$ and 1.3, 1H, H-3'), 6.88 (dt, $J = 7.2$ and 1.3, 1H, H-5'), 7.20–7.30 (m, 3H, H-4', H-6' and H-6), 7.32 (d, $J = 8.3$, 1H, H-8), 7.48 (dt, $J = 7.5$ and 1.2, 1H, H-7), 7.61 (dd, $J = 7.8$ and 1.2, 1H, H-5), 7.91 (s, 1H, H-4) and 11.68 (br s, $w_{1/2} = 21.6$, 1H, NH). ^{13}C NMR δ 115.6 (C-8), 117.2 (C-3'), * 119.1 (C-5'), * 120.3 (C-5a), 123.0 (C-6), 123.8 (C-1'), 127.9 (C-5), 129.5 (C-4'), 130.5 (C-7), 131.4 (C-6'), 132.7 (C-3), 137.8 (C-8a), 141.4 (C-4), 145.9 (C-2') and 162.6 (C-2). Without further purification, the cyclization procedure of Method A was applied on **18** (14 mg, 0.06 mmol), employing anhydrous $\text{Py}\cdot\text{HCl}$ (1.0 g). This afforded the tetracycle **8** (12.0 mg, 93%), as a yellow solid. Alternatively, POCl_3 (0.046 mL, 0.49 mmol) was added dropwise to a stirred solution of **18** (38 mg, 0.16 mmol) in MeCN (2.2 mL) at 0 °C, the tube was sealed and the mixture was heated overnight at 90 °C. After evaporation of the solvent and the POCl_3 , the residue was treated with a solution of DIPEA (0.175 mL, 1.00 mmol) in MeCN (3 mL) and the reaction was heated overnight at 120 °C in a sealed tube. After evaporation of the solvent and the DIPEA, the residue was chromatographed to give **8** (33 mg, 94%), as a yellow solid. In both cases, the spectroscopic data of the product were in full agreement with those of the solid obtained employing Method A and with the literature.



6-Methyl-6*H*-indolo[2,3-*b*]quinoline (6-methylquinindoline, **10**)^{10b}

A mixture of **8** (10 mg, 0.046 mmol), DMC (15 μ L, 0.18 mmol), calcined MgO (7 mg, 0.18 mmol) and anhydrous DMF (1 mL) was poured in a sealed reaction vessel and heated in a microwave reactor at 170 °C for 30 minutes. The slurry was cooled to room temperature, the solids filtered off and washed with EtOAc (3 \times 10 mL). The organic phase was washed with H₂O (5 mL), dried (MgSO₄) and concentrated under reduced pressure to afford **10** (9.5 mg, 89%), as an orange-brown solid, mp 78–81 °C (lit.: 83–87 °C).^{14d} IR (KBr, ν): 3050, 2953, 2918, 2849, 2358, 2305, 2150, 1714, 1607, 1574, 1495, 1472, 1430, 1396, 1321, 1258, 1119, 1010, 786 and 743 cm⁻¹. ¹H NMR: δ 4.01 (s, 3H, N-CH₃), 7.32 (ddd, J = 7.7, 7.4 and 0.9, 1H, H-9), 7.40–7.50 (m, 2H, H-2 and H-7), 7.60 (ddd, J = 7.5, 7.3 and 1.2, 1H, H-8), 7.72 (ddd, J = 8.5, 6.7 and 1.4, 1H, H-3), 8.02 (dd, J = 8.1 and 1.3, 1H, H-1), 8.14 (d, J = 8.5, 1H, H-10), 8.17 (d, J = 7.9, 1H, H-4) and 8.73 (s, 1H, H-11). ¹³C NMR: δ 27.8 (N-Me), 108.7 (C-7), 118.3 (C-10b), 120.0 (C-9), 120.4 (C-10a), 121.4 (C-4), 122.9 (C-2), 124.1 (C-11a), 127.4 (C-10 and C-11), 128.1 (C-8), 128.5 (C-1), 128.9 (C-3), 142.9 (C-6a), 146.8 (C-4a) and 152.8 (C-5a).

1-Methyl-3-(2-nitrophenyl)quinolin-2(1*H*)-one (**14**)^{12h}

A solution of **11** (130 mg, 0.48 mmol), DBU (7.2 μ L, 0.048 mmol) and DMF (68 μ L, 0.88 mmol) in DMC (0.68 mL, 8.1 mmol) was stirred overnight at 90 °C. After evaporation of the volatiles, the residue was chromatographed to give **14** (130 mg, 95%), as an amber solid, mp 141–143 °C. IR (KBr, ν): 3250, 3063, 2957, 2917, 2849, 2359, 2342, 2330, 1648, 1593, 1526, 1454, 1354, 1238, 1121, 1040, 945, 860, 789, 754 and 721 cm⁻¹. ¹H NMR: δ 3.75 (s, 3H, N-Me), 7.29 (dt, J = 7.5 and 1.0, 1H, H-6), 7.40 (d, J = 8.4, 1H, H-8), 7.46 (dd, J = 7.7 and 1.5, 1H, H-5), 7.54 (dt, J = 7.9 and 1.4, 1H, H-4'), 7.60–7.70 (m, 3H, H-5', H-6', H-7), 7.40 (d, J = 8.4, 1H, H-8), 7.81 (s, 1H, H-4) and 8.07 (dd, J = 8.1 and 1.3, 1H, H-3'). ¹³C NMR: δ 30.0 (N-Me), 114.3 (C-8), 120.5 (C-4a), 122.4 (C-6), 124.9 (C-3'), 129.0 (C-6'), 129.1 (C-4'), 130.9 (C-7), 131.5 (C-1'),* 131.9 (C-5), 132.0 (C-3), 133.1 (C-5'),* 136.4 (C-4), 140.0 (C-8a), 149.5 (C-2') and 160.5 (C=O).

3-(2-Aminophenyl)-1-methylquinolin-2(1*H*)-one (**19**)^{12g,h}

A stirred solution of **14** (120 mg, 0.45 mmol) in EtOH : H₂O (10 : 1 v/v, 8 mL) was treated with NH₄Cl (16.8 mg, 0.315 mmol) and iron powder (138.6 mg, 2.48 mmol). The mixture was heated to reflux for 3 h, when it was allowed to cool to room temperature and filtered. The filtrate was diluted with brine (10 mL) and organic products were extracted with EtOAc (4 \times 10 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue was passed through a short plug of silica gel, affording **19** (102 mg, 96%), as a solid, mp 163–165 °C (lit.: 172–174 °C).^{11b} IR (KBr, film): 3416, 3335, 3223, 2916, 2849, 2361, 2328, 1643, 1584, 1568, 1557, 1495, 1454, 1304, 1236, 1038, 945, 789, 750 and 656 cm⁻¹. ¹H NMR: δ 3.82 (s, 3H, N-Me), 4.18 (br s, 2H, NH₂), 6.79 (d, J = 7.7, 1H, H-3'), 6.85 (dt, J = 7.7, 1H, H-4'), 7.15–7.21 (m, 1H, H-5'), 7.22 (dd, J = 7.4 and 1.2, 1H, H-6'), 7.28

(dt, J = 7.5 and 0.8, 1H, H-6), 7.41 (d, J = 8.5, 1H, H-8), 7.55–7.65 (m, 1H, H-7), 7.61 (d, J = 7.5, 1H, H-5) and 7.80 (s, 1H, H-4). ¹³C NMR: δ 30.1 (N-Me), 114.1 (C-8), 117.2 (C-3'), 119.0 (C-4'), 120.7 (C-4a), 122.5 (C-6), 124.5 (C-3), 129.0 (C-5), 129.4 (C-6'), 130.5 (C-7), 131.2 (C-5'), 132.6 (C-1'), 139.5 (C-4), 139.5 (C-8a), 145.8 (C-2') and 161.2 (C=O).

Neocryptolepine (**1**)

POCl₃ (0.1 mL, 1.08 mmol) was added dropwise to a stirred solution of **19** (85 mg, 0.36 mmol) in MeCN (4 mL) at 0 °C, the tube was sealed and the mixture was heated overnight at 90 °C. After evaporation of the solvent and the POCl₃, the residue was treated with a solution of DIPEA (0.35 mL, 6.48 mmol) in MeCN (4 mL) and the reaction was heated overnight at 120 °C in a sealed tube. After evaporation of the solvent and the DIPEA, the residue was chromatographed to give **1** (50 mg, 63%), as a deep orange solid, mp 104–106 °C (lit.: 104–106 °C).^{8b} IR (KBr, ν): 3528, 3462, 3422, 3404, 3383, 3366, 2918, 2800, 2400, 1951, 1750, 1647, 1558, 1419, 1203, 1101, 1061 and 746 cm⁻¹. ¹H NMR: δ 4.37 (s, 3H, N-Me), 7.24 (ddd, J = 7.6, 7.4 and 1.1, 1H, H-9), 7.42–7.48 (m, 1H, H-2), 7.55 (ddd, J = 7.4, 7.2 and 1.2, 1H, H-8), 7.73–7.79 (m, 3H, H-3, H-4 and H-7), 8.00 (d, J = 7.9, 1H, H-1), 8.05 (d, J = 7.6, 1H, H-10) and 8.54 (s, 1H, H-11). ¹³C NMR: δ 33.3 (N-Me), 114.1 (C-4), 117.7 (C-7), 119.9.4 (C-9), 120.8 (C-11a), 121.0 (C-10), 121.9 (C-2), 124.0 (C-10a), 128.1 (C-11), 128.2 (C-10b), 129.3 (C-8), 130.0 (C-1), 130.4 (C-3), 137.0 (C-4a) and 155.4 (C-6a). The spectroscopic data of the synthetic compound were in full agreement with those of the literature.

Acknowledgements

The authors gratefully acknowledge Secretaría de Ciencia y Tecnología de la UNR (SECyT-UNR), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), and Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT), Projects BIO457, PIP No. 2012-0471 and PICT No. 2011-0455, respectively, for financial support. M. V. M. and D. A. H. also thank CONICET for their fellowships.

Notes and references

- (a) A. A. Appiah, The Golden Roots of *Cryptolepis sanguinolenta*, in *Chemistry and Quality - African Natural Plant Products: New Discoveries and Challenges*, ACS, Washington, D.C., 2009, ch. 13, pp. 231–239; (b) F. R. Irvine, in *Woody Plants of Ghana*, Oxford University Press, London, 1961; (c) P. T. Parvatkar and S. G. Tilve, Bioactivities and synthesis of indoloquinoline alkaloids: cryptolepine, isocryptolepine and neocryptolepine, in *Bioactive Heterocycles: Synthesis and Biological Evaluation*, ed. K. L. Ameta, R. P. Pawar and A. J. Domb, Nova Science Publishers, 2012, ch. 10, pp. 218–233.
- (a) P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *Curr. Org. Chem.*, 2011, **15**, 1036–1057; (b) J. Lavrado, R. Moreira and A. Paul, *Curr. Med. Chem.*, 2010, **17**, 2348–2370; (c) L. R. Whittell, K. T. Batty, R. P. M. Wong, E. M. Bolitho,



- S. A. Fox, T. M. E. Davis and P. E. Murray, *Bioorg. Med. Chem.*, 2011, **19**, 7519–7525; (d) J. Lavrado, G. G. Cabal, M. Prudêncio, M. M. Mota, J. Gut, P. J. Rosenthal, C. Díaz, R. C. Guedes, D. J. V. A. dos Santos, E. Bichenkova, K. T. Douglas, R. Moreira and A. Paulo, *J. Med. Chem.*, 2011, **54**, 734–750.
- 3 (a) M. H. M. Sharaf, P. L. Schiff Jr, A. N. Tackie, C. H. Phoebe Jr and G. E. Martin, *J. Heterocycl. Chem.*, 1996, **33**, 239–243; (b) S. D. Ablordeppey, C. D. Hufford, R. F. Borne and D. Dwuma-Badu, *Planta Med.*, 1990, **56**, 416–417; (c) A. N. Tackie, M. H. M. Sharaf, P. L. Schiff Jr, G. L. Boye, R. C. Crouch and G. E. Martin, *J. Heterocycl. Chem.*, 1991, **28**, 1429–1435; (d) D. Dwuma-Badu, J. S. K. Ayim, N. Y. Y. Fiagbe, J. E. Knapp, P. L. Schiff Jr and D. J. Slatkin, *J. Pharm. Sci.*, 1978, **67**, 433–434; (e) R. C. Crouch, A. O. Davis, T. D. Spitzer, G. E. Martin, M. H. M. Sharaf, P. L. Schiff Jr, C. H. Phoebe and A. N. Tackie, *J. Heterocycl. Chem.*, 1995, **32**, 1077–1080.
- 4 (a) J.-L. Pousset, M.-T. Martin, A. Jossang and B. Bodo, *Phytochemistry*, 1995, **39**, 735–736; (b) C. E. Hadden, M. H. M. Sharaf, J. E. Guido, R. H. Robins, A. N. Tackie, C. H. Phoebe Jr, P. L. Schiff Jr and G. E. Martin, *J. Nat. Prod.*, 1999, **62**, 238–240; (c) D. M. Fort, J. Litvak, J. L. Chen, Q. Lu, P. W. Phuan, R. Cooper and D. E. Bierer, *J. Nat. Prod.*, 1998, **61**, 1528–1530; (d) A. Paulo, E. T. Gomes and P. J. Houghton, *J. Nat. Prod.*, 1995, **58**, 1485–1491.
- 5 (a) G. V. Subbaraju, J. Kavitha, D. Rajasekhar and J. I. Jimenez, *J. Nat. Prod.*, 2004, **67**, 461–462; (b) K. Cimanga, T. De Bruyne, L. Pieters, M. Claeys and A. Vlietnick, *Tetrahedron Lett.*, 1996, **37**, 1703–1706.
- 6 (a) M. H. M. Sharaf, P. L. Schiff Jr, A. N. Tackie, C. H. Phoebe Jr, L. Howard, C. Myers, C. E. Hadden, S. K. Wrenn, A. O. Davis, C. W. Andrews, D. Minick, R. L. Johnson, J. P. Shockcor, R. C. Crouch and G. E. Martin, *Magn. Reson. Chem.*, 1995, **33**, 767–778; (b) A. N. Tackie, G. L. Boye, M. H. M. Sharaf, P. L. Schiff Jr, R. C. Crouch, T. D. Spitzer, R. L. Johnson, J. Dunn, D. Minick and G. E. Martin, *J. Nat. Prod.*, 1993, **56**, 653–670; (c) K. Blinov, M. Elyashberg, E. R. Martirosian, S. G. Molodtsov, A. J. Williams, A. N. Tackie, M. H. M. Sharaf, P. L. Schiff Jr, R. C. Crouch, G. E. Martin, C. E. Hadden, J. E. Guido and K. A. Mills, *Magn. Reson. Chem.*, 2003, **41**, 577–584; (d) M. H. M. Sharaf, P. L. Schiff Jr, A. N. Tackie, C. H. Phoebe Jr, R. L. Johnson, D. Minick, C. W. Andrews, R. C. Crouch and G. E. Martin, *J. Heterocycl. Chem.*, 1996, **33**, 789–797.
- 7 (a) F. Ahmed, K. Toume, T. Ohtsuki, M. Rahman, S. K. Sadhu and M. Ishibashi, *Phytother. Res.*, 2011, **25**, 147–150; (b) S. W. Yang, M. Abdel-Kader, S. Malone, M. C. M. Werkhoven, J. H. Wisse, I. Bursuker, K. Neddermann, C. Fairchild, C. Raventos-Suárez, A. T. Menendez, K. Lane and D. G. I. Kingston, *J. Nat. Prod.*, 1999, **62**, 976–983; (c) E. Clinquart, *Bull. Acad. R. Med. Belg.*, 1929, **9**, 627–635.
- 8 (a) S. J. Holt and V. Petrow, *J. Chem. Soc.*, 1948, 922–924; (b) L. Kaczmarek, R. Balicki, P. Nantka-Namirski, W. Peczyńska-Czoch and M. Modarsski, *Arch. Pharm.*, 1988, **321**, 463–467; (c) W. Peczyńska-Czoch, F. Pognan, L. Kaczmarek and J. Boratynski, *J. Med. Chem.*, 1994, **37**, 3503–3510; (d) K. Kamienska-Trela, L. Kania and L. Kaczmarek, *THEOCHEM*, 1995, **347**, 467–476; (e) S. P. Lathrop, M. Pompeo, W.-T. T. Chang and M. Movassaghi, *J. Am. Chem. Soc.*, 2016, **138**, 7763–7769; (f) J. Belmar and R. L. Funk, *J. Am. Chem. Soc.*, 2012, **134**, 16941–16943; (g) K. Popov, A. Hoang and P. Somfai, *Angew. Chem.*, 2016, **128**, 1833–1836.
- 9 (a) A. B. J. Bracca, D. A. Heredia, E. L. Larghi and T. S. Kaufman, *Eur. J. Org. Chem.*, 2014, 7979–8003; (b) E. L. Larghi, A. B. J. Bracca, A. A. Arroyo Aguilar, D. A. Heredia, J. L. Pergomet, S. O. Simonetti and T. S. Kaufman, *Curr. Top. Med. Chem.*, 2015, **17**, 1683–1707.
- 10 (a) R. Engqvist and J. Bergman, *Org. Prep. Proced. Int.*, 2004, **36**, 386–390; (b) S. Sharma and B. Kundu, *Tetrahedron Lett.*, 2008, **49**, 7062–7065; (c) P. T. Parvatkar and S. G. Tilve, *Tetrahedron Lett.*, 2011, **52**, 6594–6596; (d) G. A. Kraus and H. Guo, *Tetrahedron Lett.*, 2010, **51**, 4137–4139; (e) M. K. Vecchione, A. X. Sun and D. Seidel, *Chem. Sci.*, 2011, **2**, 2178–2181.
- 11 (a) T. Dhanabal, R. Sangeetha and P. S. Mohan, *Tetrahedron*, 2006, **62**, 6258–6263; (b) G. Timari, T. Soos and G. Hajós, *Synlett*, 1997, 1067–1068; (c) S. Hostyn, K. A. Tehrani, F. Lemièrre, V. Smout and B. U. W. Maes, *Tetrahedron*, 2011, **67**, 655–659.
- 12 (a) C. Shi, Q. Zhang and K. K. Wang, *J. Org. Chem.*, 1999, **64**, 925–932; (b) T.-L. Ho and D.-G. Jou, *Helv. Chim. Acta*, 2002, **85**, 3823–3827; (c) P. T. Parvatkar, P. S. Parameswarana and S. G. Tilve, *Tetrahedron Lett.*, 2007, **48**, 7870–7872; (d) M. J. Haddadin, R. M. B. Zerdan, M. J. Kurth and J. C. Fettingner, *Org. Lett.*, 2010, **12**, 5502–5527; (e) D. Basavaiah and D. Mallikarjuna Reddy, *Org. Biomol. Chem.*, 2012, **10**, 8774–8777; (f) P. Pitchai, M. Yathisateelan, A. Nepolraj and R. M. Gengan, *Indian J. Biochem. Biophys.*, 2015, **54**, 1290–1292; (g) P. M. Fresneda, P. Molina and S. Delgado, *Tetrahedron Lett.*, 1999, **40**, 7275–7278; (h) P. M. Fresneda, P. Molina and S. Delgado, *Tetrahedron*, 2001, **57**, 6197–6202; (i) T. H. M. Jonckers, S. van Miert, K. Cimanga, C. Bailly, P. Colson, M.-C. De Pauw-Gillet, H. van den Heuvel, M. Claeys, F. Lemièrre, E. L. Esmans, J. Rozenski, L. Quirijnen, L. Maes, R. Dommissie, G. L. F. Lemièrre, A. Vlietnick and L. Pieters, *J. Med. Chem.*, 2002, **45**, 3497–3508; (j) M. Miller, J. C. Vogel, W. Tsang, A. Merrit and D. J. Procter, *Org. Biomol. Chem.*, 2009, **7**, 589–597.
- 13 Formal total syntheses. From indoles: (a) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *J. Org. Chem.*, 2008, **73**, 5558–5565; (b) H. K. Kadam, P. T. Parvatkar and S. G. Tilve, *Synthesis*, 2012, **44**, 1339–1342; (c) G. S. M. Sundaram, C. Venkatesh, U. K. Syam Kumar, H. Ila and H. Junjappa, *J. Org. Chem.*, 2004, **69**, 5760–5762; (d) P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *J. Org. Chem.*, 2009, **74**, 8369–8372; (e) R. Ghorbani-Vaghei and S. M. Malaekhepoor, *Tetrahedron Lett.*, 2012, **53**, 4751–4753; (f) H. K. Kadam and S. G. Tilve, *J. Heterocycl. Chem.*, 2016, **53**, 2066–2069; From quinolones: (g) B. Bogányi and J. Kámán, *Tetrahedron*, 2013, **69**, 9512–9519. From



- benzenoids: (h) M. Alajarín, P. Molina and A. Vidal, *J. Nat. Prod.*, 1997, **60**, 747–748.
- 14 (a) O. Amiri-Attou, T. Terme and P. Vanelle, *Synlett*, 2005, 3047–3050; (b) S. Ali, Y.-X. Li, S. Anwar, F. Yang, Z.-S. Chen and Y.-M. Liang, *J. Org. Chem.*, 2012, **77**, 424–431; (c) Z. Yan, C. Wan, J. Wan and Z. Wang, *Org. Biomol. Chem.*, 2016, **14**, 4405–4408; (d) S. Badigenchala, V. Rajeshkumar and G. Sekar, *Org. Biomol. Chem.*, 2016, **14**, 2297–2305.
 - 15 S. O. Simonetti, E. L. Larghi, A. B. J. Bracca and T. S. Kaufman, *Org. Biomol. Chem.*, 2012, **10**, 4124–4134.
 - 16 (a) R. H. Dave and B. D. Hosangadi, *Tetrahedron*, 1999, **55**, 11295–11308; (b) A.-H. Li, E. Ahmed, X. Chen, M. Cox, A. P. Crew, H.-Q. Dong, M. Jin, L. Ma, B. Panicker, K. W. Siu, A. G. Steinig, K. M. Stolz, P. A. R. Tavares, B. Volk, Q. Weng, D. Werner and M. J. Mulvihill, *Org. Biomol. Chem.*, 2007, **5**, 61–64; (c) C. Zhang, C. Kanta De and D. Seidel, *Org. Synth.*, 2012, **89**, 274–282.
 - 17 (a) S. Chandrappa, T. Vinaya, T. Ramakrishnappa and K. S. Rangappa, *Synlett*, 2010, 3019–3022; (b) B. Gabriele, G. Salerno, L. Veltri, M. Costa and C. Massera, *Eur. J. Org. Chem.*, 2001, 4607–4613; (c) X. Pang, Z. Lou, M. Li, L. Wen and C. Chen, *Eur. J. Org. Chem.*, 2015, 3361–3369.
 - 18 (a) S. Bhandari and S. Ray, *Synth. Commun.*, 1998, **28**, 765–771; (b) G. Bartoli, M. Bosco, A. Carlone, R. Dalpozzo, E. Marcantoni, P. Melchiorre and L. Sambri, *Synthesis*, 2007, 3489–3496; (c) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347; (d) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31–36; (e) H. Ueki, T. K. Ellis, M. A. Khan and V. A. Soloshonok, *Tetrahedron*, 2003, **59**, 7301–7306; (f) R. J. Ternansky, C. L. Jordan, J. A. Eudaly and J. S. Kasher, *J. Med. Chem.*, 1993, **36**, 2332–2334.
 - 19 M. L. Nielsen, J. V. Pustinger Jr and J. Strobel, *J. Chem. Eng. Data*, 1964, **9**, 167–170.
 - 20 (a) A. V. Aksenov, A. N. Smirnov, N. A. Aksenov, I. V. Aksenova, J. P. Matheny and M. Rubin, *RSC Adv.*, 2015, **5**, 8647–8656; (b) C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927–934.
 - 21 (a) K. K. Park and J. Y. Jung, *Heterocycles*, 2005, **65**, 2095–2105; (b) M. Rowley, J. J. Kulagowski, A. P. Watt, D. Rathbone, G. I. Stevenson, R. W. Carling, R. Baker, G. R. Marshall, J. A. Kemp, A. C. Foster, S. Grimwood, R. Hargreaves, C. Hurley, K. L. Saywell, M. D. Tricklebank and P. D. Leeson, *J. Med. Chem.*, 1997, **40**, 4053–4068.
 - 22 (a) D. V. Kravchenko, Y. A. Kuzovkova, V. M. Kysil, S. E. Tkachenko, S. Maliarchouk, I. M. Okun, K. V. Balakin and A. V. Ivachtchenko, *J. Med. Chem.*, 2005, **48**, 3680–3683; (b) V. V. Mulwad and M. V. Lohar, *J. Heterocycl. Chem.*, 2003, **42**, 2567–2572.
 - 23 (a) X. Bu, L. W. Deady and W. A. Denny, *Aust. J. Chem.*, 2000, **53**, 143–147; (b) *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, Germany, 2nd edn, 2008, pp. 319–321.
 - 24 R. Oberkobusch, *Chem. Ber.*, 1953, **86**, 975–978.
 - 25 (a) S. Yu, Y. Li, X. Zhou, H. Wang, L. Kong and X. Li, *Org. Lett.*, 2016, **18**, 2812–2815; (b) L. Shi and B. Wang, *Org. Lett.*, 2016, **18**, 2820–2823; (c) A. Khorshidi and K. Tabatabaeian, *J. Mol. Catal. A: Chem.*, 2011, **344**, 128–131; (d) C. Venkatesh, G. S. M. Sundaram, H. Ila and H. Junjappa, *J. Org. Chem.*, 2006, **71**, 1280–1283.
 - 26 S. T. Gadge, A. Mishra, A. L. Gajengi, N. V. Shahi and B. M. Bhanage, *RSC Adv.*, 2014, **4**, 50271–50276.
 - 27 (a) R. Bernini, F. Crisante and M. C. Ginnasi, *Molecules*, 2011, **16**, 1418–1425; (b) W.-C. Shieh, S. Dell and O. Repic, *Org. Lett.*, 2001, **3**, 4279–4281.
 - 28 (a) P. Tundo, L. Rossi and A. Loris, *J. Org. Chem.*, 2005, **70**, 2219–2224; (b) P. Tundo, *Pure Appl. Chem.*, 2001, **73**, 1117–1124.
 - 29 (a) E. Chrystiuk and A. Williams, *J. Am. Chem. Soc.*, 1987, **109**, 3040–3046; (b) T. H. Black, S. M. Arrivo, J. S. Schumm and J. M. Knobeloch, *J. Org. Chem.*, 1987, **52**, 5425–5430.
 - 30 (a) J. Fossey, A. Loupy and H. Strzelecka, *Tetrahedron*, 1981, **37**, 1935–1941; (b) M. F. Pereira, V. Thiéry and T. Besson, *Tetrahedron Lett.*, 2007, **48**, 7657–7659; (c) M. J. Reyes, F. Delgado, M. L. Izquierdo and J. Alvarez-Builla, *Tetrahedron*, 2002, **58**, 8573–8579; (d) H. Wu, F. Xue, X. Xiao and Y. Qin, *J. Am. Chem. Soc.*, 2010, **132**, 14052–14054.
 - 31 (a) L. G. Mardenborough, X. Y. Zhu, P. Fan, M. R. Jacob, S. I. Khan, L. A. Walker and S. Y. Ablordeppey, *Bioorg. Med. Chem.*, 2005, **13**, 3955–3963; (b) T.-L. Ho and D.-G. Jou, *Helv. Chim. Acta*, 2002, **85**, 3823–3827; (c) T. K. Lai, A. Chatterjee, J. Banerji, D. Sarkar and N. Chattopadhyay, *Helv. Chim. Acta*, 2008, **91**, 1975–1983.
 - 32 (a) W.-C. Shieh, S. Dell, A. Bach, O. Repic and T. J. Blacklock, *J. Org. Chem.*, 2003, **68**, 1954–1957; (b) S. Ouk, S. Thiébaud, E. Borredon and B. Chabaud, *Synth. Commun.*, 2005, **35**, 3021–3026.
 - 33 (a) T. N. Glasnov, J. D. Holbrey, C. O. Kappe, K. R. Seddon and T. Yan, *Green Chem.*, 2012, **14**, 3071–3076; (b) M. L. Laurila, N. A. Magnus and M. A. Staszak, *Org. Process Res. Dev.*, 2009, **13**, 1199–1201; (c) H. Yan, L. Zeng, Y. Xie, Y. Cui, L. Ye and S. Tu, *Res. Chem. Intermed.*, 2016, **42**, 5951–5960.
 - 34 (a) N. Vôte, D. Philp, A. M. Z. Slawin and N. J. Westwood, *Org. Biomol. Chem.*, 2010, **8**, 442–450; (b) Y.-L. Chen, H.-M. Hung, C.-M. Lu, K.-C. Li and C.-C. Tzeng, *Bioorg. Med. Chem.*, 2004, **12**, 6539–6546; (c) H. Mastalarz, R. Jaszold-Howorko, F. Rulko, A. Croisy and D. Carrez, *Arch. Pharm.*, 2004, **337**, 434–439.
 - 35 H. Wagner, S. Blatt and V. Rickl, *Drug Analysis: A Thin Layer Chromatography Atlas*, Springer, Heidelberg, Germany, 2nd edn, 2009, p. 360.

