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A Concise Approach for the Synthesis of the ABCD Ring System of Alpkinidine

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Dedicated to Prof. B. R. Srinivasan on the occasion of his 60th birthday

A two step synthesis of a benzo analog of alpkinidine is described via Negishi coupling followed by a base mediated annulation reaction strategy. The organozinc compound prepared from ethyl 2-iodobenzoate was coupled with 4-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one to obtain ethyl 2-(2-methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-yl)-benzoate which on further treatment with a base provided ABCD ring system of alpkinidine.

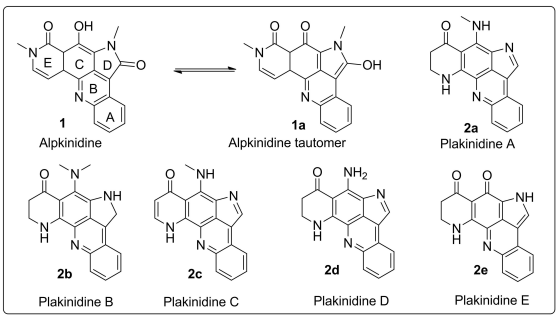

Figure 1. Members of pyrroloacridine family.

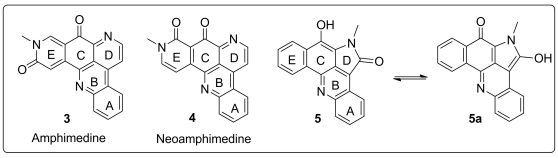

Figure 2. Structurally similar natural products to **1** and it's benzo derivative.

Introduction

Alpkinidine **1** is a purple colored pentacyclic marine natural product belonging to the pyrroloacridine class of alkaloids isolated from marine sponge *Xestospongia* cf. *carbonaria*.[1a] So far the family of pyrroloacridine has only six members including alpkinidine. The other members of this family are plakinidine A–E (Figure 1).[1a–f]

Alpkinidine **1** has an acridine ring (ABC) system fused to a pyridone (E), and pyrrolidone ring (D) at the ring C. Spectroscopic data of alpkinidine is not available due to its limited accessibility and insolubility in most organic solvents. The structure of **1** was finalized based on its X-ray crystallographic analysis.[1a]

The members of this family are not well explored; however, the closely related members of another pyridoacridine class of compounds viz. amphimedine **3**, neoamphimedine **4** and others are comparatively well studied.[2] They are believed to be a co-metabolites of alpkinidine.[1a] Till date over 100 alkaloids are isolated belonging to this family.[2,3] Members of this family display a wide range of biological activities like antiviral, antiparasitic, antifungal, insecticidal, cytotoxic and antibacterial.[2,4] Topoisomerase IIA is an important clinical drug target for the treatment of cancer. Modeling studies have indicated that the CE ring system of neoamphimedine **4** is a vital functionality for binding interaction with Topoisomerase IIA, and selective cytotoxicity towards solid tumor cell lines.[5] The same pharmacore is also present in alpkinidine suggesting that **1** may display similar properties as that of **4**.

Till date to our knowledge, there is no report on the total synthesis of alpkinidine **1**. One report on the synthesis of the pentacyclic core of plakinidine and another on a, structurally similar dimethyl-deoxyamphimedine is available. Kitahara *et al.*[6a] in 2004 reported a route to synthesize the pentacyclic pyrroloacridine framework present in plakinidine A–E alkaloids. Recently in 2014 Bracher *et al.*[6b] developed an interesting route for the synthesis of pyridoacridine alkaloid demethyl-deoxyamphimedine.

For synthetic simplicity and to develop a method we thought of replacing the E ring of alpkinidine with a phenyl ring (**5**). This structure having a fused pentacyclic ring system would also possess the keto-enol tautomerism as shown by alpkinidine.

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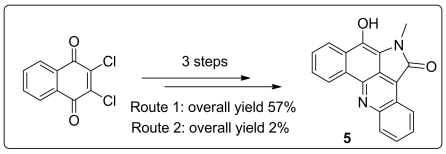
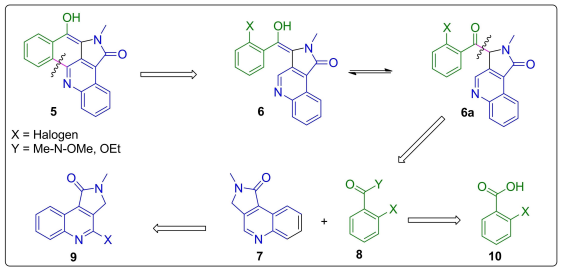
In literature, two successful routes for the synthesis of **5** which contains ABCD ring structure present in alpkinidine are reported by Piggott et al.[7] in 2013 by bisannulation of 2,3-dichloro-1,4-naphthoquinone with *o*-nitrophenylacetic acid derivative in good yield and with oxindole derivative in poor yield (Scheme 1).



Scheme 1. Literature methods for the synthesis of the ABCD ring.

Results and Discussion

In our very initial approach towards the synthesis of **5**, we intended to construct ring 'C' using intramolecular coupling of intermediate **6** *via* metal mediated or radical cyclization.[8] The intermediate **6** can be drawn in its keto form as **6a**, and the synthesis of it could be achieved by acylation of 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **7** with carbonyl compound **8**. Compound **7** could be synthesized by dehalogenation of **9** and **8** could be obtained from 2-iodobenzoic acid **10** (Scheme 2).

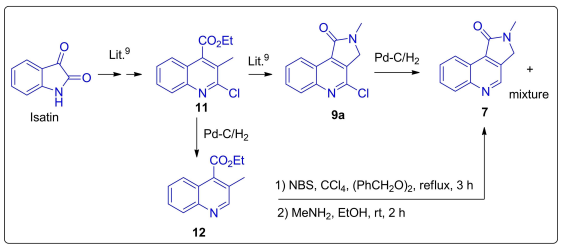


Scheme 2. Retrosynthetic approach to **5**.

The required starting 4-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **9a** was synthesized from isatin using the protocol described by Cappelli *et al.*[9] (Scheme 3).

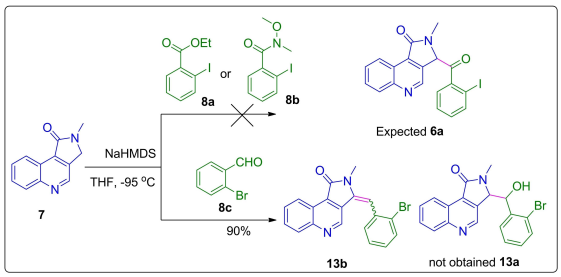
Compound **9a** was subjected to hydrogenolysis over Pd/C at 1 atmosphere for 1 h in ethyl acetate in the presence of triethylamine to get dehalogenated derivative 2-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinolin-1-one **7** (Scheme 3). However, along with the product **7**, some other by-products were forming making the purification tedious. Hence hydrogenolysis of **11** was carried out to get **12** which was then converted to **7** in 46% yield from **11**.

Once compound **6** was synthesized, it was subjected to deprotonation with NaHMDS to give a deep green coloration. Further treatment with ethyl 2-iodobenzoate[10a] **8a** or 2-iodo-



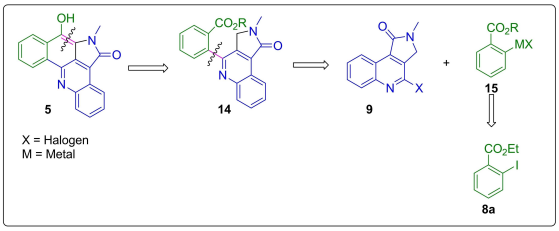
Scheme 3. Synthesis of key intermediate **7**.

N-methoxy-*N*-methylbenzamide[10b,c] **8b** failed to give expected the product **6a**. The result could be due to the failure of the stable anion **7** to react with a less electrophilic ester **8a** or Weinreb amide **8b**. Hence, the reaction was attempted in refluxing THF without any success. However, when the anion was reacted with aldehyde **8c**, it gave the corresponding dehydrated product **13b** whose geometry was not assigned (scheme 4).



Scheme 4. Attempted synthesis **6a**.

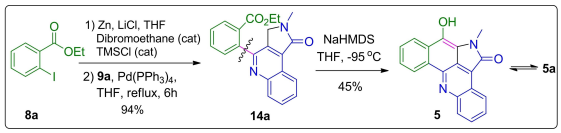
Failure to obtain the required product prompted us to change the strategy. So, it was decided to couple the ring E first and then build the ring C (Scheme 5). Conversion of **14** to



Scheme 5. Retrosynthetic approach 2.

5 was planned using anion chemistry of isoindolinone.[11] The compound **14** in turn could be obtained using coupling methods.

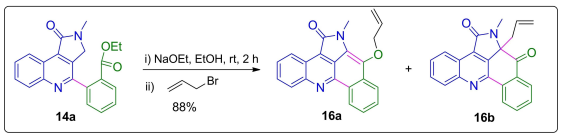
Thus **9a** was coupled to **8a** by Negishi coupling to obtain **14a** in 94% yield (Scheme 6).[12] The **14a** on deprotonation



Scheme 6. Synthesis of **5**.

gave **5** in 45% yields. The structure of **5** was confirmed by comparing with the reported data.[7]

While purification of **5**, by column chromatography a purple colored compound was also eluted. The structure of this purple compound could not be assigned. The slightly less yield (45%) of **5** was attributed to the formation of this purple compound and its lower solubility in most organic solvents. Hence, to increase the yield of this reaction, we thought to isolate it as its alkyl derivative, which would increase the solubility of this compound as well as eliminate the problem of tautomerism (Scheme 7).



Scheme 7. One pot cyclisation and derivatization.

Thus, on treating **14a** with sodium ethoxide at room temperature followed by reaction with allyl bromide gave two distinct compounds **16a** and **16b**. The formation of product **16b** could be accounted *via* C-allylation of intermediate phenoxide ion. As expected the combined yield of **16a** and **16b** increased to 88%.

Conclusions

A concise synthesis of a benzo analog of alpkinidine has been developed using Negishi coupling followed by a base mediated annulation strategy in two steps. The methodology may be useful for the synthesis of ring E analogs of bezoalpkinidine. Further studies towards the synthesis of the alpkidine using the present strategy will be undertaken shortly.

Supporting Information summary

Supporting Information contains details about synthetic procedures, experimental data and soft copies of NMR-spectra.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alpkinidine · Marine alkaloid · Heterocycles · Marine alkaloid · Negishi · Pyrroloacridine

[1] a) Z. Thale, T. Johnson, K. Tenney, P. J. Wenzel, E. Lobkovsky, J. Clardy, J. Media, H. Pietraszkiewicz, F. A. Valeriote, P. Crews, *J. Org. Chem.* **2002**, *67*, 9384–9391; b) W. D. Inman, M. O'Neill-Johnson, P. Crews, *J. Am. Chem. Soc.* **1990**, *112*, 1–4; c) R. R. West, C. L. Mayne, C. M. Ireland, L. S. Brinen, J. Clardy, *Tetrahedron Lett.* **1990**, *31*, 3271–3274; d) P. W. Ford, B. S. Davidson, *J. Nat. Prod.* **1997**, *60*, 1051–1053; e) C. J. Smith, D. A. Venables, C. Hopmann, C. E. Salomon, J. Jompa, A. Tahir, D. J. Faulkner, C. M. Ireland, *J. Nat. Prod.* **1997**, *60*, 1048–1050; f) P. Ralifo, L. Sanchez, N. C. Gassner, K. Tenney, R. S. Lokey, T. A. Holman, F. A. Valeriote, P. Crews, *J. Nat. Prod.* **2007**, *70*, 95–99.

[2] a) T. F. Molinski, *Chem. Rev.* **1993**, *93*, 1825–1838; b) E. Delfourne, J. Bastide, *Med. Res. Rev.* **2003**, *23*, 234–252.

[3] a) D. Skyler, C. H. Heathcock, *J. Nat. Prod.* **2002**, *65*, 1573–1581; b) L. P. Sandjo, V. Kuete, M. W. Biavatti, *Beilstein J. Org. Chem.* **2015**, *11*, 1667–1699; c) G. Gellerman, A. Rudi, Y. Kashman, *Tetrahedron* **1994**, *50*, 12959–12972.

[4] a) C. J. Moody, R. Thomas, *Adv. Heterocycl. Nat. Prod. Synth.* **1992**, *2*, 377–400; b) K. M. Marshall, L. R. Barrows, *Nat. Prod. Rep.* **2004**, *21*, 731–751.

[5] a) J. Ponder, B. H. Yoo, A. D. Abraham, Q. Li, A. K. Ashley, C. L. Amerin, Q. Zhou, B. G. Reid, P. Reigan, R. Hromas, J. A. Nickoloff, D. V. LaBarbera, *Mar. Drugs* **2011**, *9*, 2397–2408; b) K. M. Marshall, S. S. Matsumoto, J. A. Holden, G. P. Concepcion, D. Tasdemir, C. M. Ireland, L. R. Barrows, *Biochem. Pharmacol.* **2003**, *66*, 447–458.

[6] a) Y. Kitahara, T. Mizuno, A. Kubo, *Tetrahedron* **2004**, *60*, 4283–4288; b) B. Melzer, A. Plodek, F. Bracher, *J. Org. Chem.* **2014**, *79*, 7239–7242.

[7] M. Buccini, S. Y. Jeow, L. Byrne, B. W. Skelton, T. M. Nguyen, C. L. L. Chai, M. J. Piggott, *Eur. J. Org. Chem.* **2013**, 3232–3240.

[8] a) W. R. Bowman, M. R. J. Elsegood, T. Stein, G. W. Weaver, *Org. Biomol. Chem.*, **2007**, *5*, 103–113; b) A. Cappelli, M. Anzini, S. Vomero, L. Mennuni, F. Makovec, E. Doucet, M. Hamon, M. C. Menziani, P. G. De Benedetti, G. Giorgi, C. Ghelardinig, C. Collinah, *Bioorg. Med. Chem.* **2002**, *10*, 779–801.

[9] A. Cappelli, A. Gallelli, M. Manini, M. Anzini, L. Mennuni, F. Makovec, M. C. Menziani, S. Alcaro, F. Ortuso, S. Vomero, *J. Med. Chem.* **2005**, *48*, 3564–3575.

[10] a) V. V. Zhdankin, A. Y. Koposov, D. N. Litvinov, M. J. Ferguson, R. McDonald, T. Luu, R. R. Tykwinski, *J. Org. Chem.* **2005**, *70*, 6484–6491; b) V. S. Chan, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 15122–15123; c) K. Kawai, Y. Bunno, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2018**, *24*, 10231–10237.

[11] a) A. Couture, E. Deniau, D. Ionescu, P. Grandclaudon, *Tetrahedron Lett.* **1998**, *39*, 2319–2320; b) Z. Guo, A. G. Schultz, *J. Org. Chem.* **2001**, *66*, 2154–2157; c) C. Hoarau, A. Couture, H. Cornet, E. Deniau, P. Grandclaudon, *J. Org. Chem.* **2005**, *66*, 8064–8069.

[12] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.

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