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A practical entry to C18-constrained-E-ring analogues of methyllycaconitine (MLA): a concise new stereoselective approach to 8-oxa-decahydroisoquinolines accompanied by a simple microwaves-assisted synthesis of the succinimidobenzoate appendage of MLA

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Abstract—A Mannich-type intramolecular cyclization afforded access to a 8-oxa-decahydroisoquinoline heterocyclic system. Good stereoselectivity was observed. A promising microwave-assisted synthesis of the methylsuccinimidobenzoate moiety of methyllycaconitine has also been carried out.

Methyllycaconitine (MLA) (**1**) is a natural competitive nicotinic acetylcholine receptor (nAChR) antagonist isolated and purified from several *Delphinium* an *Aconitum* plants.[1] Its structure is based on a hexacyclic norditerpenoid (lycoctonine) esterified at C-18 with a 2-[(*S*)-methylsuccinimido]benzoyl moiety.

MLA (**1**) displays particularly high affinity for the α7-subtype nAChRs, thus appearing an intriguing pharmacological tool, as well as a potential lead compound for the rational design of new nAChR selective ligands.[2] Structurally less complex analogues of MLA,[3a–d] bearing an homocholine backbone corresponding to the E-ring of lycoctonine and the *N*-methylsuccinylanthranilate moiety, have been recently synthesized that are endowed with interesting pharmacological properties.[3e–h]

In this context, in order to explore new areas of structural alteration of MLA with the aim to obtain potent nAChRs antagonists, we believed that it would be informative to study conformationally restricted E-ring analogues of the natural compound. Accordingly, we introduced a new ring as a replacement of the norditerpenoid fragment of MLA, thus obtaining C-18-constrained-E-ring analogues, such as compounds **2a**,**b** and **3a**,**b**, based on a decahydroisoquinoline framework (Fig. 1).

With this aim, we needed to obtain the alcoholic precursors **4a**,**b** and **5a**,**b** (Fig. 2) in appreciable amounts. The synthesis of **4a** and **5a** starting from **6** as described in the literature (PtO_2-catalyzed hydrogenation),[4] while straightforward, was quite expensive since equimolar amounts of the catalyst were used. An additional published synthesis of **5a** required many synthetic steps and, in some cases, expensive reagents were also used.[5] As we needed access to large amounts of the advanced intermediates **4a**,**b** and **5a**,**b**, a more efficient approach starting from inexpensive starting materials was devised. We speculated that a rational entry to the desired compounds could involve a Mannich-type intramolecular

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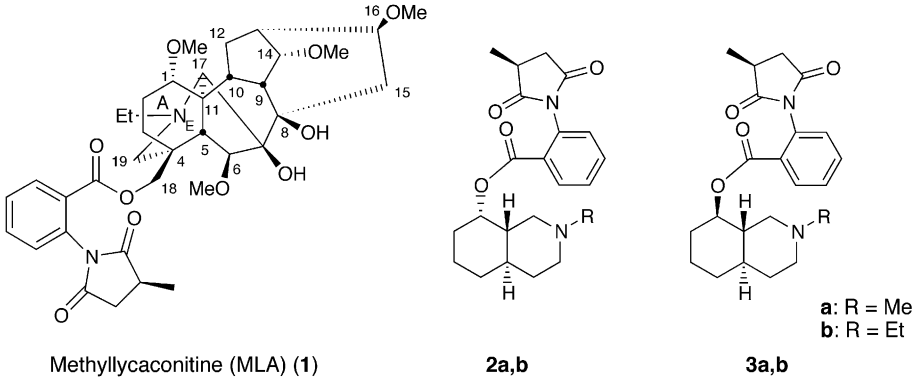


Figure 1. Natural MLA and C-18 constrained analogues.

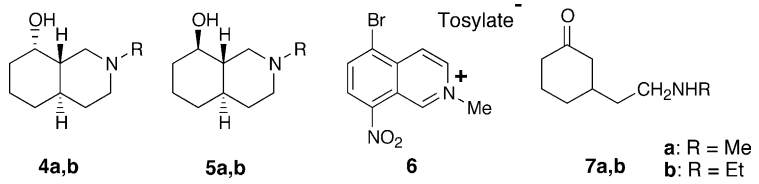


Figure 2. Synthetic precursors for decahydroisoquinoline moieties.

cyclization of the aminoketones **7a**,**b**. It was then apparent that the 3-oxocyclohexyl-acetic acid ethyl ester (**10**, Scheme 1) could constitute a suitable and common starting material. The value of our approach is exemplified in a five-step synthetic route that provided the 8-oxa-2-alkyl-decahydroisoquinolines **13a**,**b** in a very good overall yield.

Briefly, magnesium ethyl malonate (**9**) (Scheme 1) underwent facile Michael addition to 2-cyclohexenone (**8**) and the resulting malonate mono ethyl ester intermediate was decarboxylated by means of warm acetic acid (McMurry's procedure).[6] Protection of the ketone **10** as its ethylene acetal allowed its subsequent conversion into amides **11a**,**b** by simple treatment with aqueous amines.[7] Reduction of **11a**,**b** to the amines **12a**,**b** was performed in about 90% yield with $LiAlH_4$ in THF at rt. Heating a dilute solution of **12a**,**b** and paraformaldehyde in 2% sulfuric acid for 24 h afforded with stereoselectivity the *trans*-decahydroisoquinolines **13a**,**b** in 48–53% yield.[8,9] In summary, our approach provided a simple and productive five-stage approach to the 8-oxa-decahydroisoquinoline system by means of inexpensive materials and the overall yield was in the range 28–30%.

Having secured good access to compounds **13a**,**b**, an efficient coupling reaction with the *N*-succinyl anthranilate appendage to obtain the desired **2a**,**b** and **3a**,**b** was required. Thus, after the $NaBH_4$-mediated reduction of **13a**,**b** afforded a 3/7 mixture of the corresponding epimer alcohols **4a**,**b** and **5a**,**b** in 95% yield, these intermediates were then reacted with the 2-nitrobenzoylchloride to give the corresponding nitro derivatives **14a**,**b** and **15a**,**b**, which were then reduced by means of hydrogen in presence of 5% Pd/C affording the anthranilate derivatives **16a**,**b** and **17a**,**b** (Fig. 3) in approximately 85% overall yield. Relative stereochemistry in decahydroisoquinoline ring was established with NOE experiments on **14a** and **15a**.[9]

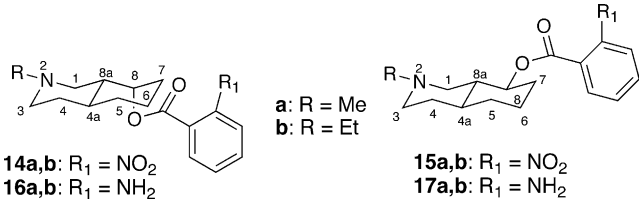
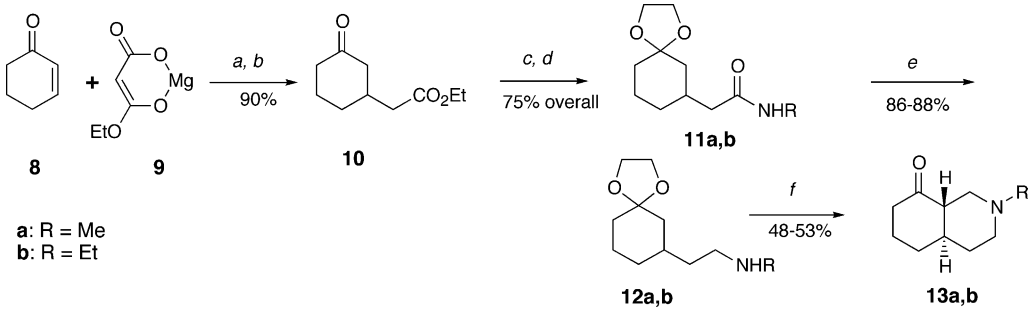
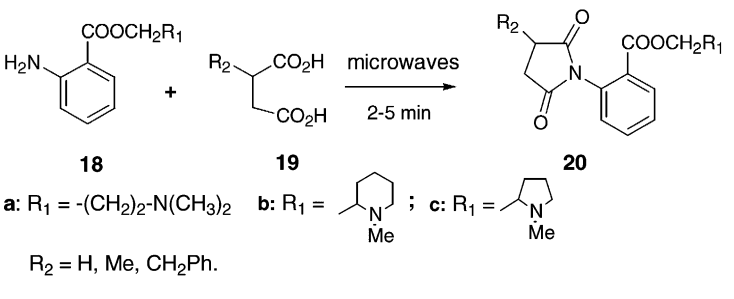


Figure 3. Synthetic intermediates for MLA derivatives.



Scheme 1. Reagents and conditions: (a) DMF, 60 °C; (b) AcOH, Δ; (c) ethylene glycol, H^+, Δ; (d) aq RNH_2; (e) $LiAlH_4$, THF, rt; (f) 1,3,5-trioxane, 2% H_2SO_4, Δ.



Yields %			
R_1/R_2	a	b	c
H	48	54	41
Me	52	52	50
Benzyl	21	28	

Scheme 2.

Conversion into the desired imides **2a**,**b** and **3a**,**b** was attempted under a variety of conditions, mainly by fusion with methylsuccinic anhydride, resulting in poor yields of the desired compounds (3–5%). Taking into account the low yield achieved applying some described procedures,[3f] we exploited the possibility to perform this type of transformation using microwave-assisted chemistry.[10]

The reaction between **16a**,**b** and **17a**,**b** and (*S*)-methylsuccinic acid in absence of solvent proceeds efficiently affording the desired diastereoisomers **2a**,**b** and **3a**,**b** in few minutes and 30–40% yields.

The microwave irradiation was then used for the preparation of a small array of simplified succinimidobenzoate analogues **20** (Scheme 2), by heating 2 equiv of the different di-carboxylic acid derivatives **19**, typically for 2–5 min in a domestic microwave oven, with the appropriate amines **18**. The isolated yields of the 2-succinimidobenzoates **20** were in the range 21–54% as described in Scheme 2.

In summary, an efficient and cost effective synthesis of 8-hydroxydecahydroisoquinolines derivatives has been described. The results of the proposed approach are satisfactory being **13a**,**b** obtained in 28–30% overall yield, thus securing a facile access to the desired **2a**,**b** and **3a**,**b** and allowing the gram scale synthesis of the advanced intermediates **4a**,**b** and **5a**,**b** for further structure–activity relationship exploration and single enantiomers biological evaluation.

Moreover, the microwave-assisted introduction of the succinimidobenzoate moiety, the appendage of methyllicaconitine, appears to be a useful access to imide derivatives as well as also of extreme importance for the preparation of quantities of MLA analogues bearing differently substituted ester side chains. Further synthetic activities aimed to optimize and extend the microwave-assisted technique as well as to generate a succinimidobenzoate library in order to further investigate MLA structure–activity relationships are currently ongoing in our laboratory.

Acknowledgements

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References and notes

1. (a) Manske, R. H. F. *Can. J. Res.* **1938**, *16B*, 57; (b) Atta-ur-Rahman; Choudhary, M. I. *Nat. Prod. Rep.* **1997**, *14*, 191–203; (c) Ward, J. M.; Cockroft, V. B.; Lunt, G. G.; Smillie, F. S.; Wonnacott, S. *FEBS Lett.* **1990**, *270*, 45.
2. Schmitt, J. D. *Curr. Med. Chem.* **2000**, *7*(8), 749–800.
3. (a) Coates, P. A.; Blagbrough, I. S.; Rowan, M. G.; Pearson, D. P. J.; Lewis, T.; Potter, B. V. L. *J. Pharm. Pharmacol.* **1996**, *48*, 210–213; (b) Grangier, G.; Trigg, W. J.; Lewis, T.; Rowan, M. G.; Potter, B. V. L.; Blagbrough, I. S. *Tetrahedron Lett.* **1998**, *39*, 889–892; (c) Kraus, G. A.; Dneprovskaia, E. *Tetrahedron Lett.* **1998**, *39*, 2451–2454; (d) Baillie, L. C.; Bearder, J. R.; Li, W.-S.; Sherringham, J. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4047–4055; (e) Doisy, X.; Blagbrough, I. S.; Wonnacott, S.; Potter, B. V. L. *Pharm. Pharmacol. Commun.* **1998**, *4*, 313–317; (f) Bergmeier, S. C.; Lapinsky, D. J.; Free, R. B.; McKay, D. B. *Bioorg. Med: Chem. Lett.* **1999**, *9*, 2263–2266; (g) Bryant, D. L.; Free, R. B.; Thomasy, S. M.; Lapinsky, D. J.; Ismail, K. A.; McKay, S. B.; Bergmeier, S. C.; McKay, D. B. *Neurosci. Res.* **2002**, *42*, 57–63; (h) Ismail, K. A.; Bergmeier, S. C. *Eur. J. Org. Chem.* **2002**, *37*, 469–474.
4. Mathison, I. W.; Morgan, P. H. *J. Org. Chem.* **1974**, *39*(22), 3210–3215.
5. (a) Kimoto, S.; Okamoto, M. *Chem. Pharm. Bull.* **1962**, *10*, 362–365; (b) Okamoto, M. *Chem. Pharm. Bull.* **1967**, *15*, 168–172.
6. (a) McMurry, J. E.; Andrus, W. A.; Musser, J. H. *Synth. Commun.* **1978**, *8*(1), 53–57; (b) Pollet, P.; Gelin, S. *Synthesis* **1978**, 142–143.
7. Milcent, R.; Akhnazarian, A.; Lensen, N. *J. Heterocycl. Chem.* **1996**, *33*, 1829–1833.
8. Mannich-type cyclization. To a solution of 1,3,5-trioxane (673 mg, 7.5 mmol) in 100 mL of sulfuric acid 2% heated to reflux is added during 3 h a solution of 1,1-ethylenedioxy-3-methylaminoethylcyclohexane (1 g, 5.02 mmol) in ethanol (5 mL). The reflux is maintained for 24 h. After cooling, the solution is washed with dichloromethane (2×30 mL), basified with NaOH 40% (5 mL) and extracted with other dichloromethane (2×30 mL). The combined organic layers are dried over Na_2O_4 and concentrated. Chromatographic purification (chloroform/methanol 20/1) gives **13a** as an oil 400 mg (yield 48%). ^{1}H NMR: ($CDCl_3$) δ 3.05 (m, 1H) 2.86 (m, 1H) 2.39–2.20 (m, 3H) 2.30 (s, 3H) 2.18–2.05 (m, 1H) 1.96–1.25 (m, 8H).
9. Stereochemistry for compound **15a** has been assigned based on both coupling constant pattern and NOE effect. Proton 8 is a doublet of triplets, with two *trans* diaxial coupling constants (*J*–10.7 Hz) and an axial–equatorial one (*J*–4.5 Hz): protons 8 and 8a are both axial thus indicating a relative *trans* configuration. NOE effects are observed between H8 and H6(ax) and H4a, thus indicating

a *trans* configuration between position 8a and 4a. Stereochemistry for compound **14a** has been assigned for comparison with the isomer **15a** and confirmed by coupling constant pattern of proton 8.

10. (a) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2000**, *9*, 1251–1283; (b) Sejias, J. A.; Vàzquez-Tato, M. P.; Montserrat Martìnez, M.; Nùnez-Corredoira, G. *J. Chem. Res.* **1999**, 420–421.