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Stereoselective synthesis of (−)-lepadins A–C†

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Cite this: *Chem. Commun.*, 2013, **49**, 11032

Received 5th September 2013,
Accepted 5th October 2013

DOI: 10.1039/c3cc46801a

www.rsc.org/chemcomm

A concise synthesis of the marine alkaloids (−)-lepadins A–C from a phenylglycinol-derived tricyclic lactam is reported. Key steps from the stereochemical standpoint involve stereoselective cyclocondensation, double bond hydrogenation, oxazolidine opening, hydroboration–oxidation, and Horner–Wadsworth–Emmons reactions.

The lepadin alkaloids are a small group of *cis*-decahydroquinoline alkaloids isolated during the period 1991–2002 from different marine sources such as the tunicate *Clavelina lepadiformis*[1] and its predator the flatworm *Prostheceraeus vittatus*,[1b] as well as the Australian Great Barrier Reef tunicate *Didemnum* sp.[2] and ascidian *Aplidium tabascum*.[3] Structurally, all of them incorporate a methyl substituent at the C-2 position of the decahydroquinoline nucleus, a functionalized eight-carbon chain at C-5, and a free or acylated hydroxy group at C-3. However, they display a diversified array of relative stereochemical relationships (Fig. 1). Lepadins A and B have been shown to exhibit significant *in vitro* cytotoxicity against several human cancer cell lines.[1b] In addition, lepadin B is a potent blocker for neuronal nicotinic acetylcholine receptors.[4] Lepadins D–F exhibit low cytotoxicity but significant and selective antiplasmodial and antitrypanosomal activity.[2] Further pharmacological research on these alkaloids has been hampered by the low quantities of samples available from natural sources. This has stimulated considerable synthetic effort in this area,[5] although the development of facile enantioselective routes to lepadins or synthetic analogs is still required.

In the context of our studies[6] on the use of phenylglycinol-derived chiral tricyclic lactams for the enantioselective synthesis of alkaloids, we present herein a straightforward synthesis of (−)-lepadins A–C.

Our approach takes advantage of unsaturated tricyclic lactams **B**, functionalized platforms that are assembled in a straightforward manner by a cyclocondensation reaction between (*R*)-phenylglycinol and an appropriate cyclohexenone-derived δ-keto ester **A**. As outlined in Scheme 1, the synthesis of lepadins A–C from lactams **B** would involve (i) the stereoselective hydrogenation of the C–C double bond to obtain the required configuration at C-5, (ii) the stereoselective opening of the oxazolidine ring to give the natural *cis*-decahydroquinoline stereochemistry, (iii) the stereoselective introduction of the C-2 methyl and C-3 hydroxy substituents, taking advantage of the lactam carbonyl, and (iv) the elongation of the C-5 side chain.

As a model system for evaluating the viability of our strategy, we selected the known[6] lactam **1**, which lacks the functionalized

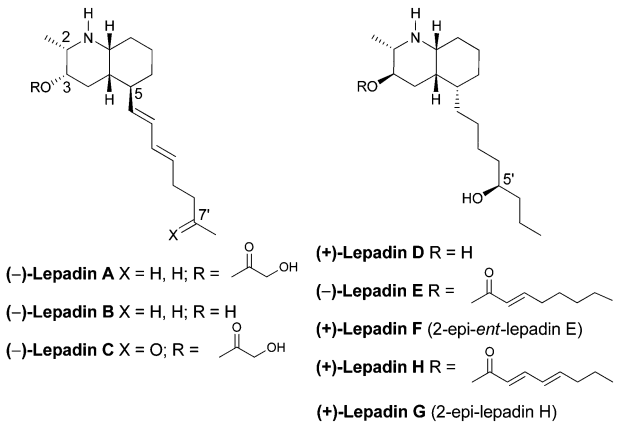
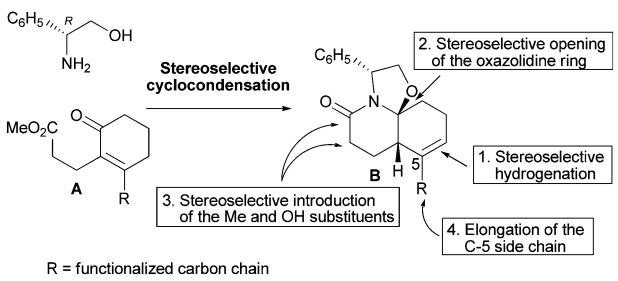


Fig. 1 Lepadin alkaloids.



Scheme 1 Synthetic strategy.

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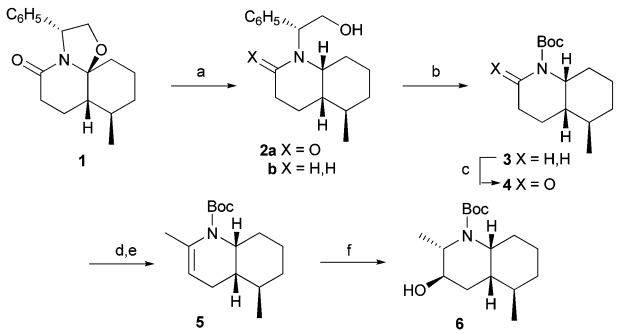
† Electronic supplementary information (ESI) available: Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/c3cc46801a



Scheme 2 Model studies. *Reagents and conditions*: (a) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 30 min, then −78 °C, 1.5 h and rt, 3 h, 79%; (b) H_2, $Pd(OH)_2$, $(Boc)_2O$, MeOH, rt, 20 h, 72%; (c) $RuCl_3{\cdot}nH_2O$, $NaIO_4$, CCl_4–CH_3CN–H_2O, 0 °C, 5 min, then rt 1 h, 73%; (d) LiHMDS, THF, −78 °C, 2 h; 5-Cl-2-NTf_2-Pyr, THF, then rt, 1.5 h, 95%; (e) CuI, MeLi, THF, −20 °C, 30 min, −78 °C, then rt, 16 h; (f) $BH_3{\cdot}SMe_2$, THF, −78 °C, then rt, 16 h, then $Me_3NO{\cdot}2H_2O$, THF, reflux, 45 min, 78% (steps e and f).

carbon chain at C-5 but bears a methyl substituent instead. Slightly disappointingly, reductive cleavage of the oxazolidine C–O bond using Et_3SiH–$TiCl_4$ took place with only moderate stereoselectivity, leading to decahydroquinolone **2a** as a 5 : 1 mixture of *cis*–*trans* epimers. A great improvement was achieved by using $LiAlH_4$–$AlCl_3$ as the reductant, *cis*-decahydroquinoline **2b** being stereoselectively obtained under these conditions. Although alane additionally caused the reduction of the lactam carbonyl, this functionality was satisfactorily reinstalled, after *N*-debenzylation with simultaneous *N*-Boc protection, by ruthenium-promoted oxidation[7] of *N*-Boc derivative **3** (Scheme 2). From the resulting *N*-protected lactam **4**, the introduction of the C-2 methyl substituent was accomplished *via* the corresponding vinyl triflate, prepared by Comins' protocol, by reaction with lithium dimethylcuprate.[8] With enecarbamate **5** in hand, hydroboration with the $BH_3{\cdot}SMe_2$ complex[9] and subsequent oxidation of the intermediate borane with trimethylamine *N*-oxide[10] stereoselectively provided alcohol **6** in excellent overall yield. The facial selectivity, with exclusive formation of the H-2/H-8a *cis* isomer, was not unexpected as it involves the *syn* addition of borane from the less hindered face of the double bond, *via* a transition state in which the C_8–C_{8a} bond is axially oriented to avoid the $A^{(1,3)}$ strain (Fig. 2).

The application of the above strategy to the synthesis of (−)-lepadins A–C required starting from a tricyclic lactam bearing a functionalized carbon chain, for instance a protected hydroxymethyl substituent, at the 5 position of the quinoline ring. The overall synthetic sequence is outlined in Scheme 3. Such a lactam, **8**, was prepared in two steps by cyclocondensation of δ-keto ester **7**[11] with (*R*)-phenylglycinol followed by catalytic hydrogenation of the resulting unsaturated tricyclic lactams.[12] The conversion of **8**, which possesses the appropriate configuration at the 4a and 5 positions of the hydroquinoline ring, to alcohol **12** was

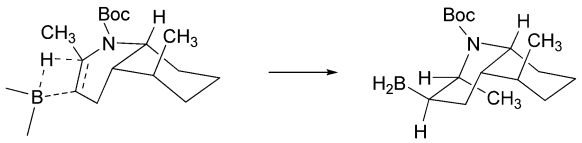
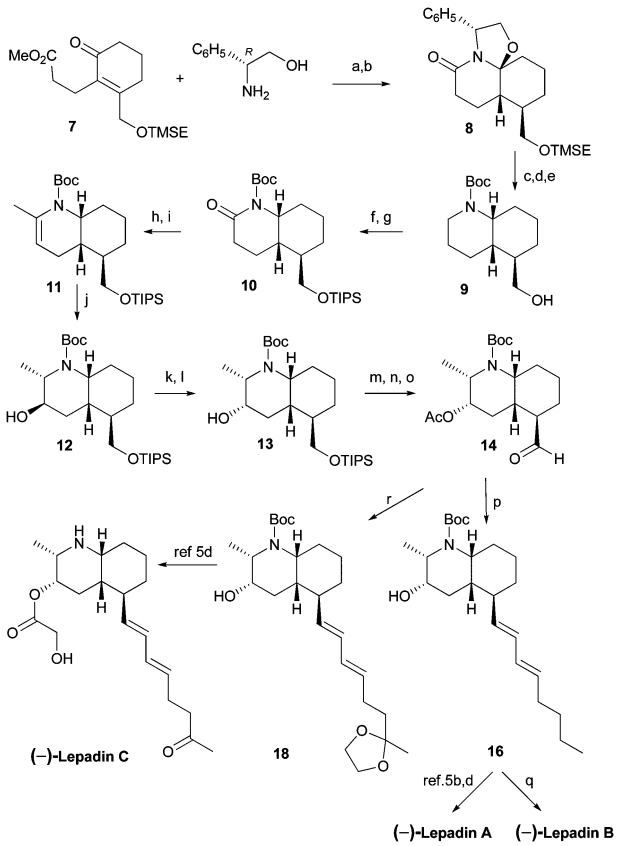


Fig. 2 Stereoselectivity of the hydroboration reaction.



Scheme 3 Enantioselective synthesis of (−)-lepadins A–C. *Reagents and conditions*: (a) AcOH, benzene, reflux, 72 h; (b) H_2, Pt_2O, MeOH, 5 h, 67% (steps a and b); (c) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 30 min, then −78 °C, 1.5 h and rt, 3 h, 76%; (d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, then rt, 2 h; (e) H_2, $Pd(OH)_2$, $(Boc)_2O$, MeOH, rt, 20 h, 79% (steps d and e); (f) TIPSCl, imidazole, DMF, 16 h, 93%; (g) $RuCl_3{\cdot}nH_2O$, $NaIO_4$, CCl_4–CH_3CN–H_2O, 0 °C, 5 min, then rt 1 h, 97%; (h) LiHMDS, THF, −78 °C, 2 h; 5-Cl-2-NTf_2-Pyr, THF, then rt, 2.5 h, 90%; (i) CuI, MeLi, THF, −20 °C, 30 min, −78 °C, then rt, 16 h; (j) $BH_3{\cdot}SMe_2$, THF, −78 °C, then rt, 16 h, then $Me_3NO{\cdot}2H_2O$, THF, reflux, 45 min, 81% (steps i and j); (k) Dess–Martin, CH_2Cl_2, rt, 2.5 h; (l) $NaBH_4$, MeOH, −40 °C, 16 h, 84% (steps k and l); (m) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C, then rt, 3 h, 91%; (n) TBAF, AcOH, 30–40 °C, 24 h, 83%; (o) Dess–Martin, CH_2Cl_2, rt, 3 h; (p) KHMDS, (*E*)-C_4H_9–CH═CH–$CH_2P(O)(OEt)_2$ (**15**), THF, −78 °C, 16 h, 68% (steps n–p); (q) TFA, CH_2Cl_2, 0 °C, then rt, 1 h, 99%; (r) NaHMDS, (*E*)-$MeC(O_2C_2H_4)(CH_2)_2$–CH═CH–$CH_2P(O)(OEt)_2$ (**17**), DME, −78 °C, 57%.

carried out in satisfactory overall yield as in the above model series. However, the trimethylsilylethyl (TMSE) protecting group had to be replaced by TIPS to avoid its oxidation to trimethylsilylacetyl during the ruthenium-mediated oxidation step.[13] Thus, $LiAlH_4$–$AlCl_3$ reduction of **8**, followed by $BF_3{\cdot}Et_2O$-promoted deprotection and hydrogenolysis of the benzylic C–N bond in the presence of $(Boc)_2O$ gave *cis*-decahydroquinoline **9**. After reprotection of the hydroxyl group as a TIPS derivative, the ruthenium oxidation step took place in nearly quantitative yield to give lactam **10**, which was efficiently converted to enecarbamate **11** *via* a triflate, and then to alcohol **12** by stereoselective hydroboration–oxidation.

The next step was to install the correct C-3 absolute configuration. As anticipated, complete inversion of the C-3 stereochemistry was accomplished (83% overall yield) by Dess–Martin oxidation of alcohol **12** followed by $NaBH_4$ reduction, with hydride delivery from the more accessible face of the ketone carbonyl. The resulting alcohol **13** has the same absolute configuration as

lepadins A–C at the five stereogenic centers of the decahydroquinoline ring. After protection of the hydroxy group as an acetate, removal of the TIPS protecting group and subsequent Dess–Martin oxidation led to aldehyde **14**, which was used in the next step without purification.

Finally, for the elongation of the C-5 side chain to install the octadienyl moiety present in lepadins A–C and ensure the required *E*,*E* stereochemistry, we selected the Horner–Wadsworth–Emmons methodology using an appropriate *E*-configurated phosphonate. Thus, reaction of aldehyde **14** with the anion derived from diethyl (*E*)-hept-2-enylphosphonate (**15**),[14] which occurred with concomitant hydrolysis of the acetate ester, gave alcohol **16**. The synthesis of (−)-lepadin B was completed by cleaving the Boc protecting group. The preparation of alcohol **16** also represents a formal total synthesis of (−)-lepadin A.[5b,d] Similarly, the (*E*,*E*)-7-oxooct-1,3-dienyl side chain of (−)-lepadin C was stereoselectively assembled by reaction of aldehyde **14** with diethyl (*E*)-6,6-(ethylenedioxy)hept-2-enylphosphonate (**17**),[5d] leading to alcohol **18**, a known[5d] synthetic precursor of (−)-lepadin C.

In summary, we have developed a concise route to (−)-lepadins A–C using a phenylglycinol-derived lactam as the starting enantiopure scaffold, which allows the stereocontrolled generation of the five stereogenic centers on the decahydroquinoline ring. Our synthesis (lepadin B: 17 steps; 11.3% overall yield from **7**) compares advantageously in terms of both overall yield and number of synthetic steps with previous syntheses of these alkaloids. Inversion of the configuration at C-5 in the intermediate aldehyde **14** could provide access to other members of this family of natural products.

Financial support from the Spanish Ministry of Economy and Competitiveness (Project CTQ2012-35250) and the AGAUR, Generalitat de Catalunya (Grant 2009-SGR-1111), is gratefully acknowledged.

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13 This oxidation was observed from the TMSE derivative of **9**.

14 Phosphonate **15** was prepared in 76% overall yield from (*E*)-2-hepten-1-ol, by tosylation (BuLi, TsCl, THF, −78 °C) followed by reaction with diethyl phosphonate (KHMDS, THF, 0 °C to −78 °C).

