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Stereoselective synthesis of (–)-lepadins A–C

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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 *Prosthececaeus villatus*,[1b] as well as the Australian Great Barrier Reef tunicate *Didemnun* 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 have 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.

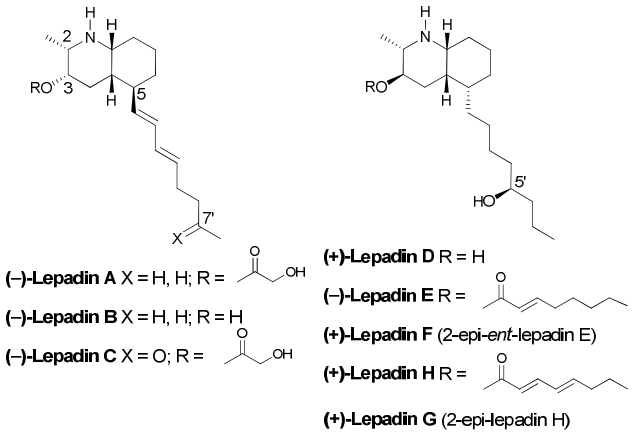
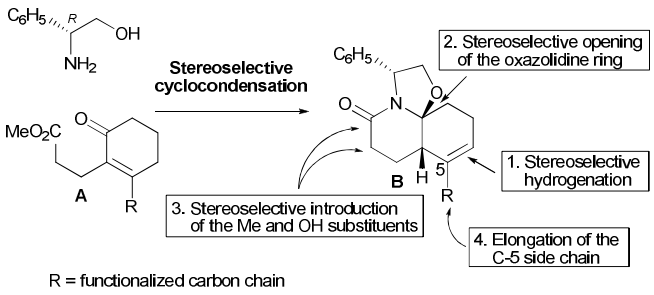


Fig. 1 Lepadin alkaloids.

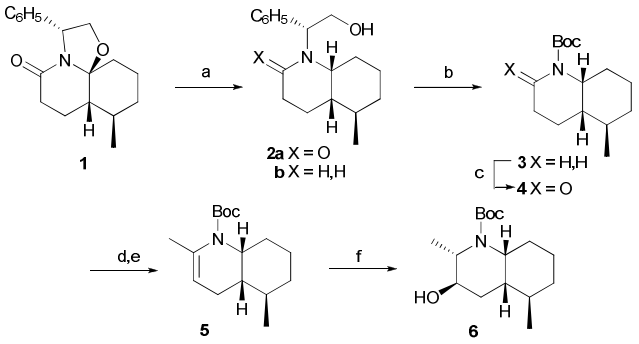
In the context of our studies[6] on the use of phenylglycinol-derived chiral tricyclic lactams for the enantioselective synthesis of alkaloids, we present herein a straightforward synthesis of (–)-lepadins A–C.

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 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.



Scheme 1 Synthetic strategy.

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



Scheme 2 Model studies. *Reagents and conditions*: (a) $LiAlH_4$, $AlCl_3$, THF, 0 ºC, 30 min; then –78 ºC, 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 ºC, 5 min, then rt 1 h, 73%; (d) LiHMDS, THF, –78 ºC, 2 h; 5-Cl-2-NTf_2-Pyr, THF, then rt, 1.5 h, 95%; (e) CuI, MeLi, THF, –20 ºC, 30 min, –78 ºC, then rt, 16 h; (f) $BH_3{\cdot}SMe_2$, THF, –78 ºC, then rt, 16 h, then $Me_3NO{\cdot}2H_2O$, THF, reflux, 45 min, 78% (steps e-f).

the C-2 methyl substituent was accomplished via the corresponding vinyl triflate, prepared by the 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).

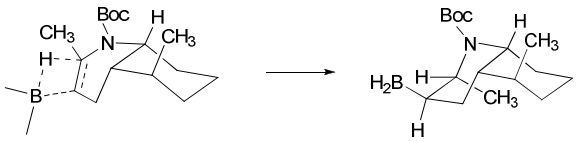
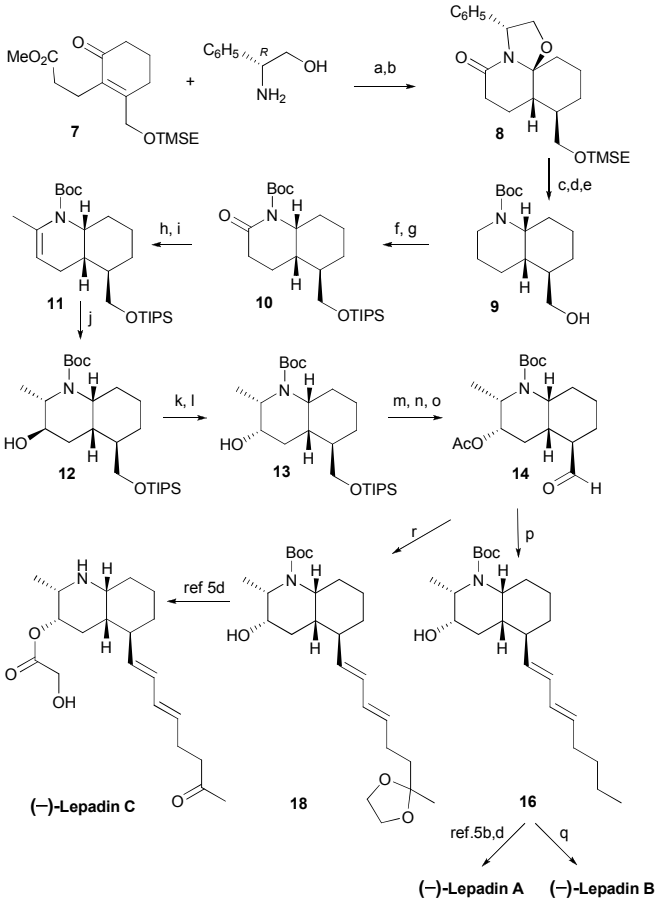


Fig. 2 Stereoselectivity of the hydroboration reaction.

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 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



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-b); (c) $LiAlH_4$, $AlCl_3$, THF, 0 ºC, 30 min; then –78 ºC, 1.5 h and rt, 3 h, 76%; (d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 ºC, then rt, 2 h; (e) H_2, $Pd(OH)_2$, $(Boc)_2O$, MeOH, rt, 20 h, 79% (steps d-e); (f) TIPSCl, imidazole, DMF, 16 h, 93%; (g) $RuCl_3{\cdot}nH_2O$, $NaIO_4$, CCl_4-CH_3CN-H_2O, 0 ºC, 5 min, then rt 1h, 97%; (h) LiHMDS, THF, –78 ºC, 2 h; 5-Cl-2-NTf_2-Pyr, THF, then rt, 2.5 h, 90%; (i) CuI, MeLi, THF, –20 ºC, 30 min, –78 ºC, then rt, 16 h; (j) $BH_3{\cdot}SMe_2$, THF, –78 ºC, then rt, 16 h, then $Me_3NO{\cdot}2H_2O$, THF, reflux, 45 min, 81% (steps i-j); (k) Dess-Martin, CH_2Cl_2, rt, 2.5 h; (l) $NaBH_4$, MeOH, –40 ºC, 16 h, 84% (steps k-l); (m) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 ºC, then rt, 3 h, 91%; (n) TBAF, AcOH, 30-40 ºC, 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 ºC, 16 h, 68% (steps n-p); (q) TFA, CH_2Cl_2, 0 ºC, 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 ºC, 57%.

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-oxoocta-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.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/b000000x/

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12 Minor amounts of an epimeric lactam at the 4a, 5, and 8a positions of the decahydroquinoline ring were also isolated.

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 ºC) followed by reaction with diethyl phosphonate (KHMDS, THF, 0 ºC to –78 ºC).