

Enantioselective synthesis of lepadins A–D from a phenylglycinol-derived hydroquinolone lactam

Mercedes Amat*, Alexandre Pinto, Rosa Griera, and Joan Bosch*

Abstract: The marine alkaloids (–)-lepadins A–C and (+)-lepadin D, belonging to two diastereoisomeric series, were synthesized from an (*R*)-phenylglycinol-derived tricyclic lactam *via* a common *cis*-decahydroquinoline intermediate. Crucial aspects of the synthesis are the stereochemical control in the assembly of the *cis*-decahydroquinoline platform, in the introduction of the C-2 methyl and C-3 hydroxy substituents, and in the generation of the C-5 stereocenter.

Introduction

Decahydroquinoline (DHQ) alkaloids constitute an important group of natural products, which exhibit a wide range of biological activities. Rather than in plants, they occur mainly in other terrestrial (amphibians, arthropods) and marine (tunicates, flatworms) organisms.^[1] Most of these alkaloids are 2,5-disubstituted DHQs (for instance, pumiliotoxin C, the most representative member of this group), but they also include 5,7-disubstituted (the phlegmarine-type *Lycopodium* alkaloids)^[2] and 2,3,5-trisubstituted derivatives (lepadins). The latter are a relatively small group of *cis*-DHQ alkaloids isolated from marine sources, characterized by a C-2 methyl substituent, a C-3 oxygenated (hydroxy or acyloxy) group, and a C-5 functionalized eight-carbon chain. From the stereochemical standpoint, lepadins can be classified into three series, as shown in Figure 1.

The first isolation of a member of this group, lepadin A, was reported by Steffan in 1991^[3] from the tunicate *Clavelina lepadiformis*. A few years later, Andersen *et al.* described the isolation of lepadins A–C from the flatworm *Prostheceraeus villatus* and its prey *C. lepadiformis*.^[4] Lepadins A and B were found to exhibit significant *in vitro* cytotoxicity against several human cancer cell lines. Then in 2002, Wright and coworkers reported the isolation of lepadins D–F from the tunicate *Didemnum sp.*^[5] and Carroll *et al.*, lepadins F–H from the Australian ascidian *Aplidium tabascum*.^[6,7] Lepadins D–F possess significant and selective antiplasmodial and antitrypanosomal activity. Their low cytotoxicity makes them attractive models for the development of new antimalarial agents.

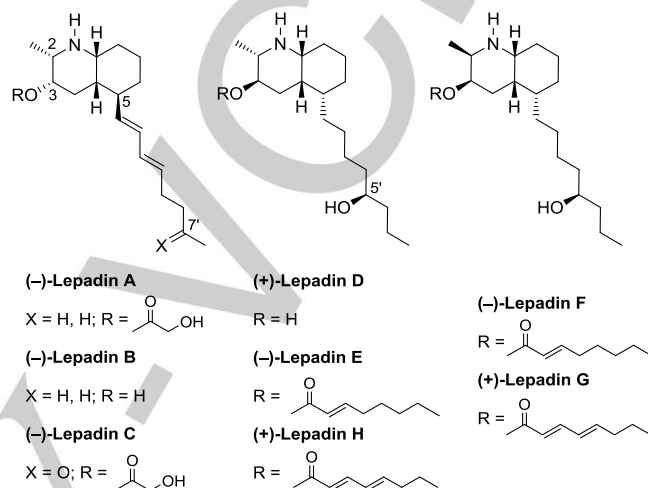


Figure 1. Lepadin alkaloids.

More recently, lepadin B was found to block neuronal nicotinic acetylcholine receptors.^[8] However, extensive bioactivity studies with lepadin alkaloids have been thwarted by the minute amounts isolated from natural sources.

Several enantioselective total syntheses of lepadins have been reported so far,^[9,10] which have allowed the relative and absolute configuration of these alkaloids to be unequivocally established. All these syntheses involve two phases: i) construction of a protected 3-hydroxy-2-methyl-*cis*-hydroquinoline platform, either functionalized at C-5 or bearing an oxidized one-carbon substituent at this position, and ii) installation of the appropriate C-5 eight-carbon chain. A variety of methodologies have been developed for the first phase: closure of the carbocyclic ring by aldol cyclization^[9a,b] or a ring-closing/ring-opening metathesis sequence,^[9d] closure of the piperidine ring by intermolecular [3+3]-azacycloaddition,^[9f,g,11] xanthate-mediated free radical cyclization,^[10] or alkylative cyclization processes;^[9c] and sequential one-pot construction of both rings from an acyclic precursor by a tandem ene-yne-ene ring-closing metathesis.^[9e]

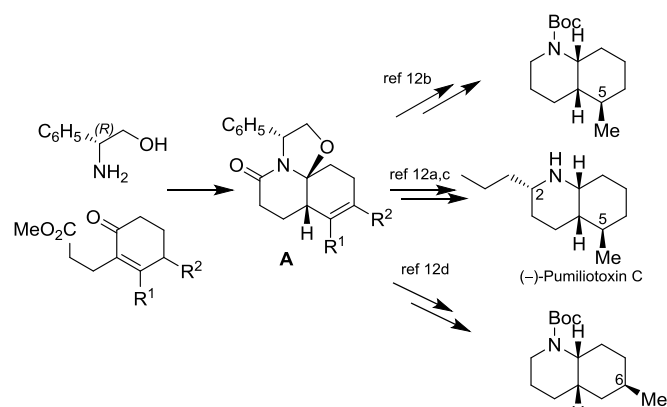
On the other hand, different strategies have been used to assemble the eight-carbon chain at the DHQ C-5 position: i) starting from a C-5 unsubstituted DHQ, direct introduction of an eight-carbon chain (C₀+C₈ strategy),^[9d] or sequential introduction of either one carbon and a seven-carbon chain (C₀+C₁+C₇)^[9a,c] or two and six carbons (C₀+C₂+C₆);^[9c,f,g] ii) starting from a DHQ bearing a functionalized one-carbon substituent at C-5, direct elongation of a seven-carbon chain (C₁+C₇ strategy)^[9e] or sequential elongation of one carbon and a six-carbon chain (C₁+C₁+C₆).^[9b]

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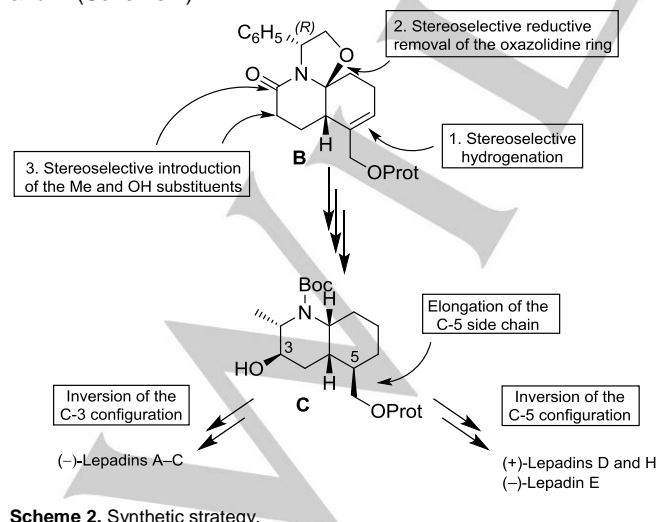
Results and Discussion

In previous work, we have developed straightforward procedures for the enantioselective synthesis of *cis*-DHQs bearing substituents at the 2-, 5-, and 6-positions, for instance the dendrobatid alkaloid (–)-pumiliotoxin C, using phenylglycinol-derived oxazoloquinolone lactams **A** as enantiomeric scaffolds^[12] (Scheme 1). These lactams are easily accessible by a stereoselective cyclocondensation reaction between (*R*)-phenylglycinol and appropriate cyclohexenone-derived δ -keto esters.^[13]



Scheme 1. Enantioselective access to substituted *cis*-decahydroquinolines from oxazoloquinolone lactams.

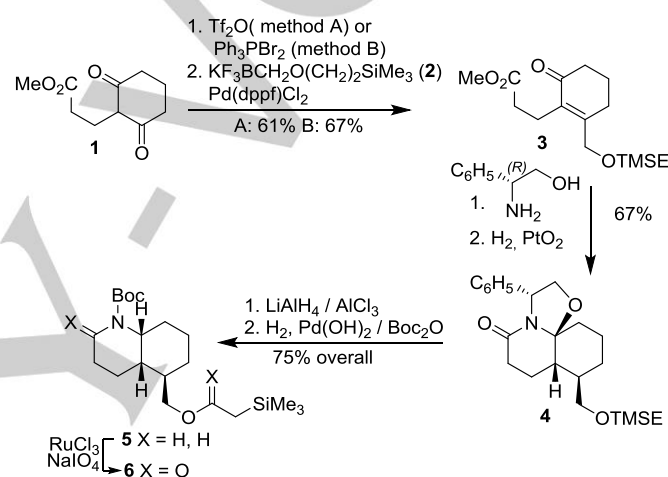
We envisaged tricyclic lactams **A** as suitable synthetic precursors of lepadins A–C and D, E, H, belonging to two different stereochemical series. Starting from a lactam **B** (**A**; R¹ = CH₂OProt, R² = H), bearing an oxidized one-carbon substituent at the quinoline C-5 position, after stereoselective hydrogenation of the C–C double bond and reductive removal of the oxazolidine ring, the stereoselective introduction of the methyl and hydroxy substituents, taking advantage of the lactam functionality, would give rise to a *cis*-DHQ **C**, which was visualized as a common intermediate *en route* to lepadins A–E and H (Scheme 2).



Scheme 2. Synthetic strategy.

The synthesis of (–)-lepadins A–C from **C** would involve the inversion of the configuration of the DHQ C-3 position and the elongation of the C-5 side chain.^[14] In turn, an inversion of the configuration at C-5 followed by the elongation of the C-5 chain would afford (+)-lepadin D and their acylated derivatives (–)-lepadin E and (+)-lepadin H.

Scheme 3 outlines the initial steps of the synthesis. The required δ -keto ester **3**, bearing a trimethylsilylethyl (TMSE)-protected hydroxymethyl substituent, was prepared in two steps from diketo ester **1**, by Pd-catalyzed cross-coupling of either the corresponding vinyl triflate or, more conveniently, bromo enone with potassium alkoxymethyltrifluoroborate **2**^[15] (Scheme 3).



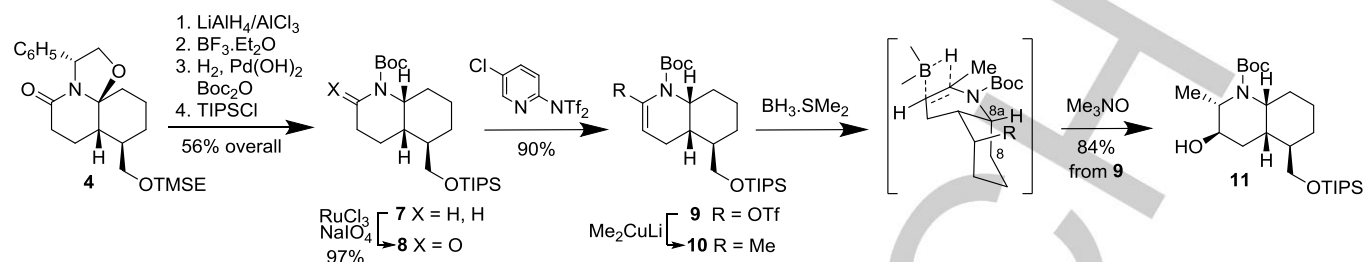
Scheme 3. Initial steps of the synthesis.

A cyclocondensation reaction of δ -keto ester **3** with (*R*)-phenylglycinol, followed by catalytic hydrogenation of the resulting mixture of endocyclic and exocyclic unsaturated lactams led to saturated tricyclic lactam **4** in 67% overall yield.^[16]

The reductive opening of the oxazolidine ring was accomplished with complete retention of configuration by alane reduction, which also caused the reduction of the lactam carbonyl. A subsequent hydrogenolysis of the benzylic C–N bond in the presence of Boc₂O stereoselectively gave *cis*-DHQ **5** in 75% overall yield. Although the use of the above sequence requires an additional oxidation step to recover the lactam functionality, it ensures the *cis* DHQ ring fusion characteristic of lepadins.^[17] The lactam carbonyl was efficiently reinstalled by ruthenium-promoted oxidation,^[18] although these conditions unexpectedly caused the concomitant oxidation of the silylethoxy moiety to give lactam ester **6**.

To overcome this inconvenience, the TMSE protecting group was replaced by TIPS^[19] as shown in Scheme 4 and, satisfactorily, the ruthenium-mediated oxidation of the TIPS-substituted DHQ **7** afforded lactam **8** in nearly quantitative yield.

Following our synthetic plan, the next step of the synthesis was the stereoselective introduction of the C-2 methyl and C-3 hydroxy substituents. This was achieved in three steps, *via* the enecarbamate **10**, which was prepared by treatment of lactam **8**

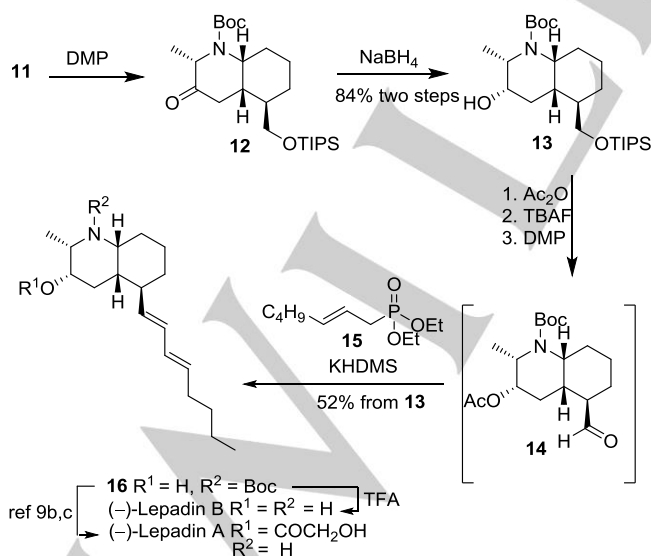


Scheme 4. Access to the advanced common intermediate **11**.

with Comins' triflating reagent^[20] followed by reaction of the resulting vinyl triflate **9** with Me_2CuLi ^[21] (Scheme 4).

A subsequent hydroboration-oxidation sequence using $\text{BH}_3\cdot\text{SMe}_2$ complex^[22] and trimethylamine *N*-oxide^[22,23] stereoselectively provided the C-2/C-3 *trans* alcohol **11** (**C**, Prot = TIPS) in 84% overall yield from **9**. The formation of a single stereoisomer in the process is a consequence of borane approaching the most accessible face of the double bond of **10**, which adopts a conformation with an axial C₈-C_{8a} bond to avoid the A^(1,3) strain caused by the Boc substituent.

The inversion of the C-3 configuration, required for the synthesis of lepadins A–C from intermediate **11**, was accomplished in 84% yield by Dess-Martin oxidation followed by NaBH_4 reduction of the resulting ketone **12**, which occurred stereoselectively from the less hindered face of the carbonyl group (Scheme 5). After protection of the C-3 hydroxy group of **13** as an acetate, and conversion of the protected hydroxymethyl substituent into a formyl group, the required *E,E*-configured eight-carbon chain at C-5 was directly assembled, in a stereoselective manner, from aldehyde **14** by the Horner-Wadsworth-Emmons methodology using the anion derived from diethyl (*E*)-hept-2-enylphosphonate (**15**) (C₁+C₇ strategy).

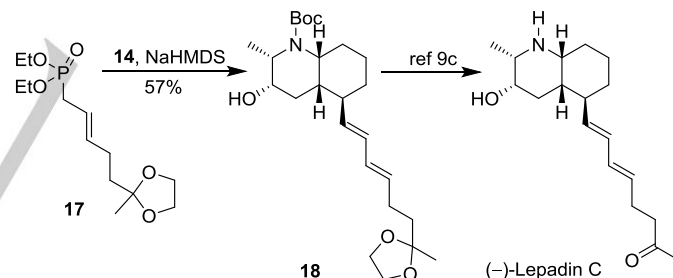


Scheme 5 Inversion of the C-3 configuration and elongation of the C-5 side chain. Enantioselective synthesis of (–)-lepadins A and B.

Diene **16**, in which deprotection of the C-3 hydroxy group had occurred, was obtained in 52% overall yield from **13**. A final removal of the Boc protecting group gave (–)-lepadin B. The synthesis of **16** also constitutes a formal total synthesis of (–)-lepadin A.^[9b,c]

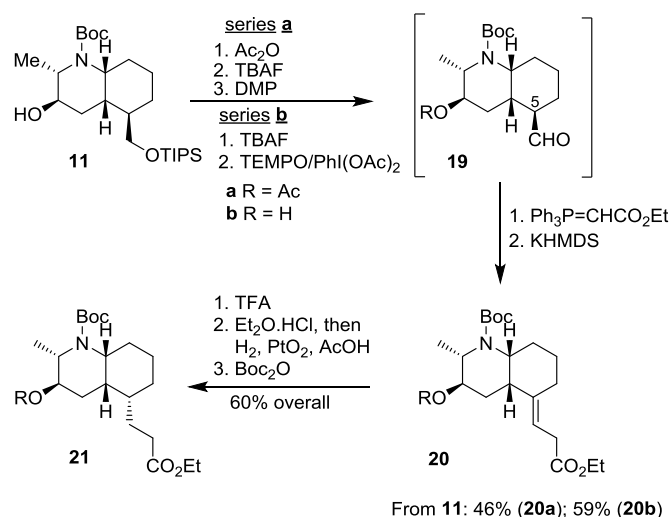
The NMR data of our synthetic (–)-lepadin B were coincident with those reported in the literature, while its specific rotation was in good agreement with the value reported for this compound.^[9a] The synthesis of (–)-lepadin B consists of 19 synthetic steps from δ -keto ester **3** and takes place in 7.6% overall yield, which represents a significant improvement with regard to previous syntheses of this alkaloid.

Starting from the above aldehyde **14**, a similar Horner-Wadsworth-Emmons reaction using the functionalized phosphonate **17**, led to **18**, a known precursor^[9c] of (–)-lepadin C (Scheme 6).



Scheme 6. Elongation of the C-5 side chain. Enantioselective synthesis of (–)-lepadin C.

The key step to access lepadin D, and the configurationally related lepadins E and H, from the common intermediate **11** was the inversion of the C-5 configuration. To accomplish this, we envisaged a synthetic sequence involving the stereoselective hydrogenation of a substituted DHQ, such as **20a**, bearing an exocyclic double bond at the C-5 position. In this way, the eight-carbon chain would be assembled in two phases (C₁+C₂+C₅ strategy). Following the same three-step sequence used for the above conversion **13**→**14**, alcohol **11** was converted to aldehyde **19a** in excellent overall yield (Scheme 7).



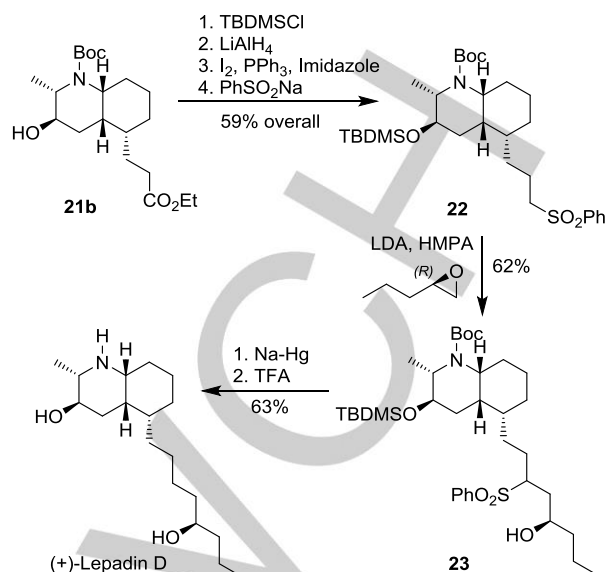
Scheme 7. Inversion of the C-5 configuration and two-carbon elongation.

An initial two-carbon elongation by Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane, followed by base-promoted isomerization of the resulting conjugated carbon-carbon double bond to an exocyclic position^[24] led to unsaturated ester **20a**.^[25,26] After removal of the Boc protecting group,^[27] catalytic hydrogenation of the resulting secondary amine (as hydrochloride^[28]) in AcOH stereoselectively installed the required C-5 stereochemistry. A subsequent protection with Boc₂O afforded **21a**.^[29]

A notable improvement in terms of simplicity and chemical yield was achieved when the above sequence was directly carried out without protecting the C-3 hydroxy group, and the TEMPO/PhI(OAc)₂ system was used in the oxidizing step in a one-pot oxidation-olefination process.^[30] Thus, removal of the TIPS protecting group of **11**, followed by chemoselective oxidation of the primary alcohol function with TEMPO and *in situ* Wittig homologation of the resulting aldehyde **19b**, gave an α,β -unsaturated ester, which was converted to DHQ-5-propionate **21b** via olefinic ester **20b**, as in the above **a** series.

To complete the functionalized eight-carbon chain of (+)-lepadin D from the advanced intermediate **21b**, it was necessary to perform a five-carbon elongation. After protection of the C-3 hydroxy group as a TBDMS ether, LiAlH₄ reduction of the ester group, followed by conversion of the resulting alcohol to an iodide using the I₂-PPh₃-imidazole protocol and subsequent reaction with sodium benzenesulfinate gave sulfone **22** (Scheme 8).

Coupling of the sulfonyl carbanion derived from **22** with the easily accessible epoxide (*R*)-propyloxirane^[31] gave hydroxy sulfone **23** (mixture of epimers) in 60% yield. Finally, reductive desulfonation with sodium amalgam, followed by simultaneous removal of the Boc and silyl protecting groups, completed the synthesis of (+)-lepadin D, in a total of 25 steps and 1.4% overall yield. Both the specific rotation and NMR data of our synthetic (+)-lepadin D were consistent with those reported for the natural product.^[5]



Scheme 8. Completion of the C-5 side chain. Enantioselective synthesis of (+)-lepadin D.

Conclusions

In conclusion, enantioselective synthetic routes to two stereochemical groups of lepadins have been developed from a common DHQ intermediate. The synthesis relies on the versatility of phenylglycinol-derived lactams as multipurpose scaffolds for the enantioselective construction of complex nitrogen-containing natural products.

The main features of the synthesis are: i) the straightforward construction of a DHQ system bearing a functionalized one-carbon substituent at the C-5 position; ii) the incorporation of the C-2 methyl and C-3 hydroxy substituents taking advantage of the lactam carbonyl; and iii) the elongation of the C-5 chain, either directly with a seven-carbon fragment (lepadins A-C) or sequentially using two- and five-carbon fragments (lepadin D).

Key aspects from the stereochemical standpoint are: i) the stereoselective generation of the *cis*-DHQ ring fusion by reductive opening of the oxazolidine ring; ii) the control of the configuration of the C-5 stereocenter by stereoselective hydrogenation of a carbon-carbon double bond, either endocyclic in a tricyclic lactam or exocyclic in an *N*-unsubstituted DHQ derivative; iii) the installation of the *trans* 2-Me/3-OH relationship by a stereoselective hydroboration-oxidation sequence from a methyl-substituted *N*-Boc enamine, with subsequent inversion of the C-3 configuration *via* a ketone; and, finally, iv) the stereoselective achievement of the (*E*, *E*)-configuration of the C-5 chain *via* a Horner-Wadsworth-Emmons reaction.

Acknowledgements

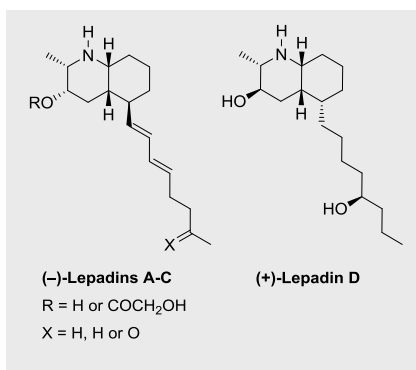
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Keywords: alkaloids • asymmetric synthesis • lactams • nitrogen heterocycles • total synthesis

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- [26] The direct introduction of a functionalized seven-carbon chain (C₁+C₇ strategy) by *B*-alkyl Suzuki-Miyaura coupling was not studied because the required vinyl triflate derived from **19a** was obtained in low yield.
- [27] Due to conformational factors, the presence of an *N*-Boc substituent decreases the stereoselectivity of the catalytic hydrogenation of the exocyclic double bond in 5-alkylidene-DHQ derivatives: see ref 9c.
- [28] Somewhat unexpectedly, the catalytic hydrogenation (PtO₂ or Pt/C, MeOH or AcOH) of the free base was extremely slow and led to considerable amounts of the corresponding *N*-methyl-DHQ-5-propionate.
- [29] The stereochemical assignment of **21a** was confirmed by comparing its ¹³C NMR data [δ 18.5 (C-4), 53.0 and 54.2 (two rotamers, C-8a)] with those of 5-epi-**21a** [δ 27.8 (C-4), 50.4 (C-8a)], which was prepared by direct catalytic hydrogenation of the Wittig adduct formed from **19a**.
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FULL PAPER

Using (*R*)-phenylglycinol as the source of chirality, the marine alkaloids (–)-lepadins A–C and (+)-lepadin D, with opposite absolute configuration at the C-3 and C-5 ring positions, have been synthesized. The synthesis features the use of a tricyclic oxazoloquinolone lactam as the key enantiomeric scaffold and proceeds via an advanced common decahydroquinoline intermediate.



Mercedes Amat*, Alexandre Pinto, Rosa Griera, and Joan Bosch*

Page No. – Page No.

Enantioselective synthesis of lepadins A–D from a phenylglycinol-derived hydroquinolone lactam