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Heterolignans: Stereoselective Synthesis of an 11-Amino Analog of Azaelliptitoxin

Julie Routier,[a] Mihaela Calancea,[a] Marion David,[a] Yannick Vallée,[a] and Jean-Noël Denis*[a]

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The 11-amino-azaelliptitoxin analog (11*R*,11a*S*,5*R*)-**15** has been prepared stereoselectively in eight steps and 24 % overall yield from commercially available (*S*)-glycidol (**7**) via the original enantiopure chiral α-amino aldehyde **9**, used as chiral precursor for the creation of the two other stereogenic centers of the target framework.

Introduction

Lignans represent a large class of natural products, which possess a great variety of structures and a broad range of biological activities.[1,2] For these reasons, these compounds are attractive targets for biomedical and synthetic purposes.[2]

Podophyllotoxin (**1**) is the most well-known of them, studied for its inhibition activity on microtubule assembly in the mitotic apparatus.[3] It has been used to develop semi-synthetic analogs such as etoposide (VP-16, Figure 1) (**2a**) and tenoposide (VM-26) (**2b**), which have no activity on microtubule assemblies, but are potent inhibitors of DNA topoisomerase II. The knowledge of those biologically active compounds[3] led to design a new compound by molecular modelling, azaelliptitoxin (**3**) (or azatoxin, a new heterolignan),[4,5] considered as a hybrid[5a] based on etoposide (**2a**) and ellipticine (**4**), another well-established topoisomerase II inhibitor (Figure 1).[6]

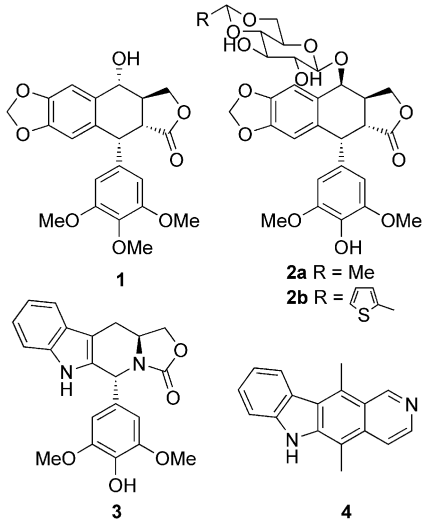

Figure 1. Structures of bioactive lignans and ellipticine: podophyllotoxin (**1**), etoposide (**2a**), teniposide (**2b**), azaelliptitoxin (**3**), ellipticine (**4**).

Modifications of the azaelliptitoxin skeleton have been investigated (Figure 2).[5c–5g] The results revealed that 11-alkoxy compounds **5a** do not have any activity towards topoisomerase II, but introduction of an 11-amino or -polyamino substituent, and in particular, introduction of a 4-substituted anilino group at this C-11 position, led to 11-amino compounds **5b**, which have topoisomerase II inhibitory activity.[5c]

To the best of our knowledge, only one preparation of 11-amino analogues **5b** is reported.[5c] Moreover, this strategy is based on the use of L-tryptophanol as starting material precursor for the creation of the two other stereogenic centers of the target framework.

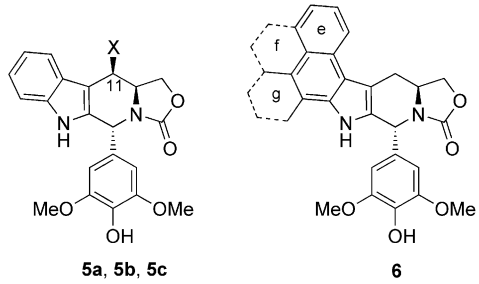

Figure 2. Structures of some azaelliptitoxin derivatives: **5a** (X = OR), **5b** (X = NHR[1]), **6** (benz[*e*, *f* and *g*]azaelliptitoxins).

[a] Département de Chimie Moléculaire (SERCO), UMR-5250, ICMG FR-2607, CNRS, Université Joseph Fourier
B. P. 53, 38041 Grenoble Cedex 9, France
Fax: +33-4-76635983
E-mail: jean-noel.denis@ujf-grenoble.fr
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rial, limiting the scope of structural and stereochemical modifications.

Later, the synthesis of benzannulated azaelliptitoxin derivatives has been described, affording benz[*e*, *f* and *g*]azatoxins **6** (Figure 2). It has been shown that these derivatives do not interact with topoisomerase II but are strong inhibitors of tubulin polymerization. Biological data showed that azaelliptitoxin derivatives could be either inhibitors of the tubulin polymerization or inhibitors of the DNA topoisomerase II depending on their structure.

In order to flesh out the available information on structure/activity relationships, we have developed an original strategy, allowing the access to 11-aminoazaelliptitoxin derivatives from three commercially available compounds: (*S*)-glycidol, indole and *p*-methoxybenzaldehyde dimethylacetal.

Results and Discussion

In this paper, we describe the stereoselective synthesis of the 11-(pivaloylamino) analog (11*R*,11a*S*,5*R*)-**15** as summarized in the retrosynthetic analysis depicted in Figure 3. All parts of the azaelliptitoxin skeleton could be modified according to the proposed disconnections shown in target compound **15**, with the possibility to prepare several derivatives by using the same strategy.

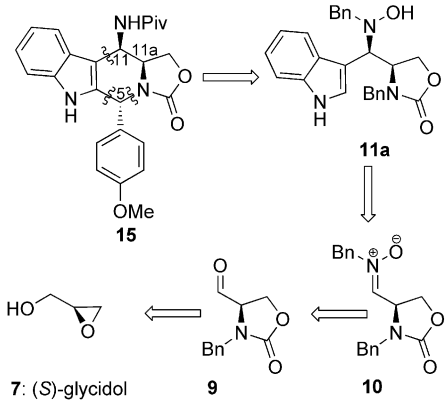
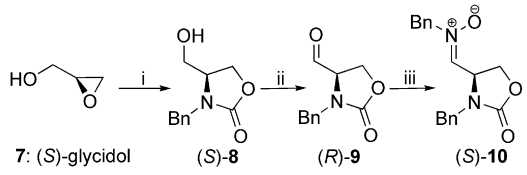


Figure 3. Retrosynthetic analysis for the preparation of the 11-(pivaloylamino) analog (11*R*,11a*S*,5*R*)-**15**.

The strategy is first based on the stereoselective synthesis of the indolic *N*-benzyl-*N*-hydroxylamine **11a** by reaction of indole with the highly functionalized nitrone **10**, which could be prepared from the commercially available (*S*)-glycidol (**7**) via the chiral α-amino aldehyde **9**, which has been chosen as the chiral precursor to induce the stereoselective creation of the two other stereogenic centers (Figure 3).

Adequate transformation of the *N*-benzyl-*N*-hydroxylamine **11a** to an indolic free-oxazolidinone intermediate should afford the expected adduct **15** after a Pictet–Spengler reaction with *p*-methoxybenzaldehyde dimethylacetal.

The first stage of the strategy consisted of the synthesis of the alcohol **8** from commercial (*S*)-glycidol (**7**) by reaction with benzyl isocyanate in the presence of triethylamine in CH_2Cl_2, according to the method described by Katsumura and co-workers (Scheme 1).[7] We obtained (*S*)-**8** in 74% chemical yield with an optical rotation of $[\alpha]_D = -31.4$ ($c = 2.2$, $CHCl_3$); this value is in good accordance with the one described for the (*R*)-alcohol {$[\alpha]_D = +29.8$ ($c = 1.03$, $CHCl_3$),[7a] $[\alpha]_D = +32.3$ ($CHCl_3$)[7b]}, showing the enantiopurity of our (*S*) compound.

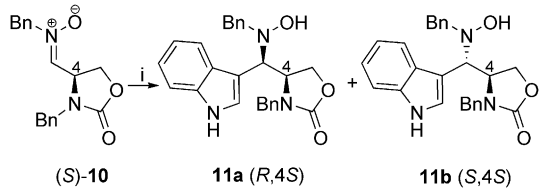


Scheme 1. Enantioselective synthesis of the nitrone (*S*)-**10**. Reagents and conditions: (i) BnNCO (1 equiv.), Et_3N (1.8 equiv.), CH_2Cl_2, 40 °C, 18 h (74%); (ii) DMP (2 equiv.), CH_2Cl_2, room temp., 1.5 h (60%), or IBX (3 equiv.), EtOAc, 80 °C, 3 h (quant.); (iii) BnNHOH (1.7 equiv.), $MgSO_4$ (excess), CH_2Cl_2, room temp., 3 h (98%).

The next step was the oxidation of the alcohol (*S*)-**8** into the chiral α-amino aldehyde (*R*)-**9**. To the best of our knowledge, this aldehyde (as well as its enantiomer) has never been isolated nor characterized. Katsumura and coworkers reported that the oxidation of alcohol (*R*)-**8** under Swern conditions, or by using PCC, PDC, tetra-*n*-propylammonium perruthenate, or sulfur trioxide–pyridine complex only gave unstable compounds, which decomposed into a complex mixture.[7b]

We then chose to study the oxidation of the alcohol (*S*)-**8** by using two well-known mild oxidants, namely, Dess–Martin periodinane and *o*-iodoxybenzoic acid. The alcohol (*S*)-**8**, oxidized with Dess–Martin periodinane (DMP, 2 equiv.)[8] in CH_2Cl_2 (Scheme 2), led to the aldehyde (*R*)-**9** in a modest 60% isolated yield, whereas the use of *o*-iodoxybenzoic acid (IBX, 3 equiv.)[9] in EtOAc at 80 °C led to the same aldehyde in 99% isolated yield. It is a stable solid that could be stored under argon at 0 °C for several days and could be purified by flash column chromatography. The ^1H NMR spectrum in $CDCl_3$ showed that it exists in several forms, among which hydrates are predominant, whereas the aldehyde form predominates (≥98%) in the ^1H NMR spectrum in [D_8]toluene. The optical purity of aldehyde (*R*)-**9** was determined by comparison of the ^1H NMR spectrum of the Mosher ester of its corresponding alcohol (*S*)-**8** (obtained by reduction with $NaBH_4$ in ethanol)[10] and the ^1H NMR spectra of Mosher esters derived from the (*R*)- and racemic (±)-alcohols **8**. This result showed that (*R*)-**9** was enantiopure.[11]

It is expected that enantiopure α-oxazolidino aldehyde (*R*)-**9** could become an important alternative to Garner's aldehyde in organic synthesis because of its straightforward and efficient access in only two steps from commercially available enantiopure (*S*)-glycidol (**7**). Furthermore, the oxazolidin-2-one moiety is present in many bioactive compounds and is widely used as pattern in chiral auxiliaries.[12]

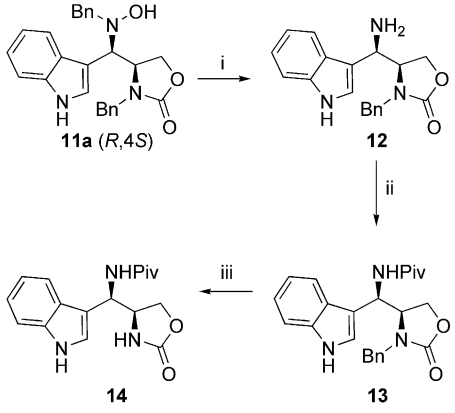


Scheme 2. Preparation of the *N*-hydroxylamine **11a**. Reagents and conditions: Method A: (i) indole (1 equiv.), AcCl (2 equiv.), MeOH, 0 °C, 4 h (52%), *dr* = 3:2. **11a** (*R*,4*S*) (31.5%), **11b** (*S*,4*S*), (20.5%); method B: (i) indole (1 equiv.), HCl (2 equiv., 2 N in Et_2O), MeOH/CH_2Cl_2 (4:1), 0 °C to room temp., 5 h, *dr* = 5:1, **11a** (*R*,4*S*) (42%), **11b** (*S*,4*S*) (8%).

The reaction of aldehyde (*R*)-**9** with *N*-benzylhydroxylamine in CH_2Cl_2 in the presence of an excess of anhydrous magnesium sulfate[13] gave the α-chiral nitrone (*S*)-**10** in a nearly quantitative yield (Scheme 1).

When nitrone (*S*)-**10** was added to indole under acidic conditions in methanol at 0 °C (Method A, Scheme 2),[13] a mixture of diastereoisomers **11a** (*R*,4*S*) and **11b** (*S*,4*S*)[13c] in a 3:2 ratio (determined by ^{1}H NMR of crude mixture) was obtained. Compounds **11a** and **11b** were isolated in 32% and 20% yield, respectively. Optimization of experimental conditions (Method B, Scheme 2) led us to obtain the two diastereoisomers **11a** and **11b** in a 5:1 ratio (determined by ^{1}H NMR spectroscopy of crude product), which were separated to obtain compounds **11a** and **11b** in 42% and 8% yield, respectively.

We then prepared the α-(pivaloylamino)-β-oxazolidinone **13** from the *N*-hydroxylamine **11a**. In the first step, *N*-hydroxylamine **11a** was transformed into the corresponding free primary amine **12** in quantitative yield by hydrogenolysis in the presence of Pearlman's catalyst in a MeOH/AcOH mixture (85:15) (Scheme 3).

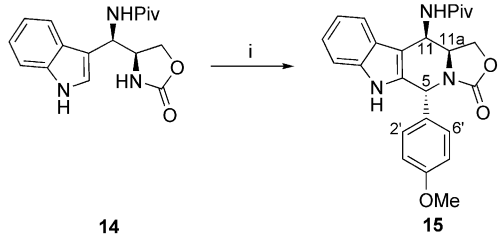


Scheme 3. Synthesis of the key intermediate **14**. Reagents and conditions: (i) H_2, cat. $Pd(OH)_2$, MeOH/AcOH (85:15), room temp., 48 h (quant.); (ii) PivCl (2.6 equiv.), Et_3N (1.6 equiv.), THF, room temp., 5 h (96%); (iii) Li (7 equiv.), NH_3/THF, –78 °C, 30 min (quant.).

The choice of the adequate protecting group for the primary amine **12** was then essential for the development of our strategy: it has to be electron-withdrawing and bulky[14] to avoid its implication in the final Pictet–Spengler cyclization. This protecting group must also be stable under both acidic and basic conditions; the pivaloyl group meets all these criteria.

Treatment of the primary amine **12** with pivaloyl chloride (2.6 equiv.) in CH_2Cl_2 in the presence of Et_3N gave the amide **13** in 96% isolated yield. The debenzylation reaction of the oxazolidinone moiety of **13** with lithium (7 equiv.) in liquid NH_3/THF at –78 °C gave compound **14** in a nearly quantitative yield (Scheme 3).[15] Overall, this key intermediate was obtained in three steps from *N*-hydroxylamine **11a** in 96% yield and in seven steps from the commercial (*S*)-glycidol (**7**) in 29% overall yield.

The next goal of the multi-step synthesis of the (11*R*,11a*S*,5*R*)-11-(pivaloylamino) analog **15** consisted of the implementation of the Pictet–Spengler reaction by treatment of compound **14** with *p*-methoxybenzaldehyde dimethylacetal under acidic conditions.[16] We found that the best results were obtained in an anhydrous CH_2Cl_2/CF_3COOH (3:1) mixture at 40 °C. Under these conditions, adduct **15** was obtained in 82% yield as a single diastereoisomer (Scheme 4).



Scheme 4. Pictet–Spengler reaction. Reagents and conditions: (i) *p*-methoxybenzaldehyde dimethylacetal (3 equiv.), CH_2Cl_2/TFA (3:1), 40 °C, 7 h (82%).

Similar Pictet-Spengler reactions have already been described in the literature for the synthesis of indole alkaloids,[17] azaelliptitoxin and analogs[5] as well as azapodophyllotoxin derivatives.[18] It is reported that the C-5 stereogenic center created during the reaction has a *trans* relationship with the C-11a center of the oxazolidinone moiety to afford a 1,3-*trans* stereochemistry.

The relative and absolute stereochemistries of the stereogenic centers C-5, C-11 and C-11a in **15** were determined by NOE experiments (^{1}H NMR, 500 MHz, C_6D_6) (Figure 4). It was observed that irradiation of 11a-H induced a positive NOE on 11-H, showing the expected *syn* relationship.

Moreover, the coupling constant between these two hydrogen atoms ranged from 3.1 Hz (^{1}H NMR, 400 MHz, $CDCl_3$) to 3.0 Hz (^{1}H NMR, 500 MHz, C_6D_6), which is in accordance with the values given in the literature for a similar structure.[19] On the other hand, irradiation of 11a-H did not induce an NOE on 5-H, demonstrating a *trans* relationship between them. Finally, an NOE was observed on

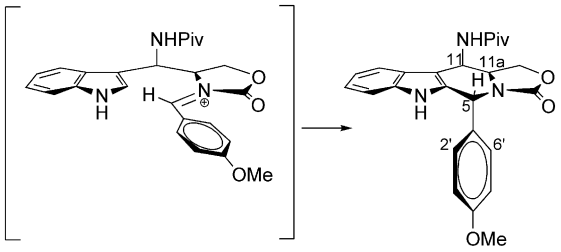


Figure 4. Stereoselectivity model for the Pictet–Spengler reaction.

the aromatic 2′-H and 6′-H protons after irradiation of 11a-H, confirming that the aromatic pendant group was on the α side of the molecule (Figure 4). These results correspond well with those described in the literature.[19] In our reaction, the corresponding *cis* 5-H/11a-H stereoisomer was not observed. It is possible to conclude that in compound **15** the aromatic pendant group adopts a pseudo-axial orientation. For steric reasons, the plane of this aromatic pendant ring is approximately orthogonal to the rest of the molecule.

This result is in good agreement with the conclusions described by Lemaire and co-workers[12d] who reported that, during the synthesis of tetrahydroisoquinoline derivatives, the stereochemical outcome of the Pictet–Spengler reaction could be rationalized by a cyclization step involving the attack of the aromatic core on the (*Z*)-iminium moiety from the less hindered side, leading to the 1,3-*trans* derivatives (Figure 4).

During reaction of **14** with *p*-methoxybenzaldehyde dimethylacetal, the nucleophilic attack of the indole ring on the less hindered side of the (*Z*)-iminium moiety led to the expected compound **15**. The stereochemistry of the newly created stereogenic center C-5 is governed by the stereochemistry of the oxazolidinone core, leading to a 1,3-*trans* relationship between the two implicated substituents, not by the presence of the 11-amino substituent.

Conclusions

Enantiopure 11-(pivaloylamino) analog **15** of azaelliptitoxin **3** has been prepared in eight steps from (*S*)-glycidol (**7**) in 24% overall yield. The strategy is based on the preparation of the enantiopure α-chiral aldehyde (*R*)-**9** and its use as a building block in the stereoselective synthesis of **15**, which has the same absolute stereochemistry (11*R*,11a*S*,5*R*) than azaelliptitoxin (**3**) and the corresponding 11-amino derivatives **5b**. We described the first enantioselective synthesis of the key intermediate (*R*)-**9** in a two-step sequence from (*S*)-glycidol (**7**). Application of this stereoselective multistep sequence to the preparation of more complex analogs of azaelliptitoxin is currently under investigation in our group.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data and NMR spectra for compounds **8**–**15**.

Acknowledgments

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