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Synthesis of advanced intermediates for the preparation of aza-analogues of podophyllotoxin

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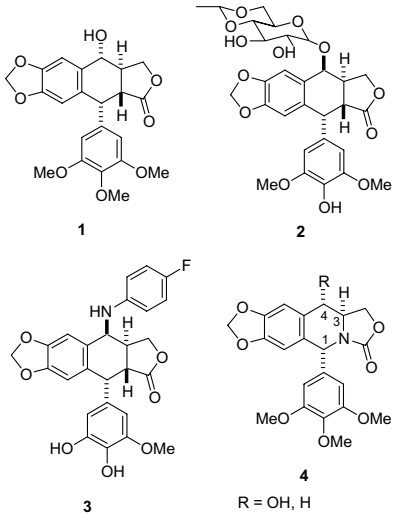
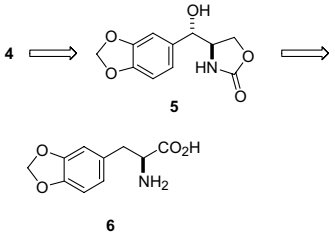
Abstract—Some central intermediates useful for the synthesis of aza-analogues of the anti-cancer drug podophyllotoxin have been prepared starting from L-DOPA and (*R*)-Garner aldehyde.

The interesting biological properties displayed by podophyllotoxin **1** and its congeners, have spurred the development of several synthetic approaches for the assembling of this polycyclic molecule.[1] A consistent number of structural modifications have been introduced in the original skeleton of **1** in order to overcome some toxic side effects associated with its utilization as anti-cancer drug. Among these derivatives, etoposide **2** seems the most effective one as topoisomerase II inhibitor.[2] Aza-analogues of **1** as compounds **3** and **4**, incorporating a nitrogen atom in the molecular framework, also show an enhanced pharmacological profile.[3]





Scheme 1.

The assembling of aza derivatives of type **4** often requires as pivotal intermediate oxazolidin-2-one **5** that can be prepared from α-amino acid **6** (Scheme 1).[4]

Compound **6** in optically pure form was originally prepared by resolution of the corresponding racemic mixture[5] and only recently by asymmetric synthesis.[6]

We have devised a new procedure to accede to derivative **5** that makes use of L-DOPA methyl ester **7** as chiral source. α-Amino acid derivative **7** is transformed into carbamate **8** and then converted into methylene acetal **9** using CH_2Cl_2/CsF in DMF (Scheme 2).[7] Reduction of the ester function in **9** with $NaBH_4/CaCl_2$ and then base induced cyclization gives oxazolidin-2-one **10**.[8] Benzylic

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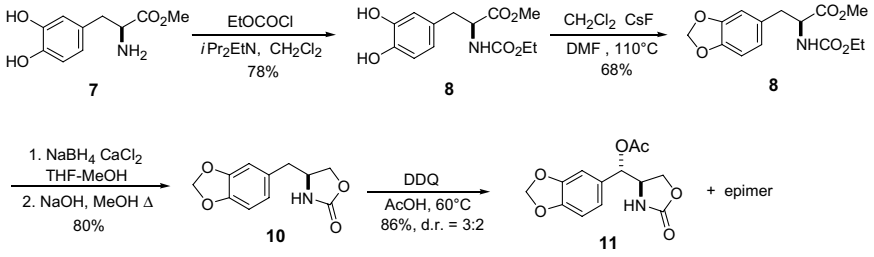
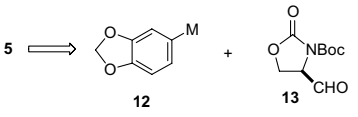


Scheme 2.



Scheme 3.

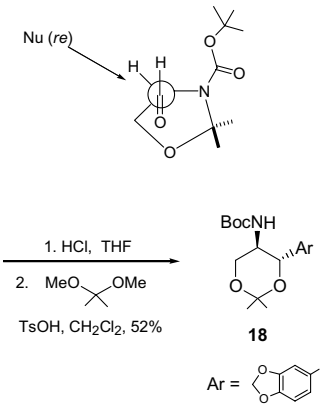
oxidation of compound **10** is carried out with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in AcOH giving acetoxy derivative **11** and its epimer in 3:2 diastereomeric ratio and 86% yield.[9]

The low diastereoselectivity observed in the last step prompted us to elaborate an alternative protocol for the preparation of compound **11**. A possible solution could be found in the diastereoselective addition of an organometallic reagent **12** to aldehyde **13** (Scheme 3).

Unfortunately, every attempt to prepare aldehyde **13** by reduction of the corresponding ester or oxidation of the primary alcohol failed. Therefore, we decided to reverse this synthetic strategy creating the benzylic stereocenter before the oxazolidin-2-one ring. For this purpose, (*R*)-Garner aldehyde **14** is made to react with commercially available organomagnesium reagent **15** to give adduct **16** in good yield and satisfactory diastereoselectivity (*anti*:*syn* = 9:1) (Scheme 4).

Acetylation and hydrolysis of the oxazolidine ring[10] provides alcohol **17** that is converted into oxazolidin-2-one **11** using $SOCl_2$.[11]

The *anti*-diastereoselectivity observed in the formation of alcohol **16** can be rationalized taking into account for a Felkin–Ahn transition state that involves the attack of

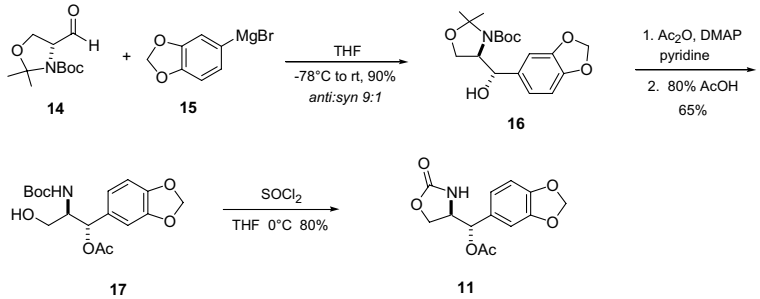


Scheme 5.

the nucleophile from the *re*-side of the substrate (Scheme 5).[12]

The assignment of the newly formed stereocenter has been made transforming alcohol **16** into the corresponding 1,3-dioxane derivative **18**. Evaluating the coupling constants between H-4 and H-5 a value $J_{4-5} = 9.3$ Hz was obtained and this reveals a *trans* relationship between the aryl and carbamoyl groups.[13]

Recently, we have demonstrated that chiral oxazolidin-2-ones can be converted into α-amidoalkylphenyl sulfones by condensation with an appropriate aldehyde and benzenesulfinic acid.[14] These sulfones react with Lewis acids at low temperature giving the corresponding *N*-acyliminium ion derivatives.[15] These electrophilic intermediates rapidly add with nucleophilic reagents and electron rich aromatics both inter- and intra-molecularly.

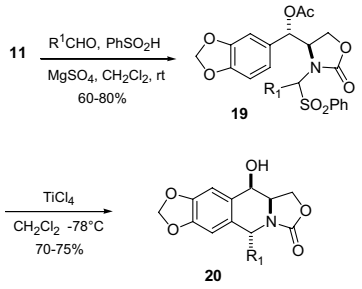


Scheme 4.

Table 1. Synthesis of derivatives **19** and **20** from oxazolidin-2-one **11**

Entry	R	19	Yield (%)[a]	20	Yield (%)[a]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)
1	Ph	**19a**	80	**20a**	75	−35.1 (0.35)
2	cC_6H_{11}	**19b**	60	**20b**	73	−81.2 (0.25)
3	Me_2CHCH_2	**19c**	61	**20c**	70	25.1 (0.40)
4	$PhCH_2CH_2$	**19d**	64	**20d**	75	32.6 (0.50)

[a] Yields of pure, isolated products.



Scheme 6.

Reaction of compound **11** with different aldehydes and $PhSO_2H$ gives the corresponding α-amidoalkylphenyl sulfones **19** as an epimeric mixture in moderate to good yield (Scheme 6).

Sulfones **19** react with $TiCl_4$ at −78 °C to produce an *N*-acyliminium ion that undergoes a rapid ring closure to afford derivative **20** in fairly good yield as a single isomer (Table 1).[16]

The acidic conditions also produce a deacetylation at the benzylic position and upon quenching with water the corresponding alcohol of opposite configuration is obtained.[17] The nature of the stereocenter at C-4 was ascertained through the analysis of the coupling constants between H-3 and H-4 ($J_{3-4} = 1.8$ Hz) that clearly indicate a *cis* relationship of the corresponding hydrogens.

In conclusion, a novel approach to the synthesis of some useful intermediates for the preparation of aza-analogues of podophyllotoxin has been devised. Compound **11** has been finally converted by a two-step procedure into 4-*epi*-aza-podophyllotoxin derivatives **20**. Further work devoted to maintain the correct stereochemistry at C-4 during the cyclization step is currently in progress in our laboratory.

Acknowledgements

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16. Compound **20a**: waxy solid; $[\alpha]_D^{20}$ −35.1° (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.21 (br s, 1H), 4.34–4.40 (m, 1H), 4.46 (dd, 1H, $J = 2.2$, 8.4 Hz), 4.62 (dd, 1H, $J = 1.8$, 8.4 Hz), 5.06 (dd, 1H, $J = 1.8$, 8.0 Hz), 5.98 (d, 1H, $J = 1.5$ Hz), 6.00 (d, 1H, $J = 1.2$ Hz), 6.41 (s, 1H), 6.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 53.1, 56.4, 59.2, 65.7, 102.0, 108.8, 109.1, 127.0, 128.6, 128.8, 129.1, 132.6, 141.6, 147.7, 149.2, 159.8.
17. A similar trend has been reported by Tomioka et al.[4a] using triflic acid in dichloromethane–methanol for the final cyclization step.