N-Substituted Tetronamides as Ambident Nucleophilic Building Blocks for the Synthesis of New 4-Aza-2,3-didehydropodophyllotoxins

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Received 13 March 2008

Dedicated to Professor Jean-Pierre Genêt in honor of his 65th birthday

Abstract: Aza-analogues of podophyllotoxin were synthesized in two steps from N-substituted tetronamides. The acid-mediated benzhydrylation of N-substituted tetronamides with a suitably functionalized benzhydrol quantitatively afforded the cyclization precursors. The target pentacyclic 4-aza-2,3-didehydropodophyllotoxins were next obtained via an intramolecular copper-mediated Ullmann-type N-arylation.

Key words: podophyllotoxin, benzhydrylation, copper, N-arylation, tetronamide

Podophyllotoxin (Figure 1), the parent member of aryltetralin lignan lactone family,[2] was first isolated in 1880 from podophyllin,[3] a resinous powder obtained by precipitating an alcoholic tincture of American Mayapple rhizome (*Podophyllum peltatum*). Although the medicinal properties of podophyllotoxin have been known for thousands of years, particular attention toward this molecule arose since the discovery of its antimitotic activity,[4] due to its high affinity for tubulin.[5] Indeed, podophyllotoxin, while altering cellular division during mitosis, triggers cellular death.[6] However, the use of this molecule as anticancer agent is hampered due to its high toxicity associated with numerous secondary effects such as nausea, diarrhea, vomiting and injury of healthy tissues.[7] As a consequence, several hemisynthetic derivatives, such as etoposide[8] or teniposide[9] have been developed and successfully used for the clinical treatment of several cancers, including small cell lung carcinoma, testicular cancer, or Kaposi's sarcoma.[10] Interestingly and in contrast to podophyllotoxin, these analogues do not target tubulin, but inhibit topoisomerase II, a nuclear enzyme involved in transitional breaks of DNA double-strand and compulsory for transcription.[11] More recently, it was reported that picropodophyllin and various aza-analogues of podophyllotoxin (Figure 1) are potent selective inhibitors of the insulin-like growth factor 1 receptor (IGF-1R).[12] These compounds blocking tyrosine phosphorylation, can be considered as interesting drugs for the treatment of IGF-1R dependent diseases, such as cancer, psoriasis, arteriosclerosis and others endocrine or metabolic disorders. Indeed, the IGF-1R plays a central role in the transformation, growth and survival of malignant cells.[13] As a consequence, the development of new aza-analogues of the podophyllotoxin family is a crucial area of research.[14] The synthesis[15] and biological evaluation of 4-aza-2,3-didehydropodophyllotoxins by Takeya et al.[16] and the development of an efficient multicomponent one-step procedure toward similar structures by Husson et al.[17] represent two relevant examples in this field.

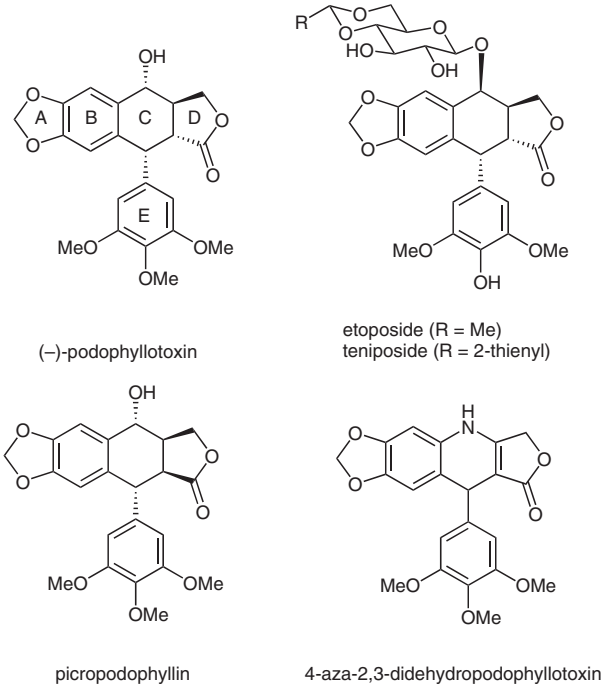
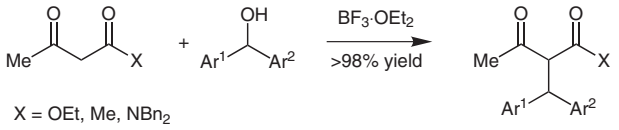


Figure 1 Structures of podophyllotoxin and related aryltetralin lignan lactones

In 2002, we described the acid-mediated reaction between active methylenes such as ethyl acetoacetate, acetylacetone and *N*,*N*-dibenzylmalonamic acid methyl ester with benzhydrols or their derivatives, to afford the corresponding alkylated products in quantitative yields (Scheme 1).[18] This new reaction could later be exploited for the preparation of an advanced intermediate of podophyllotoxin[19] and of an aza-analogue of it.[20]

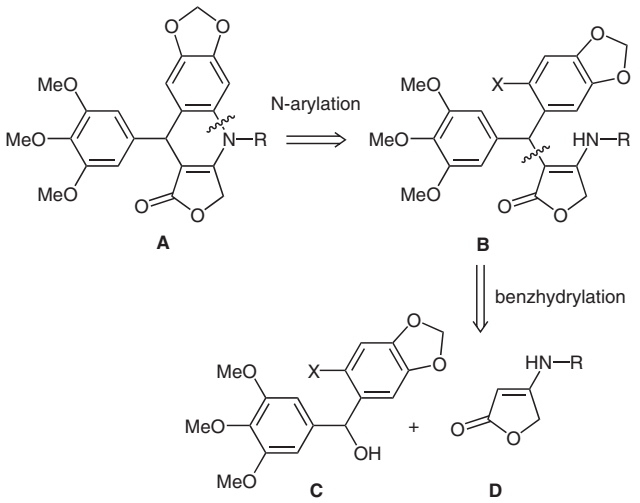
From these results and following our ongoing interest in the synthesis of aza-analogues of podophyllotoxin, we next envisaged to exploit N-substituted tetronamides,[21] vinylogous carbamates easily available from tetronic acid,

SYNLETT 2008, No. 10, pp 1475–1478
Advanced online publication: 16.05.2008
DOI: 10.1055/s-2008-1078429; Art ID: G09508ST



Scheme 1 Acid-mediated benzhydrylation of active methylenes

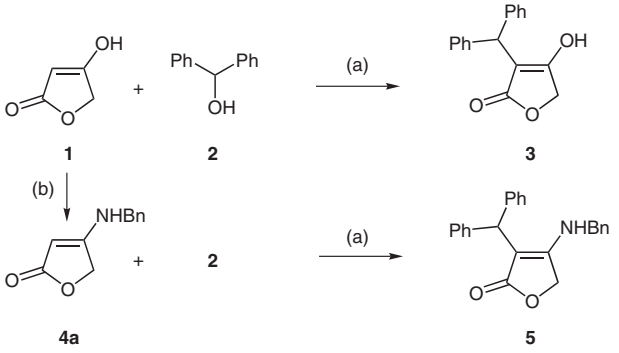
as ambident nucleophilic building blocks to generate the D-ring of 4-aza-2,3-didehydropodophyllotoxins. We describe herein the synthesis of such analogues following the retrosynthetic strategy depicted in Scheme 2.



Scheme 2 Retrosynthetic approach to 4-aza-2,3-didehydropodophyllotoxins

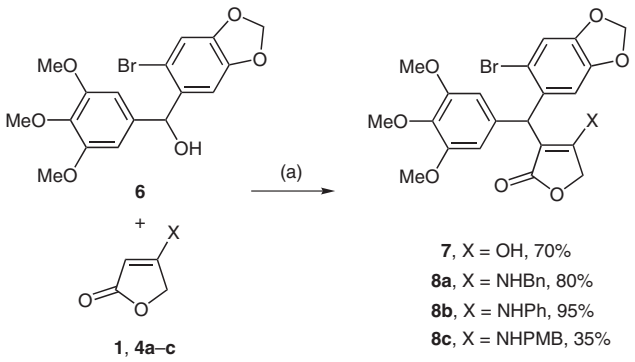
The targeted 4-aza-2,3-didehydropodophyllotoxins **A** would result from the intramolecular N-arylation of benzhydryltetronamides **B**. The latter intermediates could in turn arise from alkylation of N-substituted tetronamides **D** with the functionalized benzhydrol **C**, according to our acid-catalyzed methodology.[18]

The feasibility of this type of benzhydrylation was first studied in the direct reaction of tetronic acid (**1**) with benzhydrol (**2**; Scheme 3). In this event, treatment of an equimolar mixture of **1** and **2** with $BF_3{\cdot}OEt_2$ (1.5 equiv) in CH_2Cl_2 at room temperature gave the desired alkylated tetronic acid **3** in quantitative yield. Encouraged by this result, *N*-benzyl tetronamide (**4a**), easily obtained from tetronic acid and benzylamine,[22] was then engaged in the same procedure. Again, the expected corresponding adduct **5** was quantitatively obtained.



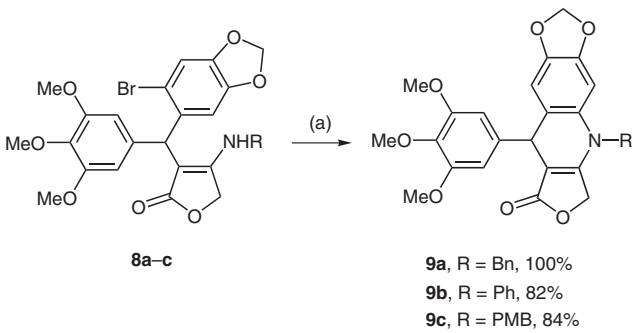
Scheme 3 *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$ (1.5 equiv), CH_2Cl_2, r.t., 2 h, quantitative; (b) $BnNH_2$ (5 equiv), AcOH, reflux, 3 h, 53%.

Properly functionalized benzhydrylic alcohol **6**, required for the synthesis of aza-analogues of podophyllotoxin, was obtained from piperonal and 1-bromo-3,4,5-trimethoxybenzene, according to the two-step procedure described by Jung et al.[23] Then, its reaction with tetronic acid (**1**) and three other *N*-alkyl tetronamides **4a–c** was studied (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$ (3 equiv), CH_2Cl_2, r.t., 2 h.

Tetronic acid (**1**) reacted with benzhydrol **6** to afford the corresponding adduct **7** in 70% yield. In this case, and not unexpectedly, the use of an excess of Lewis acid (3 equiv) was required for satisfactory kinetics. Indeed, the several Lewis basic sites present in the benzhydrylic substrate **6** are likely to interact with the Lewis acid, thereby inhibiting the ionization process, necessary for the alkylation to take place. Reaction between *N*-benzyl tetronamide (**4a**) or *N*-phenyl tetronamide (**4b**)[22] and **6**, using the above optimized reaction conditions, gave rise to the corresponding alkylated products **8a** and **8b** in 80% or 95% yields, respectively.[24] Disappointingly enough, tetronamide **4c**, derived from *p*-methoxybenzylamine, afforded the desired product **8c** in a moderate 35% yield.



Scheme 5 *Reagents and conditions*: (a) CuI (1.2 equiv), Cs_2CO_3 (2.5 equiv), DMF, 90 °C, 16 h.

With the desired intermediates **8a–c** in hand, we next studied the intramolecular C–N bond-forming reaction. Buchwald–Hartwig palladium-catalyzed N-arylation[25] was first tested using precursor **8a** as the model substrate. Unfortunately, the use of Pd_2dba_3 or $Pd(OAc)_2$ as palladium sources, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), P(*o*-Tol)$_3$ or P(*t*-Bu)$_3$ as ligands, and *t*-BuONa as base at reflux of toluene did not afford the desired pentacyclic product, the starting material being totally recovered. A copper-mediated Ullmann-type N-arylation was thus envisioned as an alternative.[26] Much to our satisfaction, treatment of the benzhydrylated *N*-benzyl tetronamide **8a** with CuI (1.2 equiv) and Cs_2CO_3 (2.5 equiv) in DMF gave, after 16 hours at 90 °C, according to Fukuyama's protocol,[27] the expected 4-aza-2,3-didehydropodophyllotoxin **9a** in quantitative yield (Scheme 5). Analogously, starting from the N-substituted tetronamide precursors **8b** and **8c**, the corresponding aza-analogues **9b** and **9c** were obtained in 82% and 84% yields, respectively.[28,29]

In summary, three aza-analogues of podophyllotoxin have been synthesized in two steps using *N*-alkyl tetronamides as suitable ambident D-ring generating building blocks. The cyclization precursors were formed through the Lewis acid mediated benzhydrylation of *N*-alkyl tetronamides with a suitably functionalized benzhydrol. The desired pentacyclic structure of the 4-aza-2,3-didehydropodophyllotoxins was next obtained via an intramolecular copper-mediated Ullmann-type N-arylation. The elaboration of the cyclization precursors by a multicomponent reaction and the development of a copper-catalyzed N-arylation of these enamines are currently under investigation.

Acknowledgment

CNRS, CNR and UPMC are acknowledged for financial support. The sponsorship of COST Action D40 'Innovative Catalysis: New Processes and Selectivities' is kindly acknowledged.

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(24) **Representative Experimental Procedure for Benzhydrylation Reaction**: To a stirred solution of benzhydrol **6** (437 mg, 1.1 mmol, 1.1 equiv) and enamine **4a** (189 mg, 1 mmol) in anhyd CH_2Cl_2 (10 mL) under a N_2 atmosphere at r.t. was added $BF_3{\cdot}OEt_2$ (0.380 mL, 3 equiv). The mixture was stirred for 2 h before a sat. aq $NaHCO_3$ solution (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were washed with brine (5 mL), dried over $MgSO_4$ and

concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane–EtOAc, 7:3) to afford the alkylated product **8a** as a white foam (455 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 6 H), 3.80 (s, 3 H), 4.05–4.16 (m, 2 H), 4.64–4.79 (d, AB system, *J* = 15.4 Hz, 2 H), 5.38 (s, 1 H), 5.93 (d, *J* = 1.3 Hz, 1 H), 6.00 (d, *J* = 1.3 Hz, 1 H), 6.35 (s, 2 H), 6.65 (s, 1 H), 6.95 (d, *J* = 7.6 Hz, 2 H), 7.07 (s, 1 H), 7.32–7.28 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.0, 47.8, 56.3, 61.0, 65.3, 95.8, 101.9, 105.7, 109.6, 113.5, 115.8, 126.6, 128.3, 129.1, 133.3, 136.0, 136.7, 137.1, 147.4, 147.5, 153.7, 163.3, 174.5. IR (neat): 3375, 2930, 2870, 1730, 1625, 1585, 1500, 1475, 1415, 1230, 1120, 1035 cm^{-1}. HRMS (CI): *m*/*z* calcd for $C_{28}H_{26}O_7N^{79}BrNa$: 590.07849 and $C_{28}H_{26}O_7N^{81}BrNa$: 592.07692; found: 590.07755 and 592.07560.

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(28) **Representative Experimental Procedure for Intramolecular Copper-Mediated N-Arylation Reaction**: To a solution of cyclization precursor **8a** (217 mg, 0.38 mmol) in anhyd DMF (4 mL) at r.t. were added CuI (87 mg, 0.46 mmol, 1.2 equiv) and Cs_2CO_3 (311 mg, 0.96 mmol, 2.5 equiv). The resulting mixture was stirred at 90 °C for 16 h. A sat. aq NH_4Cl solution (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The collected organic phases were washed with aq NH_3–NH_4Cl solution (1:1, 10 mL), brine (3 × 5 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (cyclohexane–EtOAc, 7:3) to afford aza-analogue **9a** as a yellow foam (185 mg, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 9 H), 4.75–4.89 (m, 4 H), 5.08 (s, 1 H), 5.89 (d, *J* = 1.2 Hz, 1 H), 5.91 (d, *J* = 1.2 Hz, 1 H), 6.45 (s, 1 H), 6.46 (s, 2 H), 6.59 (s, 1 H), 7.24–7.38 (m, 5 H). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.61 (s, 3 H), 3.73 (s, 6 H), 4.94 (s, 1 H), 4.96 (d, AB system, *J* = 17.4 Hz, 2 H), 5.13 (d, AB system, *J* = 15.9 Hz, 2 H), 5.87 (d, *J* = 0.8 Hz, 1 H), 5.95 (d, *J* = 0.8 Hz, 1 H), 6.53 (s, 2 H), 6.72 (s, 1 H), 6.77 (s, 1 H), 7.29–7.40 (m, 5 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.8, 48.9, 55.8, 59.9, 65.6, 95.5, 96.7, 101.4, 104.6, 110.0, 119.1, 126.5, 127.6, 128.9, 131.1, 136.0, 136.5, 142.6, 143.5, 146.7, 152.9, 159.9, 172.2. IR (neat): 2935, 2845, 1730, 1645, 1615, 1590, 1505, 1475, 1240, 1190, 1125, 1040 cm^{-1}. HRMS (CI): *m*/*z* calcd for $C_{28}H_{25}O_7NNa$: 510.15232; found: 510.15154.

(29) The cyclization of enolic precursors such as **7** to give 4-oxa-2,3-didehydropodophyllotoxin analogues will be the object of a separate study and will be reported elsewhere.