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A Domino N-Amidoacylation/Aldol-Type Condensation Approach to the Synthesis of the Topo-I Inhibitor Rosettacin and Derivatives†

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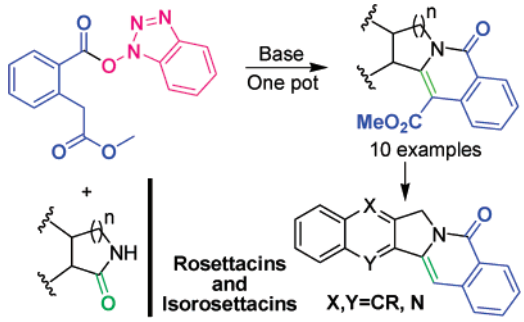
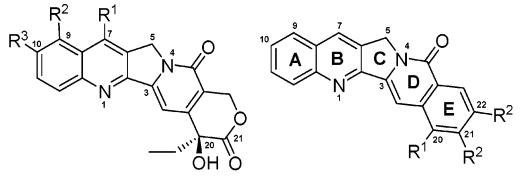


The pot, atom, and step-economic synthesis of Rosettacin topo-I poison and its derivatives has been achieved using a novel domino *N*-amidoacylation/aldol-type condensation, followed by decarboxylation of the ester function. The key domino procedure simply involves mixing HOBt ester as new reagent with lactam and NaH together in THF or THF/DMF. The reaction seems to be general and led to suitable *N*-heterocyclic products in moderate to good yields.

Camptothecin (CPT) and aromathecin alkaloids are a family of natural products containing an indolizino[1,2-*b*]quinolin-9(11*H*)-one nucleus fused to diverse hetero- and carbocyclic rings at the C_7- and C_8-positions. Among them, 20(*S*)-camptothecin (CPT, **1a**, Figure 1), first isolated from the Chinese tree *Camptotheca accuminata* in 1966 by Wall et al.,[1] still serves as a very attractive lead structure for the development of new and potent anticancer drugs due to its antiproliferative activity.[2] Two compounds in this class (Figure 1), topotecan (**1b**) and irinotecan (**1c**), have been used clinically in the United States for advanced ovarian and lung cancers and for colon carcinomas,



1a: Camptothecin; R^1=R^2=R^3=H
1b: Topotecan™ (**Hycamtin**); R^1=H, R^2=CH_2NMe_2, R^3=OH
1c: Irinotecan™ (**Camptosar**); R^1=Et, R^2=H, R^3=OCOPipPip
2a: 22-Hydroxyacuminatine; R^1=CH_2OH, R^2=H
2b: 21,22-Methoxyrosettacin; R^1=H, R^2=OMe
2g: Rosettacin; R^1=R^2=H

FIGURE 1. Camptothecins **1a**−**c** and aromathecins **2a**,**b**,**g**.

respectively.[3] Other derivatives are in preclinical development or clinical trial as exemplified by exatecan, 9-nitrocamptothecin, and BAY 38-3441.[4,5] Because CPTs have some limitations,[6,7] non-camptothecin topoisomerase-I (topo-I) inhibitors such as aromathecins **2a**,**b**,**g** (Figure 1) are being pursued for therapeutic development. This is exemplified by 22-hydroxyacuminatine (**2a**) as a novel and rare quinoline alkaloid isolated along with CPT from *C. accuminata* in very low yield (0.000006%).[8] In spite of its significant cytotoxicity against the murine leukaemia P-388 and KB cell lines in vitro,[9] only four total syntheses have been achieved (Scheme 1). By analogy to the synthesis of CPT,[10] product **2a** was obtained by strategies based on intramolecular Heck ring closure of **I** (7 steps),[11] aza Diels−Alder of **II** (8 steps)[12] and the coupling of 3-cyanophthalide derivatives and pyrroloquinoline **III** (7 steps).[13] In a parallel and recent contribution, Greene et al.[14] have illustrated a modular approach to camptothecinoids from the Padwa hydroxypyridone[15] that involves successively a Claisen rearrangement, a Heck coupling, and a classical Friedländer condensation in an ultimate stage (7 steps).

Most importantly, rosettacins **2b**,**g** belonging to the aromathecin family are scarce and have been used[16,17] as CPT/

† Dedicated to our colleague, Prof. B. Decroix, upon his retirement.
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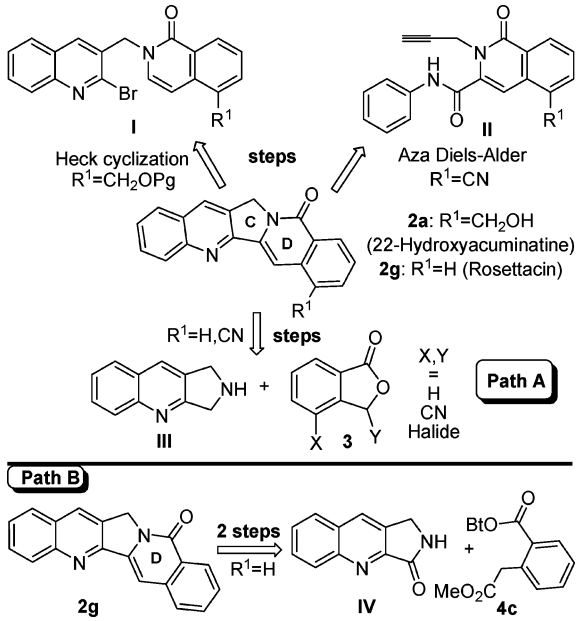
SCHEME 1. Retrosynthesis of Aromathecin Derivatives 2

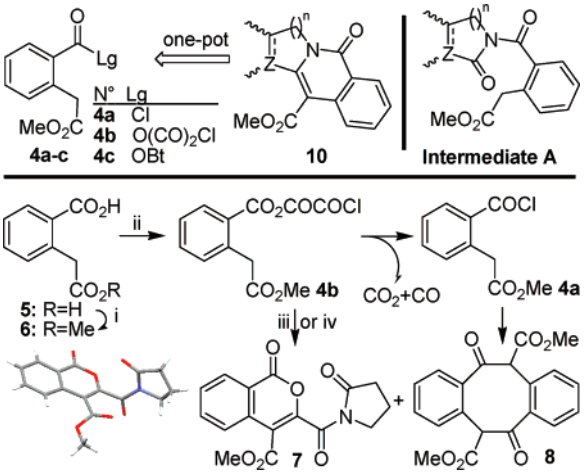


luotonin-A hybrids for binding to the topo-I/DNA covalent binary complex. Both products **2b**,**g** were obtained by improving the strategy in path **A** (Scheme 1) starting from adequately substituted phthalide **3**.[16]

In connection with our ongoing project aimed at the synthesis of aromathecins, we became interested in the reactivity profile of hitherto unknown **4b**,**c** derived from the ester−acid **6** (Scheme 2).[16] The differentiation we put between both trivalent functions in **4a**−**c** is strategically used, so that the aromatic ester can be transformed selectively into imides by different lactams under basic conditions (path **B**, Scheme 1). It was felt that the formation of the D-ring of these platforms might be accomplished by nucleophilic attack of the "enolate" species at one imide carbonyl. This attractive option was based on reports showing that 2-succinimidylbenzylphosphonium ylides underwent smooth Wittig olefination intramolecularly to give the mitosane[18] and quinocarcin[19] ring systems, respectively. Previous investigations[20,21] in isoquinolinone series also validated the practicality of this approach. In these olefination reactions, an imide serves as the electrophile and benzyltrimethylsilane[20] or benzylphosphonium bromide[21] as the nucleophile under the influence of different bases.

In this paper, we report the development of a new and rapid protocol consisting of the domino *N*-amidoacylation/aldol-type condensation on the basis of the unique reactivity of the unknown HOBt ester reagent **4c** (Scheme 2). To the best of our knowledge, no examples from this domino have been reported. Encouraged by recent advances in cascade processes, we decided to explore such sequence notably to elaborate highly functionalized modular scaffolds including the rosettacin topo-I poison, isorosettacin, and various heterocyclic analogues with promising biological profiles.

SCHEME 2. Reactivity of 4 and ORTEP Plot of Derivative 7[a]



[a] Reagents and conditions: (i) MeOH, $NiCl_2 \cdot H_2O$ 10 mol %, reflux, 6 h, 95%; (ii) $(COCl)_2$, DCM, 0 °C up to rt, 2 h, quant; (iii) pyrrolidin-2-one (**9a**), 2.5 equiv of NaH, THF, reflux, 12 h, 70% (**8**/**7** = 13:1); (iv) pyrrolidin-2-one (**9a**), toluene, reflux, 12 h, 68% (**8**/**7** = 8.5:1).

We began the development of this domino by defining its basic requirements with respect to the electrophiles **4** and the reaction conditions. Initially, coupling of **9a** with acid chloride **4b** was attempted using NaH (2.5 equiv) in refluxing THF (conditions iii, Scheme 2). This method was not effective since it provides an unexpected mixture of products **7**/**8** in a 1/13 ratio (70%), which differ only minimally (1/8.5 ratio) when a toluene solution of **4b** was simply refluxed without additional additive (conditions iv, Scheme 2, 68% yield). The formation of **8** could be attributed to the dimerization of **4a**[22] demonstrating the instability of substrate **4b**. Importantly, product **7** has an original structure confirmed further by X-ray analysis.[23] This suggests that the reaction proceeds through an amidoacylation of **4b** at the acid chloride site either with lactam **9a** or with its salt followed ultimately by an intramolecular olefination via the stable enol or enolate species of the acetate fragment. The reaction seems to take place in a one-pot procedure, and during the reaction mechanism the integrity of **4b** was maintained.

From these results, we speculated that diester **4c** would provide the intramolecular olefination of the intermediate **A** for a newly designed domino *N*-amidoacylation/aldol-type condensation (Scheme 2). So, reaction of ester−acid **6** with HOBt and DCC in THF provided the ester **4c** (∼100%).[24] Our latter proposal was then tested by reacting HOBt ester **4c** with lactam **9a** (Table 1) as a model lactam in the presence of a base under different conditions. For instance, after complete consumption of **4c**, to our satisfaction the product **10a** was isolated as the sole reaction product in 82% yield when 2.5 equiv of NaH was used (entry 6, Table 1). The effectiveness and the yield of this process varied greatly depending on both the nature and the quantity of the base used (Table 1).

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(23) See supporting information part or copies of the data of the product **7** (CCDC no. 661267) at http://www.ccdc.cam.ac.uk.
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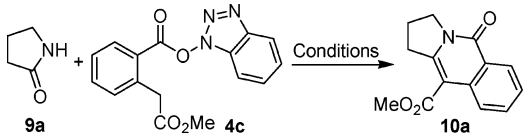
TABLE 1. Optimization of the Domino Process



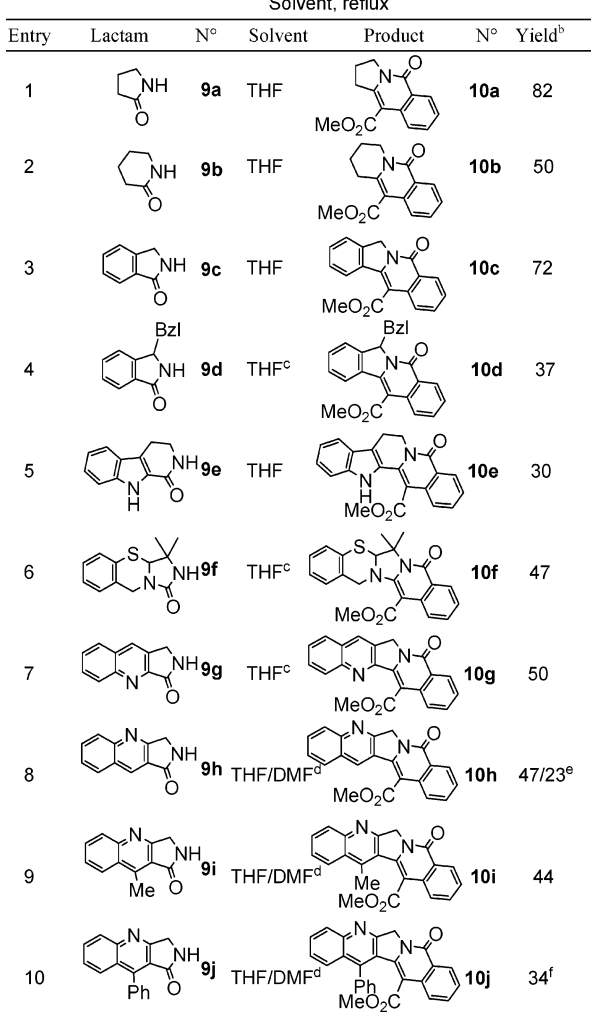
entry	base (equiv)[a]	solvent	*T* (°C)/time (h)	product yield[b] (%)
1	NEt_3 (2.5)	CH_3CN	reflux/12	no reaction
2	*t*BuOK (2.5)	THF	reflux/12	31 + 60 (SM)[c]
3	K_2CO_3 (2.5)	CH_3CN	reflux/12	60 + 23 (SM)[c]
4	NaH (1)	THF	rt/12	no reaction
5	NaH (2.5)	THF	rt/12	83
6	NaH (2.5)	THF	rt/12	83

[a] The pyrrolidin-2-one (**9a**) was purified by distillation before its use. [b] Isolated yield after silica gel chromatography. [c] Starting material.

Having established the effectiveness of the domino *N*-amidoacylation/aldol-type condensation for construction of a pyrroloisoquinolinone template, we then explored the scope of the reaction. The results are tabulated in Table 2. For these reactions, the optimized conditions were used (entry 6, Table 1). It can be seen that changing the size of the lactam (**9b**, entry 2) and its substitution (**9e**, entry 5) gave suitable products **10b**,**e**. However the yields decreased, respectively, to 50% (**10b**) and 30% (**10e**) depending in the latter case probably on the low solubility of the dihydro-*β*-carboline salt intermediate. Reaction efficiency with fused lactams as isoindolones (entries 3 and 4) was proved, and the yields remained the same for **10c** (72%) and lower for **10d** (37%), but in the last case, the reaction heating was prolonged for 12 h. Importantly, a complex substrate **9f**,[25] bearing other functionalities (*N*,*S*-acetal and urea), was also a competent substrate in this process (entry 6, product **10f**, 47% yield). The reactivity of **9g**[26] was effective with acceptable 50% yield under the same conditions. The operability of this domino process was evidenced again when **9h**−**j**[26] (entries 8−10), as the regioisomers of **9g** were submitted to our established protocol. This happened in the presence of DMF as cosolvent in a 1:1 ratio at reflux. Under these conditions, the expected products **10h**−**j** were isolated in yields of 47%, 44%, and 34%, respectively. As expected, a substituent at the C_4-position of the quinoline nucleus proved to have a dramatic effect on the reaction yields, which may be attributed to the hindrance of the methyl and phenyl groups due to their proximity to the ester group (see products **10i**,**j**). It is noteworthy that under standard conditions, **10h** was isolated in low yield (23%) and no reaction occurred starting from **9i** but only traces of **10j** were detected. The result from entry 8 also confirmed our hypothesis regarding the poor solubility during the process of the anionic species formed as intermediates.

Structure confirmation of these polyheterocyclic systems was performed chemically by an approach using a Friedländer reaction as a key step starting from the lactam **10a** (Scheme 3). So, subjected to a Bredereck's reagent (**11**)[27] followed by treatment with $NaIO_4$ in THF/H_2O (1/1), **10a** provided the keto derivative **12** (60%) that was obtained through successive benzylic oxidation and cleavage of the Csp^2−Csp^2 linkage in a one-pot procedure. After certain optimization work (DS, PTSA 10 mol %, toluene, reflux, 12 h), the latter **12** underwent smooth coupling condensation with 1 equiv of 2-aminobenzaldehyde (**13g**) according to the Friedländer reaction.[28] The isolated product **10g** (51%) is identical to that obtained by the direct synthesis via the domino process (entry 7, Table 2). Furthermore, this reaction appeared to be quite general to both aromatic keto-amines **13k**,**l** cited above and provided suitable pentacyclic products **10k**,**l** in 71% and 86% yield, respectively. It is noteworthy that these products are not reported by the direct method due to the long and laborious access to the starting materials such as 1,2-dihydropyrrolo[3,4-*b*]quinolin-3-one substituted with methyl and phenyl groups at the C_9-position. Interestingly, when the reaction was conducted in a one-pot procedure starting from **10a**, evaporation of the solvents after 4 h of the reaction and their replacement with toluene and PTSA/aromatic amine **13g**,**k**,**l** gave the expected products **10g**, **10k**,

TABLE 2. Examining the Scope of the Domino Process[a]



Entry	Lactam	N°	Solvent	Product	N°	Yield[b]
1		**9a**	THF		**10a**	82
2		**9b**	THF		**10b**	50
3		**9c**	THF		**10c**	72
4		**9d**	THF[c]		**10d**	37
5		**9e**	THF		**10e**	30
6		**9f**	THF[c]		**10f**	47
7		**9g**	THF[c]		**10g**	50
8		**9h**	THF/DMF[d]		**10h**	47/23[e]
9		**9i**	THF/DMF[d]		**10i**	44
10		**9j**	THF/DMF[d]		**10j**	34[f]

[a] **9a**,**b** were commercial, and **9c**−**j** were obtained according to known protocols.[25,26] [b] Isolated yield after chromatography. [c] In THF at reflux for 12 h. [d] In THF/DMF (1/1) at reflux for 12 h. [e] In refluxing THF without other cosolvent. [f] Only traces of **10j** were detected.

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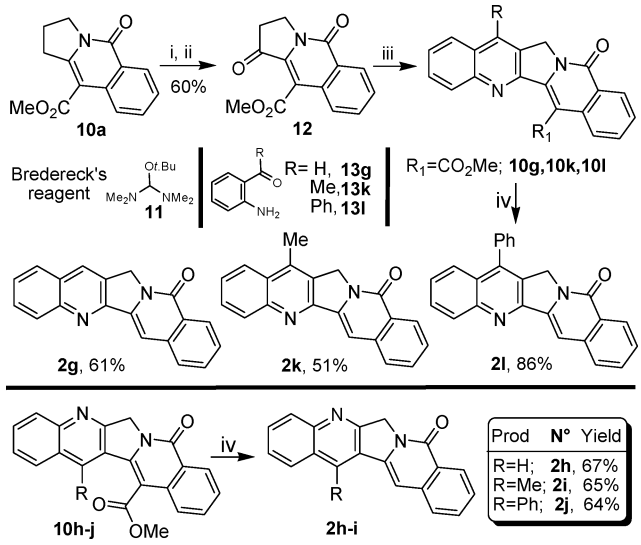
SCHEME 3. Rosettacins 2g−l and Isorosettacins 2h−j[a]



[a] Reagents and conditions: (i) Bredereck's reagent (**11**, 1.4 equiv), 110 °C, 2 h; (ii) $NaIO_4$ (3 equiv), THF/H_2O (1/1), rt, 0.5 h, 60% in two steps; (iii) Aromatic amine (**13g−l**, 1 equiv), 10% PTSA, toluene, reflux, 12 h, 51 up to 86%; (iv) 48% HBr, 135 °C, 12 h, 51 up to 86%.

and **10l** in yields comprable to those reported for the two separate steps.

The concluding step for reaching the targets rosettacin (**2g**), isorosettacin (**2h**), and other aromathecins **2k**,**l** and **2i**,**j** from the corresponding esters **10g−l** proved, however, to be unexpectedly challenging. After several unrewarding attempts, it was discovered that the conditions described by Rigo and coworkers[29] (48% HBr, 135 °C, 12 h) led to the desired products **2g−l** (Scheme 3) in yields ranging from 51% to 86%. The application of the same protocol to the regioisomers esters **10h−j** (entries 8−10, Table 2) also resulted in the formation of the expected and novel isorosettacins **2h−j** in yields around 65% in all cases.

In summary, we have developed a highly efficient, extremely simple, and novel methodology involving a domino *N*-amidoacylation/aldol-type condensation to provide poly-*N*-heterocycles. This is based on the use of HOBt ester **4c** as a new reagent and quite effective source of the quinoline nuclei. A broad variety of quinolinones fused to numerous *N*-heterocycles were prepared in this way, which was illustrated by a rapid, two-step total synthesis of the rosettacin topo I poison and derivatives. Further research from our group will focus on the use of this strategy to build efficiently a variety of compounds including alkaloids with promising therapeutic profiles.

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Experimental Section

Typical Procedure for the Synthesis of Rosettacin (2g). To a 0.1 M THF solution of HOBt ester (**4c**, 311 mg, 1 mmol) and lactam (**9g**, 184 mg, 1 equiv) was added in one portion 2.5 equiv of NaH. After 12 h at reflux, the reaction was hydrolyzed with saturated NH_4Cl solution and worked up by extracting either with Et_2O or with DCM. Pure **10g** (280 mg) was isolated by chromatography on a silica gel column (AcOEt/cyclohexane as eluent) in 82% yield. Compound **10g** (342 mg, 1 mmol) in 7 mL of 48% HBr was then heated under stirring at 135 °C for 12 h. After cooling, the solution was alkalinized and extracted twice with DCM (10 mL). A classical workup provided pure rosettacin (**2g**) as a light-yellow solid in 61% yield (171 mg): R_f 0.19 (cyclohexane/AcOEt 1:1); mp 288 °C (lit.[30] mp 289−291 °C; lit.[31] mp 286 °C); IR (KBr) ν 1663, 1628, 1602, 1504, 1479, 1398, 1384, 1239, 1216, 1166 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.31 (s, 2H, CH_2N), 7.49−7.65 (m, 3H, H_{aro}), 7.68−7.86 (m, 4H, H_{aro}), 8.17 (d, 1H, H_{aro}, J = 7.8 Hz), 8.26 (s, 1H, H_{aro}), 8.49 (d, 1H, H_{aro}, J = 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.7 (CH_2), 101.6 (CH_{aro}), 126.3 (C_q), 127.6 ($2CH_{aro}$), 127.7 (CH_{aro}), 127.8 (CH_{aro}), 128.2 (C_q), 128.3 (CH_{aro}), 129.0 (C_q), 129.6 (CH_{aro}), 130.5 (CH_{aro}), 131.1 (CH_{aro}), 132.7 (CH_{aro}), 137.7 (C_q), 140.1 (C_q), 148.9 (C_q), 153.7 (C_q), 161.2 (C═O). Anal. Calcd for $C_{19}H_{12}N_2O$ (284.09): C, 80.27; H, 4.25; N, 9.85. Found: C, 80.11; H, 4.09; N, 9.77.

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Supporting Information Available: Experimental procedures, product characterization for all new compounds synthesized, and an ORTEP plot of product **7** as well as its CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702387Q

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