New Alkylidenecyclopropane Amino Acid Derivatives for an Efficient Construction of the 6*H*-Pyrrolo[3,4-*b*]pyridine Skeleton

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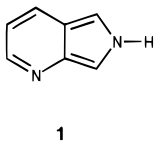
Alkylidenecyclopropanes form a peculiar class of strained olefinic compounds, with remarkable synthetic potential;[1,2] thus, they undergo ring opening with palladium dichloride to produce π-allylpalladium complexes,[3] carbopalladation with vinyl and aryl halides in the presence of Pd(0),[4] regioselective Pd(0)-catalyzed [3 + 2] cycloaddition with olefinic and acetylenic substrates,[1,5] and Pauson−Khand cyclization with dicobalt hexacarbonyl complexes of acetylene.[6,7] Most of these reactions have been reported to occur both inter- and intramolecularly.[4,8] Moreover, alkylidenecyclopropanes constitute the most suitable precursors for cyclobutanone synthesis.[9] As in the case for many cyclopropane derivatives, they are also endowed with specific bioactivities.[10] Optically active alkylidenecyclopropanes have recently been prepared by the regio- and stereoselective Pd(0)-catalyzed reduction of asymmetric 1-(1-alkenyl)cyclopropyl esters by sodium formate.[11]

The 6*H*-pyrrolo[3,4-*b*]pyridine ring system **1** (Figure 1)[12] is of current interest due to its presence in the skeleton of very important antitumor agents such as *camptothecin* **2** and to the biological properties of new related compounds (e.g., antiretroviral activity, modulation of protein synthesis, ...).[13]



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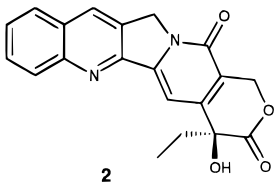

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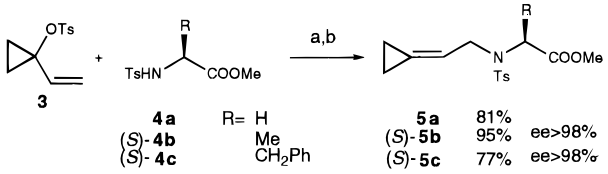
Figure 1. 6*H*-Pyrrolo[3,4-*b*]pyridine (**1**) and camptothecin (**2**).

Scheme 1[a]



[a] Key: (a) 6 mol % $Pd(dba)_2$, 7.2 mol % dppe, THF, rt; (b) 1 equiv of **4a**−**c**, 1 equiv of NaH, THF, rt, 1 h, 70−95%.

We report here a new and efficient synthesis of optically pure diazabicycloheterocycles derived from **1**. Thus, Pd(0)-catalyzed nucleophilic substitution of the 1-vinyl-1-(tosyloxy)cyclopropane **3**[14] (readily available from vinylation and tosylation[15] of cyclopropanone hemiacetal)[16] by the methyl *N*-tosylglycinate (**4a**) (R = H), (*S*)-(+)-alaninate (**4b**) (R = Me), and (*S*)-(−)-phenylalaninate (**4c**) (R = $PhCH_2$) in the presence of 1 equiv of NaH produced the methyl *N*-(2-cyclopropylideneethyl)-*N*-tosylamino acid esters **5a**, (*S*)-**5b**, and (*S*)-**5c** in 81, 95, and 77% yields, respectively; no significant epimerization of the chiral center was observed for (*S*)-**5b**,**c** (ee >98%) (Scheme 1).[17] It must be noted that the Pd(0)-catalyzed reaction of tosylate **3** with simple amines or imines led exclusively to 2-cyclopropylideneethylamine derivatives;[18] use of *N*-(diphenylmethylene)glycine esters as the nucleophile, following the same process, was shown to provide α-allyl-α-amino acids resulting from C-allylation.[19]

Partial reduction of ester **5a** by 0.9 equiv of DIBAH provided the 2-aminoethanal **6a**, which was treated directly with methylhydroxylamine hydrochloride in ether in the presence of pyridine (1.1 equiv).[20] The resulting (*Z*)-nitrone **7a**[20] was not isolated but underwent ready intramolecular 1,3-dipolar cycloaddition[8] to produce exclusively the spiro bicyclic isoxazolidine **8a**, in 70% overall yield from **5a**. Otherwise, (*S*)-**5b**,**c** were reduced by 2.5 equiv of DIBAH, and the corresponding alcohols were then oxidized under Swern conditions[21] to

(1) For a review see: Binger, P.; Büch, H. M. Cyclopropenes and Methylenecyclopropanes as Multifunctional Reagents in Transition Metal Catalyzed Reactions. *Top. Curr. Chem.* **1987**, *135*, 77−151.

(2) For a review see: Goti, A.; Cordero, F. M.; Brandi, A. Cycloadditions onto Methylene- and Alkylidenecyclopropane Derivatives *Top. Curr. Chem.* **1996**, *178*, 1−97.

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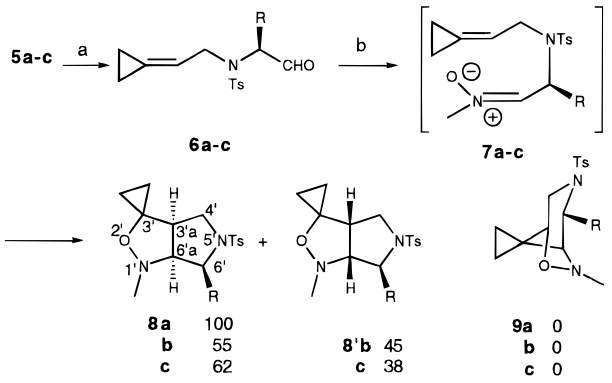
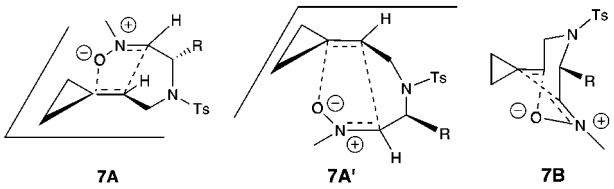
Scheme 2[a]



[a]Key: (a) 0.9 equiv of DIBAH, CH_2Cl_2, −78 °C, 1 h or (i) 2.5 equiv of DIBAH, (ii) $(COCl)_2$, DMSO, iPr_2EtN; (b) 1.2 equiv of MeNHOH−HCl, 1.4 equiv of pyridine, H_2O, rt, 18 h, 70−76% overall yield from **5a**−**c**.

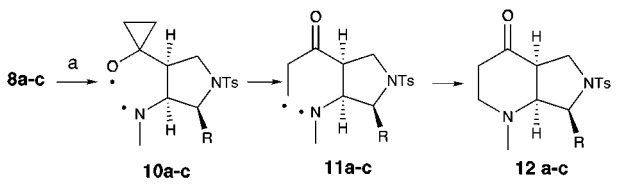
Scheme 3. Transition States of the 1,3-Dipolar Cycloaddition of (*Z*)-Nitrones 7a−c



provide the 2-aminoethanal (*S*)-**6b,c**. Upon treatment with MeNHOH−HCl, (*S*)-**6b** gave the (*Z*)-nitrone (*S*)-**7b**,[20] which underwent cycloaddition to give a 55/45 diastereomeric mixture of the fused cycloadducts (3′a*R*,6′*S*,6′a*R*)-**8b** and (3′a*S*,6′*S*,6′a*S*)-**8′b** in 76% overall yield from the amino ester (*S*)-**5b**, while the aldehyde (*S*)-**6c** (R = $PhCH_2$) led after reaction with MeNHOH−HCl via the nitrone (*Z*)-**7c**[20] to a 62/38 diastereomeric mixture of fused cycloadducts (3′a*R*,6′*S*,6′a*R*)-**8c** and (3′a*S*, 6′*S*,6′a*S*)-**8′c** in 70% overall yield (Scheme 2).

The regioselectivity of the cycloaddition, i.e., the exclusive formation of the fused adducts **8a**−**c** and the lack of bridged adducts **9a**−**c**,[22] is supported by simple molecular mechanics calculations (MAD).[23] Thus, the difference of total steric energies between the optimized geometries of the conformations of the transition states leading to cycloadducts **8a**−**c** or **9a**−**c** (ΔE = −15 kcal/mol) suggests kinetic control of the reaction. The formation of the two diastereomeric cycloadducts **8b** and **8′b** observed from the (*Z*)-nitrone (*S*)-**7b** (R = Me) and of the two diastereomeric cycloadducts **8c** and **8′c** from the (*Z*)-nitrone (*S*)-**7c** (R = $PhCH_2$) probably results from the two possible approaches of the dipolarophile by the (*Z*)-nitrone moieties, either from above (transition state **7A**) or from below (transition state **7A′**) the plane of the alkylidenecyclopropane (Scheme 3). Analogous MAD calculations of the difference of energies between the conformations of the transition states leading to cycloadducts **8b** and **8′b** (ΔE = −1.5 kcal/mol) or to **8c** and **8′c** (ΔE = −3.6 kcal/mol), respectively, confirm that the presence of a methyl or benzyl substituent on carbon 6′-C did not induce in these cases any significant diastereoselectivity ascribed to a steric effect.[24] Fortunately, cycloadducts **8b** and **8′b** as well as **8c** and **8′c** were separable by flash chromatography, and their structures were determined by ^1H and ^{13}C NMR spectroscopy. For instance, after irradiation of the methyl on carbon 6′-C at δ 1.35 ppm, the major isomer **8b** showed a doublet at δ 3.65 ppm (J = 7.40 Hz) for the 6′-H proton, while the minor isomer **8′b** showed a doublet at δ 3.20 ppm (J = 5.36 Hz) for the same proton; as J_{cis} is larger than J_{trans} in isoxazolidine and pyrrolidine rings,[22] the observed coupling constants supported the structure assignments.

Scheme 4[a]



[a] Key: (a) xylene reflux, 6 h, 43−64%.

On heating in xylene at reflux for 6 h, the N−O isoxazolidine bond of the tricyclic isoxazolidines **8a**−**c** was cleft to produce the cyclopropyloxy diradicals **10a**−**c**, which then readily underwent cyclopropane ring opening with strain release into the diradicals **11a**−**c**, followed by ring reclosure, to afford the diazaheterocycles **12a** (49%) and (1*R*,6*S*,9*S*)-**12b**,**c** (43−64%, Scheme 4). The isoxazolidines **8′b**,**c** underwent the thermal induced ring expansion to give the diastereomeric (1*S*,6*R*,9*S*)-diazaheterocycles. Epimerization of diamines **12b,c** was not observed under these conditions[25] and the whole process occurred with the maximum "*atom economy*" as no added reagent or catalyst was required after nitrone formation.

Now readily available, the derivatives of 2,4-diazabicyclo[3.4]octan-7-ones **12a**−**c** are specific substance P (SP) antagonists both in vitro and in vivo (IC_{50} ranges from 0.8 to 3 μM for the NK_1 receptor of human IM_9 cells[26,27]); they appeared as promising therapeutic agents for the treatment of important diseases (asthma, inflammation and pain, migraine, and vascular headaches).[28] Moreover, they constitute suitable precursors of bioactive alkaloids such as camptothecin (**2**), for instance, and analogous derivatives. Synthetic applications of these new diazaheterocycles are currently under investigation.

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Supporting Information Available: Full experimental procedures and complete spectral data for all reaction products (8 pages).

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(25) No interconversion was observed between **8b,c** and **8′b,c** respectively, during the radical rearrangement step.

(26) Unpublished results. Private communication from Dr. J. F. Peyronel (Medicinal Chemistry Department, Rhone-Poulenc Rohrer Central Research, France).

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