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Synthesis of a model compound of mappicine ketone based on sulfur-directed 5-*exo* selective aryl radical cyclization onto enamides

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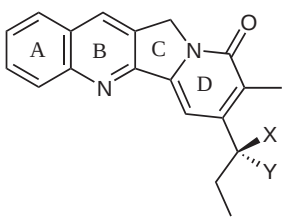
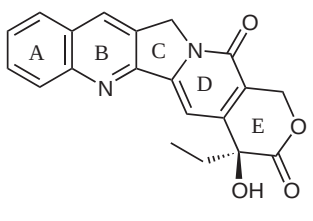
Abstract—Enamides **10**, upon treatment with Bu_3SnH–AIBN, gave 5-*exo* aryl radical cyclization products **11**, which were partially desulfurized to give 1-substituted dihydroisoindoles **7** and **12**. This method was applied to the synthesis of a model compound **4** of mappicine ketone (**1**). © 2001 Elsevier Science Ltd. All rights reserved.

Mappicine ketone (MPK) (**1**) is an oxidized derivative of mappicine (**2**) and an E ring decarboxylated analogue of camptothecin (**3**), the parent member of an important family of anticancer agents. MPK has recently been identified as an antiviral lead compound with selective activities against herpesviruses HSV-1 and HSV-2 and human cytomegalovirus (HCMV).[1] While camptothecin is now available from natural sources in quantity,[2] MPK has only been isolated in low content which prohibits isolation of useful amounts for further studies. Therefore, efforts have been made recently to improve the degradation[3] of camptothecin as well as to develop new synthetic methods of MPK and related compounds.[4] In the present paper, we describe a novel approach to MPK, exemplified by the synthesis of a model compound **4**, using sulfur-directed 5-*exo* selective aryl radical cyclization onto enamides as a key step.

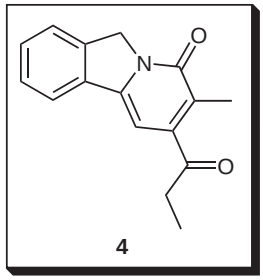
A previous study in our laboratory revealed that enamide **5a**, upon treatment with Bu_3SnH in the presence of azobiscyclohexanecarbonitrile (ACN), underwent aryl radical cyclization in a 6-*endo* manner to give a tetrahydroisoquinoline derivative **6**, whereas enamide **5b** having a (*Z*)-phenylthio group at the terminus of the *N*-vinylic bond afforded a 5-*exo* cyclization product **7**.[5] On the other hand, enamide **5c** having an (*E*)-phenylthio group showed an intermediate behavior to give approximately equal amounts of a 6-*endo* cyclization product **8** and 5-*exo* cyclization product **7**. The difference between the modes of cyclization of **5a**–**c** can be explained in terms of the difference between the conformers of their enamide double bonds.



1: X ,Y = O (Mappicine Ketone)
2: X = OH, Y = H (Mappicine)



3: Camptothecin



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Keywords: antivirals; aryl halides; enamides; isoindoles; radicals and radical reactions.
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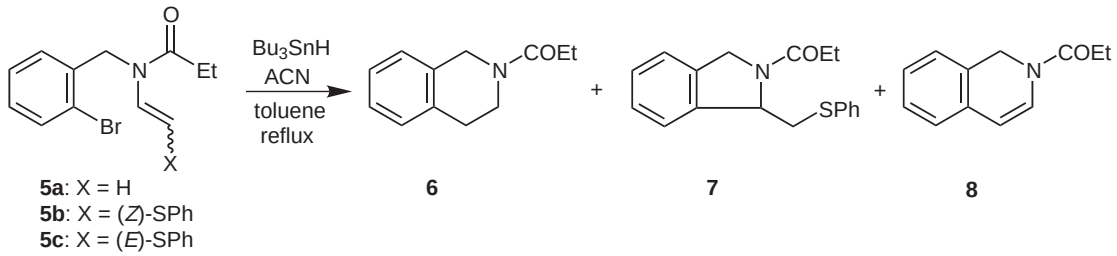
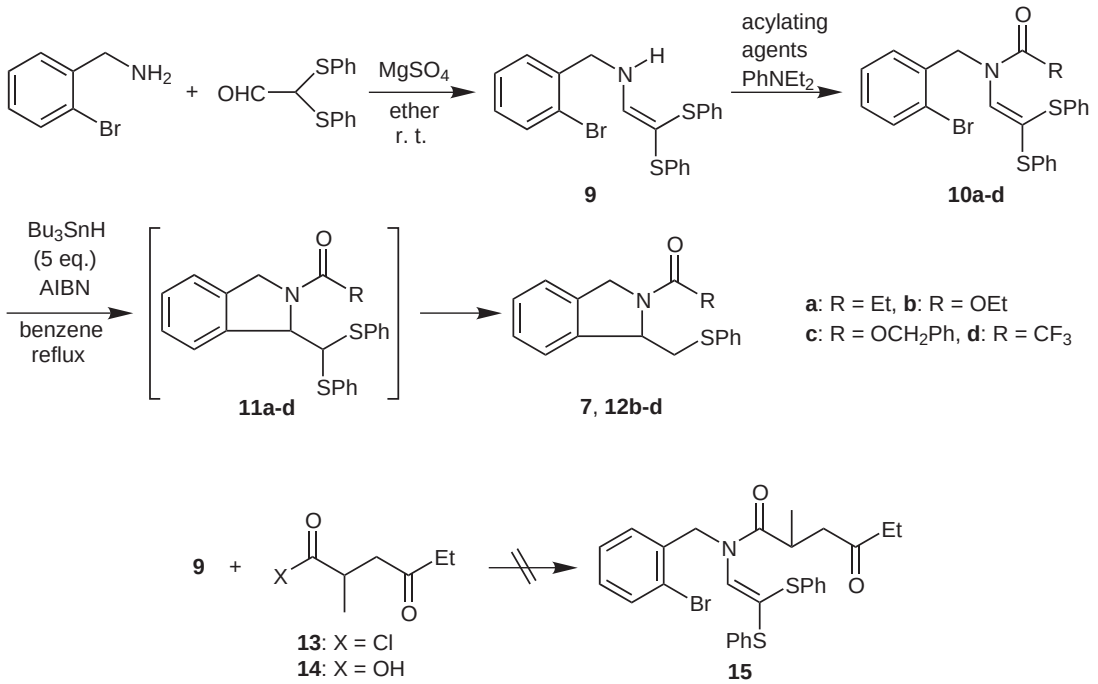


The exclusive formation of **7** from **5b** seems to be highly promising for the construction of B–C–D rings of MPK, since the sulfur atom incorporated into **7** would serve as a handle for elaboration of the C–C bond of the D ring. The (*Z*)-phenylthio-substituted enamide **5b**, however, could be obtained only as a minor product during the course of the preparation of the corresponding (*E*)-isomer **5c**. Therefore, our attention was turned to an alternative synthesis of **7** by aryl radical cyclization of **10a** having two phenylthio groups at the terminus of the *N*-vinylic bond.

Enamide **15** would be the most suitable precursor for the synthesis of **4** via the radical cyclization product **17**. However, acylation of **9** with acid chloride **13**[8] or with the parent acid **14**[8] was unsuccessful. Therefore, we decided to prepare compound **17** from **12b–d**.

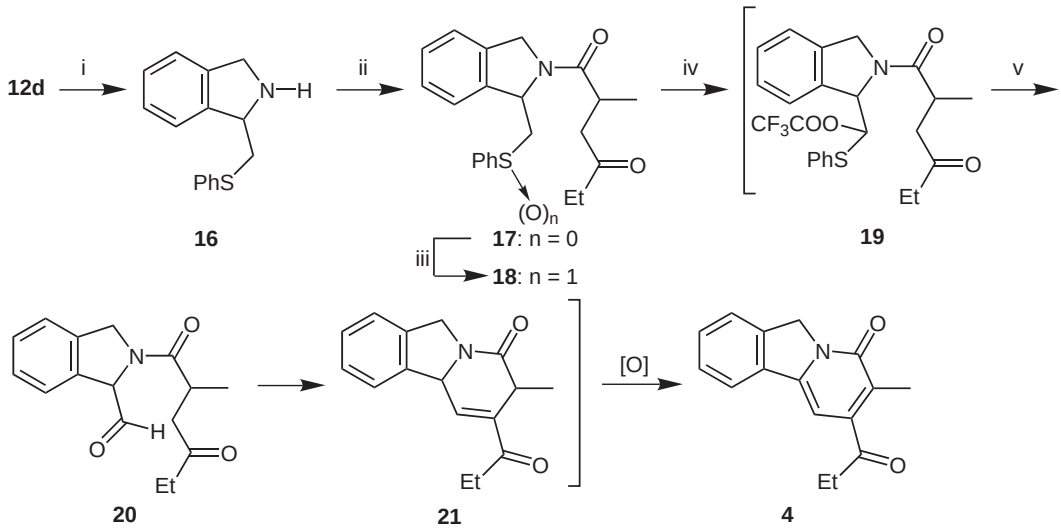


The requisite radical precursors **10a–d** were readily prepared as follows. Condensation of *o*-bromobenzylamine with bis(phenylthio)acetaldehyde gave enamine **9**[6] in 69% yield, which was then treated with acid chlorides in the presence of diethylaniline in boiling benzene [except for **10d**: $(CF_3CO)_2O$, toluene, room temp.] to give enamides **10a–d** in 78, 72, 51 and 92% yields, respectively.

Treatment of **10a** with 1.1 equiv. of Bu_3SnH in the presence of AIBN in boiling benzene gave a mixture of the 5-*exo* cyclization product **11a** and the corresponding partially desulfurized compound **7** in 38 and 27% yields, respectively, along with the recovered starting material **10a**. When enamide **10a** was treated with 5 equiv. of Bu_3SnH, compound **7** was obtained as a sole product in 68% yield. The exclusive formation of the 5-*exo* cyclization product **7** from **10a** via **11a** may be ascribed to the presence of a (*Z*)-phenylthio group in **10a** as in the case of **5b**.[5,7] Similar treatment of **10b–d** afforded **12b–d** in 84, 68 and 85% yields, respectively.

When compound **12c** was subjected to hydrogenolysis with a Wilkinson catalyst $[RhCl(PPh_3)_3]$ in benzene[9] or treated with trimethylsilyl iodide in acetonitrile, the starting material was completely consumed, but no desired amine **16** could be obtained. The preparation of amine **16** was best achieved by treating trifluoroacetamide **12d** with K_2CO_3 in MeOH–H_2O (15:1) at room temp.[10] This amine was then acylated with carboxylic acid **14** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), DMAP and 1-hydroxybenzotriazole (HOBt) to give the desired amide **17** in 64% yield (based on **12d**). Oxidation of **17** with MCPBA (73%) followed by treatment of the resulting sulfoxide **18** with trifluoroacetic anhydride (TFAA) gave a Pummerer rearrangement product **19**.

This compound, without purification, was then heated in MeOH containing 10% aq. NaOH to give the target compound **4** in 45% yield (based on **18**). Formation of **4** from **19** can be explained by a three-step sequence of the reactions involving alkaline hydrolysis of trifluoroacetate **19**, intramolecular aldol condensation of the resulting aldehyde **20**, and auto-oxidation of the six-membered unsaturated lactam **21**. Although it is not clear presently whether the compound **4** was formed from **21** or from its regioisomer with respect to the double bond, it should be noted that no specific oxidizing agent such as DDQ was required in the final step.



i) K_2CO_3, MeOH-H_2O (15:1), room temp.; ii) **14**, EDC, DMAP, HOBt, CH_2Cl_2, room temp.; iii) MCPBA, CH_2Cl_2, 0 °C; iv) $(CF_3CO)_2O$, CH_2Cl_2, 0 °C; v) 10% NaOH, MeOH, reflux.

Thus, we demonstrated the feasibility of using sulfur-directed 5-*exo* selective aryl radical cyclization of *o*-bromobenzyl enamides **10** for the synthesis of a model compound **4** of MPK. An application of this method to the synthesis of MPK is now under investigation, and the results will be reported in due course.

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6. ^{1}H NMR for **9** (diagnostic data only): δ 4.29 (d, $J=6.3$ Hz, 2 H, ArCH_2), 5.43 (dt, $J=13.2$, 6.6 Hz, 1 H, NH).
7. For other sulfur-directed *exo* selective radical cyclizations, see: (a) Ishibashi, H.; Kameoka, C.; Iriyama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* **1995**, *60*, 1276; (b) Ishibashi, H.; Kawanami, H.; Nakagawa, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2291; (c) Ishibashi, H.; Kobayashi, T.; Takamasu, D. *Synlett* **1999**, 1286.
8. Carboxylic acid **14** was prepared by alkylation of methyl 3-oxopentanoate with methyl 2-bromopropionate (K_2CO_3, Bu_4NI, acetone, 77%) followed by decarboxylative hydrolysis (AcOH, conc. HCl, 89%). Acid chloride **13** was prepared from **14** [$(COCl)_2$, pyridine, benzene].
9. It has been reported that catalytic hydrogenation of sulfur-containing compounds such as allyl phenyl sulfide is effected with a Wilkinson catalyst in benzene. See: Birch, A. J.; Walker, K. A. M. *Tetrahedron Lett.* **1967**, 1935.
10. Alkaline hydrolysis of **12b,c** required rather drastic conditions and long reaction times.