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Tetrahedron Letters 45 (2004) 997–999
Tetrahedron Letters

A facile total synthesis of rutaecarpine

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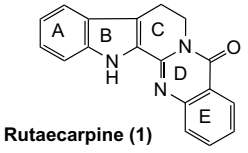
Received 29 August 2003; revised 12 November 2003; accepted 21 November 2003

Abstract—The indoloquinazoline alkaloid rutaecarpine has been synthesized efficiently by employing 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]quinazoline-4,9-dione (**4**) as a key intermediate, which was prepared by adapting a Dieckmann condensation–decarboxylation sequence from quinazolinone diester **6**.

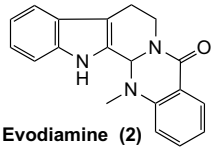
Rutaecarpine (**1**) (7,8-dihydro-5*H*,11*H*-indolo(2′,3′;3,4) pyrido[2,1-*b*] quinazolin-5-one) belongs to the quinazolino carboline type of alkaloids isolated from the genera *Evodia, Horita*, *Zanthoxylum*, *Euxylophorea*, *Phellodendron* and all members of Rutaceae.[1] It is one of the constituents of the Chinese herbal drugs' Wou-hou-Yu[2] and Shih-Hu[3], which have been used for gastrointestinal disorders, headache and dysentery.

Rutaecarpine (**1**) and its derivatives **2** containing the pharmacologically important quinazolinone[4] skeleton demand interest as hypertensive, diuretic and uterotonic, positive inotropic and platelet aggregation inhibitory agents.[5] Recently 10-bromorutaecarpine and 11-methoxy and 10,11-methylenedioxy rutaecarpines have been shown to possess cytotoxic activity.[6] The hypotensive, antiarrhythmic, antianoxic and vasorelaxant effects have been investigated more intensively and synthetic and pharmacological development in this field may lead to therapeutic applications.[5] Attracted by the impressive scaffold and pharmacological properties of this class of alkaloids we set out to develop a synthetic route to rutaecarpine, which would be able to access its analogues as well and could be readily adapted for the solid phase synthesis of this class of compounds.

Among the various approaches reported,[7] Kokosi's et al.[7f] approach involved the construction of the AB rings by the widely used Fischer indole synthesis,[8] in which an *N*-aryl hydrazone undergoes acid-catalyzed or



Rutaecarpine (1)



Evodiamine (2)

thermal sigmatropic rearrangement to generate, after elimination of ammonia, the indole skeleton. This approach has been generalized to access various analogues of rutaecarpine.[9] Obtaining phenyl hydrazones from tetrahydropyrido quinazolinones is the limiting factor of this, otherwise excellent, synthetic route to obtain the derivatives of rutaecarpine. They have been made via prior functionalization of the 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolinone, which in turn has to be made by adapting a multistep sequence.

Although a number of methods exist for the preparation of *N*-aryl hydrazones,[10] the most common is the condensation of an aldehyde or ketone with an *N*-aryl hydrazine. We have found that a convenient access to the desired *N*-aryl hydrazones for the synthesis of rutaecarpine **1** is via the ketone, hitherto not reported, with an aryl hydrazine as shown in our retrosynthetic analysis (Scheme 1). So the problem of devising a synthetic route to rutaecarpine is reduced to the preparation of the 8,9-dihydro-7*H*-pyrido[2,1-*b*]quinazoline-6,11-dione **4** as shown. A Dieckmann condensation–decarboxylation sequence from the quinazolinone diester **6** has been envisaged for the assembly of the C-ring.

Thus treatment of isatoic anhydride **7** with ethyl γ-aminobutyrate hydrochloride in DMF in the presence of DMAP as a catalyst[11] furnished amine **8**, which was condensed with ethyl oxalyl chloride to obtain the amide **9** in near quantitative yield. Cyclodehydration of the

Keywords: Rutaecarpine; Indoloquinazoline alkaloid; Dieckmann condensation–decarboxylation.
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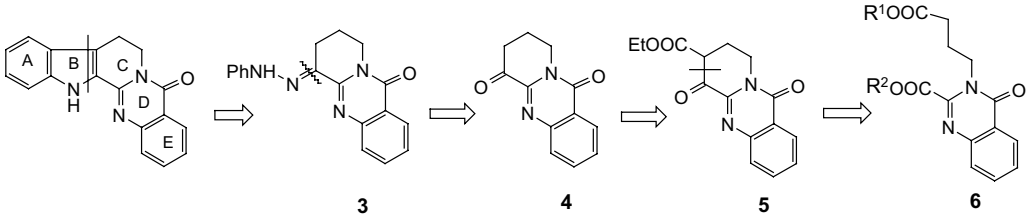
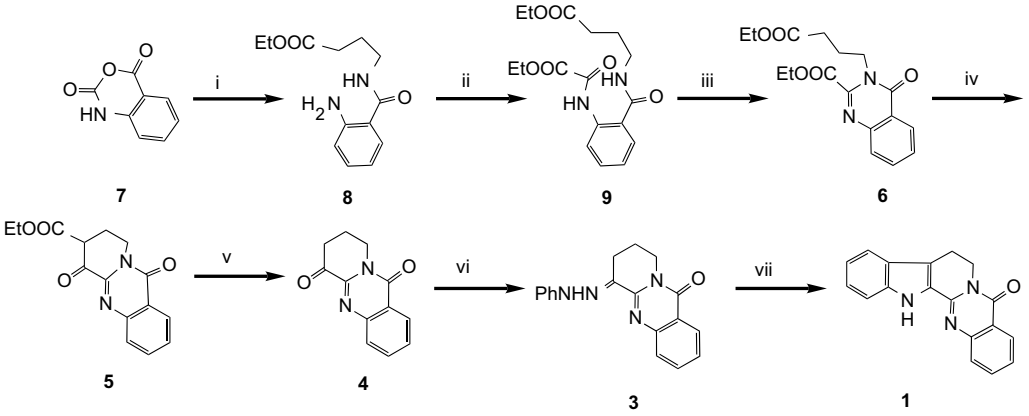
doi:10.1016/j.tetlet.2003.11.090



Scheme 1.



Scheme 2. Reagents and conditions: (i) Ethyl γ-aminobutyrate hydrochloride, DMF, Et_3N, DMAP (cat), 96%; (ii) ethyl oxalyl chloride, DCM, K_2CO_3, 98%; (iii) PCl_3, xylene, reflux, 2 h, 80%; (or) (a) Ph_3P, I_2, Et_3N, DCM, 70%; (b) piperidine, DCM; (c) CH_3CN, reflux, 1.5 h, 75%; (iv) NaH, DMF, 80%; (v) 6 N HCl, 81%, reflux; (iv) $PhNHNH_2$, 98%; (vii) PPA, 180 °C, 95%.

amide **9** to the quinazolinone diester **6** was best achieved with PCl_3 in refluxing xylene. Alternatively, treatment of amide **9** with $PPh_3/I_2/Et_3N$[12] followed by refluxing the amidine so formed with piperidine in acetonitrile furnished the quinazolinone diester **6**. Having obtained the diester **6** with suitable functionality the stage was set to investigate the proposed strategy that is, the Dieckmann condensation for the construction of the β-keto ester. Among the various bases and conditions tried, NaH/DMF afforded the β-keto ester **5** in 80% yield. β-Keto ester **5**, which existed in its enol form, was decarboxylated to afford 9,10,11,12-tetrahydro-4*H*-pyrido[2,1-*b*]-quinazoline-4,9-dione **4** under refluxing conditions with aqueous 6 N HCl. The dione **4** was treated with phenylhydrazine under acidic conditions to form hydrazone **3** in almost quantitative yield. Hydrazone **3** was subjected to the Fischer indole synthesis as reported earlier.[7f] Thus heating the hydrazone in freshly prepared PPA at 180 °C for 0.5 h furnished rutaecarpine **1** in 95% yield (Scheme 2).

In summary, we have developed a novel, concise and efficient entry to pyridoquinazolinone alkaloids, which is amenable to access analogues.

Acknowledgements

R.S. thanks CSIR for a fellowship and funding from CSIR (New Delhi) under YSA (SPC) scheme is gratefully acknowledged.

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