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A concise synthesis of furostifoline

Tibor Soós, Géza Timári [†,*] and György Hajós

Institute of Chemistry, Chemical Research Center, H.A.S., PO Box 17, H-1525 Budapest, Hungary

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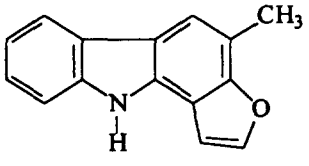
Abstract

A five-step total synthesis of the furo[3,2-*a*]carbazole alkaloid, furostifoline, was achieved using a Pd(0)-catalyzed cross-coupling reaction.

The furo[3,2-*a*]carbazole alkaloid, furostifoline (**1**) was isolated in 1990 from *Murraya euchrestifolia*.[1] The first total synthesis of **1** was reported by Knölker et al.[2] using a convergent iron-mediated construction of the carbazole nucleus. Recently, Beccalli and Hibino have developed an elegant benzofuran ring formation by way of intramolecular photocyclization and electrocyclization, leading to the preparation of **1**.[3]



Furostifoline (1)

We became interested in the synthesis of furostifoline because of its pharmacological potential as well as its structural similarity to some indolo-isoquinolines and indolo-quinolines of antiretroviral activity prepared by us recently.[4]

Herein we report our efforts resulting in a convenient total synthesis of furostifoline. As shown in Scheme 1, the synthesis of **1** was realized through a five-step procedure based on a palladium(0)-catalyzed cross-coupling reaction.[5]

As a first step, bromocresol **2**, easily prepared by bromination of *o*-cresol, was alkylated with bromoacetaldehyde diethylacetal used as a C_2 moiety for the annelation of the furan ring.[6] Formation of the furan ring was achieved by P_2O_5 promoted cyclization in 85% H_3PO_4 at 140°C which provided 5-bromo-7-methylbenzofuran (**4**) in 51% yield.[7] This bromo-compound (**4**) was then coupled with *N*-pivaloylaminophenyl boronic acid (**5**) to yield the biaryl compound (**6**) in satisfactory yield. However,

* Corresponding author. E-mail: geza.timari@sanofi.com

† Present address: CHINOIN Pharmaceutical and Chemical Works Co. Ltd, H-1325 Budapest, PO Box 110, Hungary.

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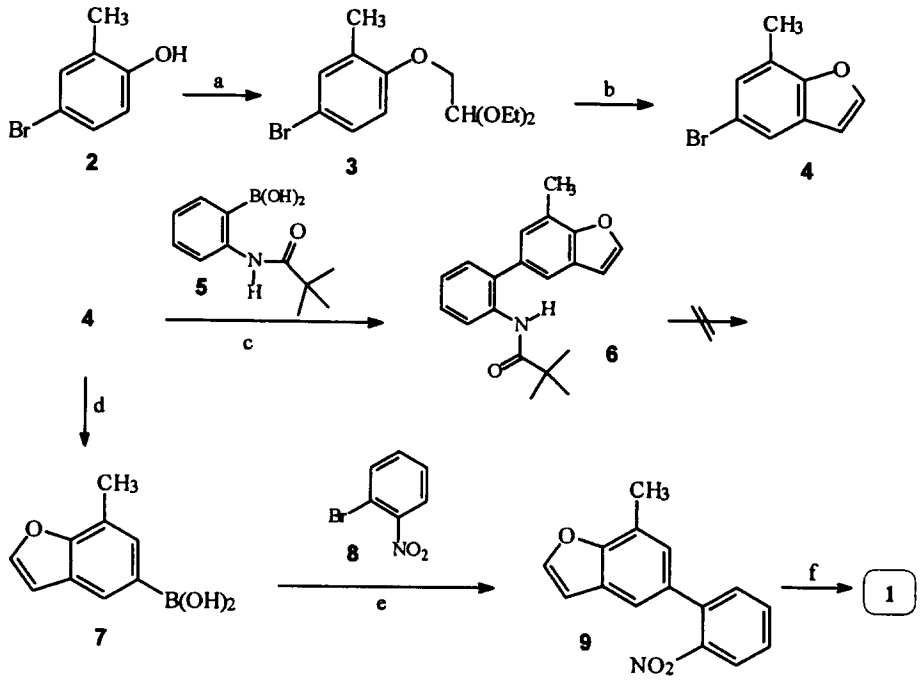

Scheme 1. (a) $BrCH_2CH(OEt)_2$, K_2CO_3, DMF, 100°C, (75%); (b) H_3PO_4, P_2O_5, Ph-Cl, 140°C, 3 h, (51%); (c) Pd(0), Na_2CO_3, DME–H_2O, reflux, 7 h, (65%); (d) THF, −70°C, *n*-BuLi, $B(OBu)_3$, H_2O, (85%); (e) Pd(0), Na_2CO_3, DME–H_2O, reflux, 5 h, (72%); (f) $P(OEt)_3$, reflux, 4 h, (42%) or ferrous oxalate, 280°C, 30 min, (26%)

our attempts to convert the amide (**6**) to the corresponding amine (a routine strategy in the course of a number of successful indolization reaction paths)[4,8] failed, probably due to decomposition of the furan ring during the acidic hydrolysis.

To overcome this difficulty, the reversely functionalized coupling components were employed. Thus, we prepared 7-methylbenzo[*b*]furan-5-boronic acid (**7**) by lithiation of **4** with *n*-BuLi and subsequent treatment with tributyl borate,[9] and this was coupled under Gronowitz conditions with 2-bromonitrobenzene (**8**) to give the biaryl compound **9** in 72% yield.[10] Generation of a nitrene from nitro-compounds is well documented in the literature: the best results being obtained by using triethyl phosphite[11] or ferrous oxalate.[12]

In accordance with our expectations, this approach proved to be successful: deoxygenation of **9** with both triethyl phosphite and ferrous oxalate resulted exclusively in the desired furostifoline (**1**) in 42% and 26% yield, respectively, whose spectral properties were identical with those described in the literature.[1]

In conclusion, we have developed a facile five-step synthesis of furostifoline by using a palladium-catalyzed cross-coupling reaction and regioselective ring closure of the nitrene intermediate generated from the corresponding nitro-compound by deoxygenation.

Acknowledgements

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7. (**4**) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (1H, d, 2.2 Hz), 7.50 (1H, d, 1.9 Hz), 7.18 (1H, d, 1.9 Hz), 6.64 (1H, d, 2.2 Hz), 2.45 (3H, s).
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9. (**7**) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (1H, d, 2.2 Hz), 7.30 (1H, d, 1.8 Hz), 7.06 (1H, d, 1.8 Hz), 6.72 (1H, d, 2.2 Hz), 2.44 (3H, s).
10. (**9**) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (1H, m), 7.64 (1H, d, 2.2 Hz), 7.57 (1H, m), 7.38 (1H, d, 1.7 Hz), 7.23 (1H, m), 7.20 (1H, m), 7.05 (1H, d, 1.7 Hz), 6.90 (1H, d, 2.2 Hz), 2.45 (3H, s).
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