Comments on the Asymmetric Synthesis of Chrysogine†

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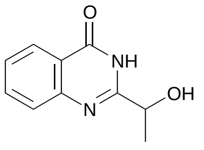
Jan Bergman*

Institute of Biosciences at Novum, Department of Organic Chemistry, S-141 57 Huddinge, Sweden and Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

The absolute configuration of the mould metabolite chrysogine, (*S*)-(−)-2-(1-hydroxyethyl)quinazolin-4(3*H*)-one, was first determined by asymmetric synthesis in 1990 and not in 1996 as recently claimed.

The mould metabolite chrysogine **1** was isolated in 1973 by Hikino *et al*. from strains of *Penicillium chrysogenum*[1] and later by Chadwick from *Alternaria citri*.[2] Related secondary metabolites such as 2-acetylquinazolin-4(3*H*)-one **2** and 2-pyruvoylaminobenzamide **3** have also been isolated, the former from *Fusarium culmorum*[3] and *Alternaria citri*[2] and the latter from *Penicillium chrysogenum*[4] and *Colletotrichum lagenarium*.[5]



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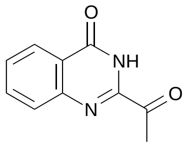

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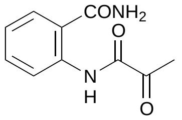

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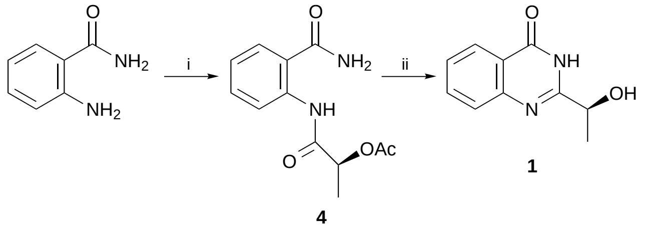
In 1990 we established, in connection with a comprehensive study,[6] the absolute configuration of chrysogine as (*S*)-(−)-2-(1-hydroxyethyl)quinazolin-4(3*H*)-one by asymmetric synthesis as outlined in Scheme 1. The sequence is conveniently completed in one pot but the intermediate **4** can be isolated in 76% yield. Ring closure of **4** and subsequent saponification by aqueous sodium carbonate at room temperature gives chrysogine **1** (75%) with an optical rotation of $[\alpha]_\mathrm{D}$ −41°. This optical rotation is higher than that ($[\alpha]_\mathrm{D}$ $-26 \pm 4°$) reported by Hikino *et al.*[1]



Scheme 1 *Reagents:* i, (*S*)-2-acetoxypropanoyl chloride; ii, Na_2CO_3 (aq)

In 1992 Tamm and co-workers,[7] unaware of our[6] previous work, incorrectly stated 'The configuration of the chiral centre of **1** has never been determined'.[7] The Swiss workers correctly arrived at the conclusion that chrysogine has the *S* configuration using NMR methods.

In 1993 Tsantrizos *et al*. isolated the *R* form of chrysogine (less than 20% ee) from *Fusarium laterritium* Nees. The absolute configuration was proposed from studies using the Mosher ester method.[8] The Canadian workers were likewise unaware of previous studies, as in fact the pure antipode of (*S*)-chrysogine had already been prepared from 2-aminobenzamide and (*S*)-2-chloropropanoyl chloride or, in a better ee, by inversion of the *S* form by the Mitsunobu reaction.[6]

The unawareness of the relevant literature already touched upon has recently led to a paper[9] which claims to report the first asymmetric synthesis of chrysogine. The method is identical with ours described in 1990, with the exception that the Indian workers used sodium hydroxide rather than sodium carbonate in the final cyclization step. This change is probably not the major cause for the relative low rotation ($[\alpha]_\mathrm{D}$ −27°) reported, rather we consider it likely that the (*S*)-2-acetoxypropanoyl chloride used by the Indian workers was partially racemic. Anyhow, it is interesting to note that both forms of chrysogine isolated from Nature are partially racemic.

Finally, Hikino *et al.* coined the name chrysogine which has been used by all subsequent workers as well as in a recent review on quinazoline alkaloids.[10] The name 'chrysogenine' was probably used by the Indian workers inadvertently.

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E-mail: jabe@cnt.ki.se.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.