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THE IMPROVED SYNTHESIS OF 7-OXYGENATED INDOLES BY FISCHER INDOLIZATION AND ITS APPLICATION TO THE FIRST TOTAL SYNTHESIS OF EUDISTOMIDIN-A

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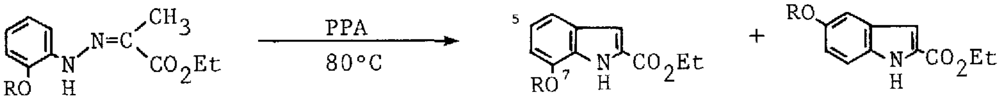
Summary: The Fischer indolization of *o*-sulfonyloxyphenylhydrazones 2b,c was found to give corresponding 7-oxygenated indoles 3 in moderate yields. This method was applied to the first total synthesis of eudistomidin-A 1.

Although Fischer indolization (FI) is known to be one of the most important reactions for construction of the indole nucleus,[1)] it has a great disadvantage[2)] that FI of *o*-methoxyphenylhydrazones does not necessarily give 7-methoxyindole as main product due to cyclization toward an *o*-methoxy group. In this paper we report the improved synthesis of 7-oxygenated indoles by FI and its application to the first total synthesis of eudistomidin-A[3)] 1, which is a recently isolated β-carboline alkaloid having calmodulin-antagonistic activity.

As FI of phenylhydrazones having an electron-attracting substituent (chloro[4a)] or nitro[4b)]) at *o*-position tends to give normal 7-substituted indoles, we attempted the reaction of O-tosyl (Ts) and O-trifluoromethanesulfonyl (Tf) derivatives 2b,c prepared from 2a. The FI of 2b or 2c with PPA gave predominantly the normal 7-sulfonyloxy derivative, 3b or 3c, respectively, along with 5-sulfonyloxy ones 4b,c, the products of abnormal cyclization[2)] (Scheme 1). The hydrazone 2c having more electron-attractive O-Tf than O-Ts 2b gave more 7-substituted indole 3c. The indoles 3b and 3c were easily hydrolyzed to the known 3a[5)] with KOH.

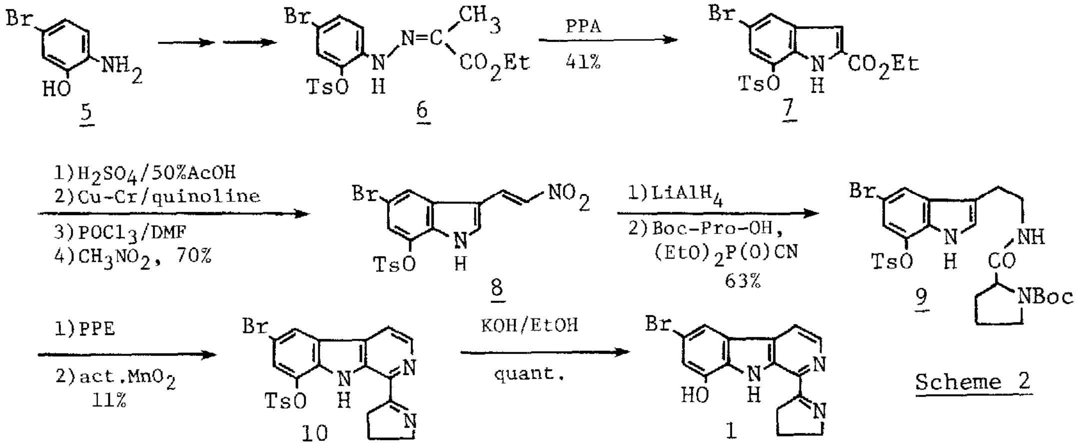
On the basis of the above successful results a synthesis of eudis-



2,a:R=H,b:R=Ts,c:R=Tf   3a,b,c   4b,c

	Reaction time	Yields of products (mp, °C)	
		3	4
2b	30 min	36.9% (135-136)	9.9% (164-166)
2c	1 h	52.8% (85-87)	6.9% (133-136)

Scheme 1



Scheme 2

tomidin-A[3] 1 was conducted. Known 4-bromo-2-hydroxyaniline 5 was converted to the *o*-OTs-phenylhydrazone 6. The FI of 6 with PPA gave the key indole 7 as a sole product. The structure was established by hydrogenolysis of 7 to 3b. An acidic hydrolysis of 7, followed by decarboxylation, formylation, and reaction with nitromethane gave the 3-(nitrovinyl)indole 8, which was converted to the amide 9 by usual manner. The Bischler-Napieralsky reaction of 9 under Hino's conditions,[6] followed by dehydrogenation gave the Ts-β-carboline 10. The alkaline hydrolysis of 10 gave 1 as colorless powder, mp 265-280°C (decomp.) [lit.,[3] mp 225-230°C (decomp.)].[7] The ^1H- and ^{13}C-NMR data of our synthetic sample coincide well with those of natural one.

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References and Notes

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7) Dr. J. Kobayashi recently informed us in a private communication that further purification of natural eudistomidin-A 1 raised its mp to 260-270°C (decomp., moistened at around 255°C).

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