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SYNTHESIS OF DUAL ACTIVITY MOLECULES WITH THROMBOXANE ANTAGONIST AND THROMBOXANE SYNTHASE INHIBITORY ACTIVITY

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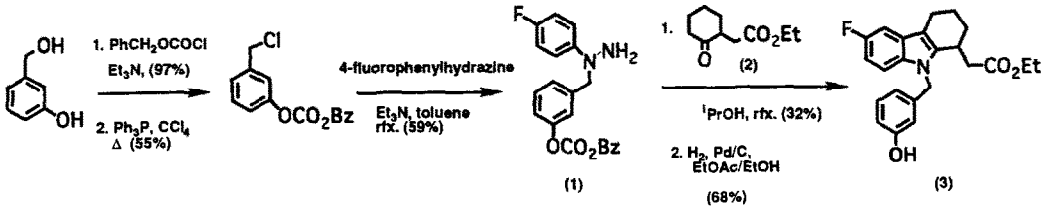
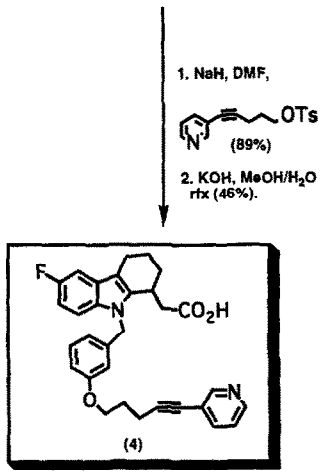
Abstract: The synthesis of a series of dual acting thromboxane antagonist/thromboxane synthase inhibitors from a key tetrahydrocarbazole phenol is described.

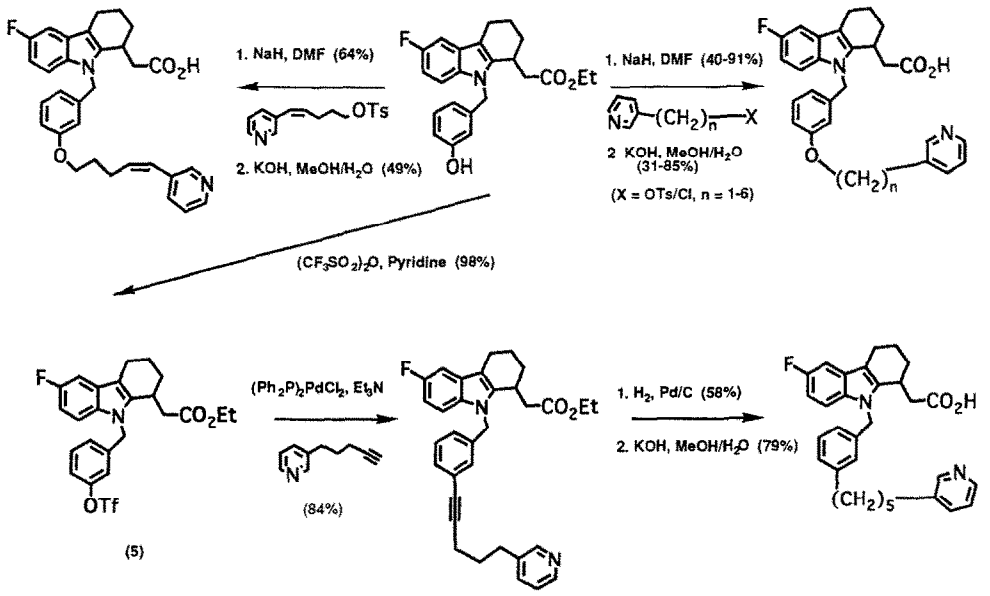
The discovery of a series of dual acting thromboxane antagonist/ thromboxane synthase inhibitors has been described in the accompanying communication.[1] The synthesis and structural characterization of the dual acting compound, **4** and related compounds are described herein. The synthesis of the tetrahydrocarbazole nucleus of **4** is based on the original Fischer indole approach adopted by Gillard.[2] Thus the hydrazine hydrochloride (**1**) was condensed with the ketone (**2**) to give the tetrahydrocarbazole. Hydrogenolytic deprotection gave the key intermediate (**3**).



Alkylation of this phenol and ester hydrolysis gave the dual acting thromboxane antagonist/thromboxane synthase inhibitor (**4**).[3,4] The tethered pyridine alkylating agent was easily available via an acetylenic coupling and tosylation approach.[5] It was found to be important to quickly purify this unstable tosylate by flash chromatography on silica gel prior to use in order to obtain high yields in the alkylation step. A series of compounds with other linking groups were prepared in a similar manner as outlined below. The olefinic and saturated alkyl tethers were accessed by reduction of the corresponding acetylene alcohols prior to tosylation and alkylation. An analogous approach was used to generate compounds derived from a 4-phenolic intermediate.



The phenol (3) could also be used to furnish carbon-linked tethers via acetylenic coupling to the triflate (5).[6]



We have thus shown a simple approach to synthesize a series of dual acting thromboxane antagonist/thromboxane synthase inhibitors by appending pyridine-containing tethers to a thomboxane antagonist - derived tetrahydrocarbazole nucleus.

References and Notes

1. See previous paper in this journal.
2. Guindon, Y., Yoakim, C., Gillard, J. W., European Patent EP 234708, 1987.
3. All compounds gave satisfacory spectral and analytical properties. Yields refer to purified materials.
4. Compound **4**: m.pt. 156-158 °C, NMR (d_6 -DMSO): 1.7-2.05 (6H, m), 2.25-2.8 (6H, m), 3.1-3.5 (1H, m), 4.0 (2H, q), 6.4-7.8 (9H, m), 8.45-8.62 (2H, m); m/e. 497 $(M+H)^+$; microanalysis, found: C, 74.9; H, 6.2; N, 5.3%; $C_{31}H_{29}N_2O_3F$ 0.25 H_2O requires C, 75.0; H, 5.8; N, 5.6%.
5. Tilley, J. W., Levitan, P., Lind, J., Crowley, H.J., Tobias, T., O'Donnell, M., *J. Med. Chem.* **30**, 185-193(1987).
6 Chen, Q-Y., Yang, Z-Y., *Tetrahedron Letts.***27**, 1171-1174(1986).