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The Synthesis of a Conformationally Restrained, Combined Thromboxane Antagonist / Synthase Inhibitor Using an Intramolecular 'Stille'- or 'Grigg'-Palladium-Catalysed Cyclisation Strategy

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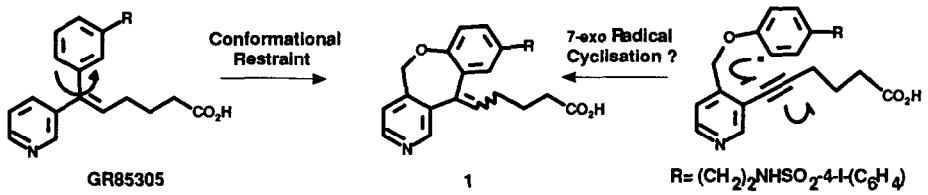
***Abstract**: The synthesis of the conformationally restrained analogues **15** and **20**, of the combined thromboxane antagonist / synthase inhibitor **GR85305**, has been achieved using novel intramolecular 'Stille'- and/or 'Grigg'-palladium-catalysed cyclisation reactions. A novel free radical cyclisation leading to an eight-membered ring is also described.*

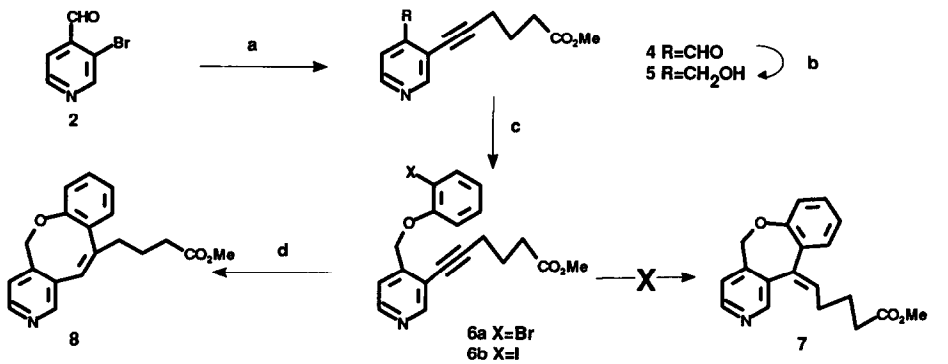
We recently described two series of compounds which possess both thromboxane antagonist and thromboxane synthase inhibitory activity.[1,2] However, the pharmacological profile of the pyridine-containing sulphonamido-acids eg **GR85305** was not considered optimal since the potency as a thromboxane antagonist was some ten fold less than the accompanying enzyme inhibitory activity.[1a] One strategy we adopted in an attempt to equalise these activities was the preparation of conformationally restrained analogues. We wished to reduced the rotational freedom of the aryl ring bearing the sulphonamide side-chain and reasoned that this could be accomplished by introducing a linker group (eg CH_2O) between the pyridine and aryl moieties eg **1**.[3] It was anticipated that such molecules could be constructed *via* a 7-*exo* free radical-induced cyclisation (Scheme 1).[4]

Scheme 1



To test this hypothesis the synthesis of the model system **7** was attempted (Scheme 2). 3-Bromopyridine-4-carboxaldehyde **2**[5] underwent a smooth Sonogashira coupling[6] with the acetylenic ester **3**[7] to provide the pyridylacetylene **4**. Reduction to the corresponding alcohol **5** followed by etherification with either 2-bromo or 2-iodo-phenol under Mitsunobu conditions[8] provided rapid access to the cyclisation precursors **6**.[9] Unexpectedly, when the iodide **6b** was subjected to Bu_3SnH/AIBN the major product isolated (40%) was the eight-membered ring compound **8**; only small quantities of the desired seven-membered ring product **7** could be detected by ^1H nmr. Subsequent hplc analysis of the product (when authentic **7** became available for comparison, *vide infra*) showed that the ratio of compounds **8**:**7** produced is 83:17 and that the seven-membered ring product is produced as a mixture of geometric isomers (ca. 1:1). Presumably this reaction is controlled by a combination of steric and electronic factors. Although a 7-*exo* process would be expected to be favoured over the alternate 8-*endo* cyclisation, the latter pathway, at least formally, dominates in this instance.[4,10]

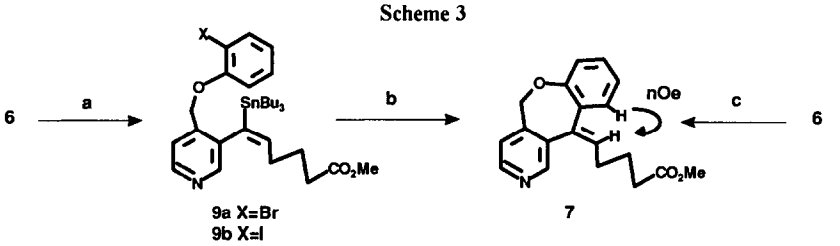
Scheme 2



a. $HC{\equiv}C(CH_2)_3CO_2Me$ (3), $(Ph_3P)_2PdCl_2$, CuI, Et_3N, MeCN, reflux 1.5hr; 77%. b. $NaBH_4$, MeOH, -20°C; 100%. c. Ph_3P, Diethyl azodicarboxylate (DEAD), THF, 2-bromophenol, 90%; 2-iodophenol, 81%. d. Bu_3SnH, azo-*iso*-butyronitrile (AIBN, cat.), C_6H_6, reflux 48hr; X=Br , 26%;, X=I, 40%.

Given the above failure we required a method by which cyclisation of the readily available acetylenes **6** could be controlled to provide exclusively the seven-membered ring product **7**. In addition, control over the geometry of newly produced exo-cyclic olefin would be advantageous since it was likely that biological activity would be found mainly in one isomer of these compounds.[1a] The new strategy chosen envisaged two consecutive palladium-catalysed processes (Scheme 3). Firstly, palladium-catalysed hydrostannylation of aryl acetylenes[12] is known to be both regio- and stereo-specific and in our case should result in the stannanes **9** which are appropriately configured for ***a seven-membered ring-forming, intramolecular Stille reaction.***[13]

Scheme 3



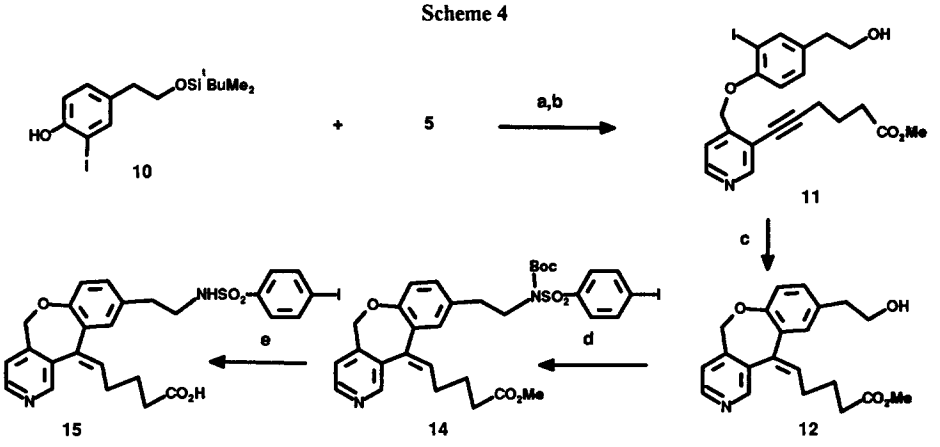
a. Bu_3SnH, $(Ph_3P)_2PdCl_2$, THF, X=Br; 83%, X=I; 55%. b. X=Br, $(Ph_3P)_4Pd$, toluene, reflux 24hr, 43% ; X=I, $(Ph_3P)_2PdCl_2$, LiCl, Ph_3P, DMF, 53%. c. $Pd(OAc)_2$, tri-*o*-tolylphosphine, HCO_2H, piperidine, MeCN, reflux 18hr, 53%.

In practice, whereas the bromo derivative **6a** underwent smooth *cis*-hydrostannylation to yield the desired stannane **9a** in 83% yield, the corresponding iodide **6b** afforded only a 55% yield of stannane **9b** since some competitive palladium-catalysed de-iodination also occurred. The desired intramolecular coupling process also proceeded as expected to afford the cyclised product **7**, with the iodide undergoing the more efficient reaction (**9a**, 43%; **9b**, 53% respectively based on 10% recovered starting material). Furthermore, as anticipated only the *E*-isomer is produced during the cyclisation reaction (confirmed by observation of the nOe depicted in Scheme 3).

A further improvement in the above sequence was achieved by adopting the elegant 'hydride-capture' strategy described by Grigg[14] (Scheme 3). Thus treatment of the acetylene **6b** with $Pd(OAc)_2$/tri-o-tolylphosphine/HCO_2H/ piperidine afforded the required product **7** in 53% yield. This is ***the first reported example of such an approach for the construction of seven-membered rings.***

Having devised a very short and efficient route to the construction of the desired conformationally restrained template attention was then turned to the synthesis of the corresponding analogues which incorporated the sulphonamido moiety. Introduction of an appropriately substituted side-chain was easily accomplished by coupling the alcohol **5** with the substituted iodo-phenol **10**.[15] Subsequent deprotection afforded the iodoacetylene **11** which underwent the 'Grigg'-cyclisation in an acceptable 56% yield (Scheme 4). Incorporation of the sulphonamide unit was achieved by a triphenylphosphine/diethyl azodicarboxylate-mediated coupling[16] of the resultant alcohol **12**[17] and Boc-protected sulphonamide **13**. Concomitant removal of the Boc group along with hydrolysis of the ester **14** afforded the E-isomer of the carboxylic acid **15** in good overall yield.

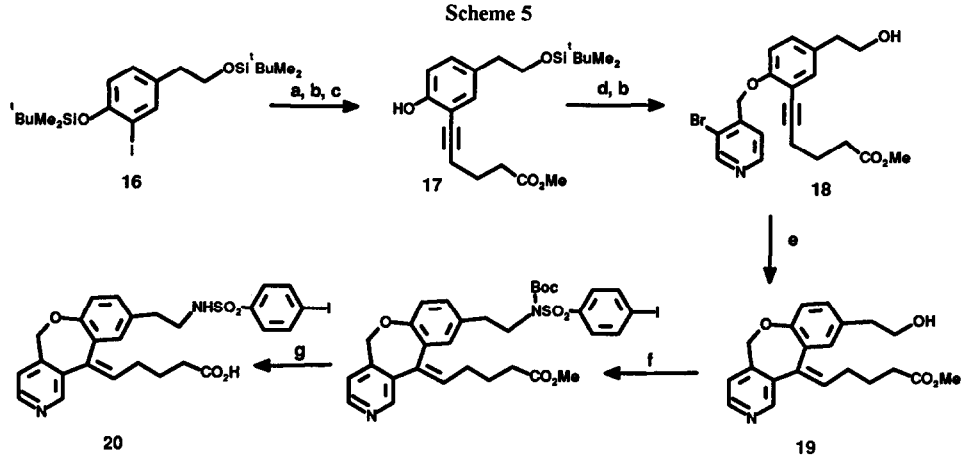
Scheme 4



a. Ph_3P, DEAD, THF, **10**, 57%. b. Bu_4NF, THF, 90%. c. $Pd(OAc)_2$, tri-*o*-tolylphosphine, HCO_2H, piperidine, MeCN, reflux 18hr, 56%. d. $BocNHSO_2$-4-I-C_6H_4 (**13**), Ph_3P, DEAD, THF, 82%. e. NaOH, MeOH, H_2O, 60%.

Implicit in the work described above was that it only produces the *E*-isomer. However, we expected that the alternate Z-isomer should be readily available by resequencing the early steps in the synthesis (Scheme 5). In this case the acetylenic ester **3** is attached via a Sonogashira reaction to the protected iodide **16**.[15] After a deprotection-reprotection sequence the resultant phenol **17** was etherified with 3-bromo-4-pyridinemethanol to provide, after desilylation, the acetylene **18**. 'Grigg'-cyclisation of **18** afforded the expected *Z*-isomer **19** in 60% yield. Conversion to the final product **20** mirrored that described above for the *E*-isomer **15**.

Scheme 5



a. **3**, $(Ph_3P)_4Pd$, CuI, dicyclohexylamine, MeCN, 31%. b. Bu_4NF, THF, 17, 95%; 18, 94%. c $^tBuMe_2SiCl$, imidazole, DMF, 99%. d. 3-bromo-4-pyridinemethanol, Ph_3P, DEAD, THF, 55%. e. $Pd(OAc)_2$, tri-*o*-tolylphosphine, HCO_2H, piperidine, MeCN, 60%. f. **13**, Ph_3P, DEAD, THF, 23%. g. NaOH, MeOH, H_2O, 39%.

In summary, the synthesis of the conformationally restrained analogues **15** and **20**,[18] of the combined thromboxane antagonist / synthase inhibitor **GR85305**, has been achieved using novel intramolecular 'Stille'- and / or 'Grigg'-palladium-catalysed cyclisation reactions.

References and Notes

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9. All new compounds had satisfactory spectroscopic and/or analytical data. None of the reactions described have been optimised.
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15. **10** and **16** were prepared using standard methodology, see Collington, E.W.; Finch, H.; Smith, I.J. *Tetrahedron Letters*, **1985**, *26*, 681.
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17. **12** was also prepared using the 'Stille' methodology, the key cyclisation occuring in 39% yield.
18. **15** and **20** possessed a similar pharmacological profile to **GR85305**[1a].

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