

A New Approach to the Core of Roseophilin

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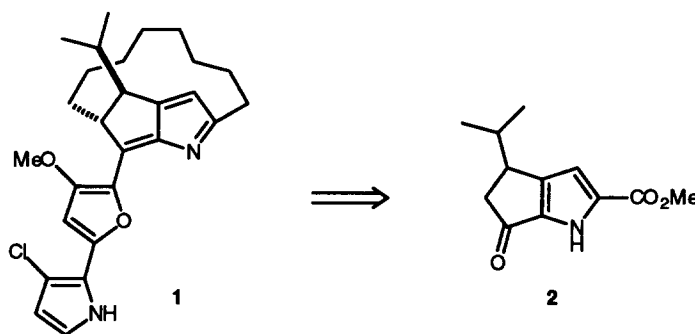
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Abstract: 5-Endo-dig iodocyclisation of the homopropargylic sulfonamide **10** gives the iodo-dihydropyrrole **11**; subsequent 5-exo-trig radical cyclisation of the derived iodopyrrole **12** followed by allylic oxidation then delivers the bicyclic core **2** of Roseophilin **1**. © 1999 Elsevier Science Ltd. All rights reserved.

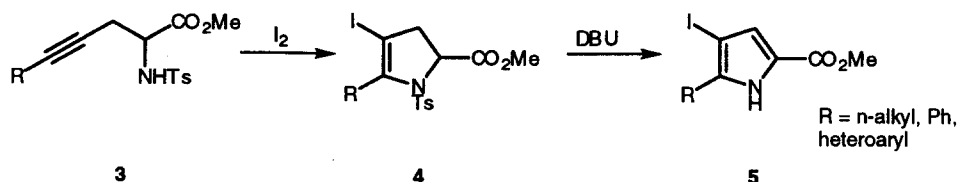
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Roseophilin **1** is a unique and extraordinary structure isolated from *Streptomyces griseoviridis* which displays significant antitumour activity.¹ Not surprisingly, these two features have provoked considerable interest in synthetic studies in this area. To date, only one total synthesis has been reported, by Furstner and Weintritt,² although a number of groups have reported significant progress towards this goal by the elaboration of various fragments. The Furstner-Weintritt approach featured an elegant application of sulfone chemistry which also played a key role in the synthesis of the bicyclic core (*cf.* **2**) of roseophilin **1** by Kim and Fuchs.³

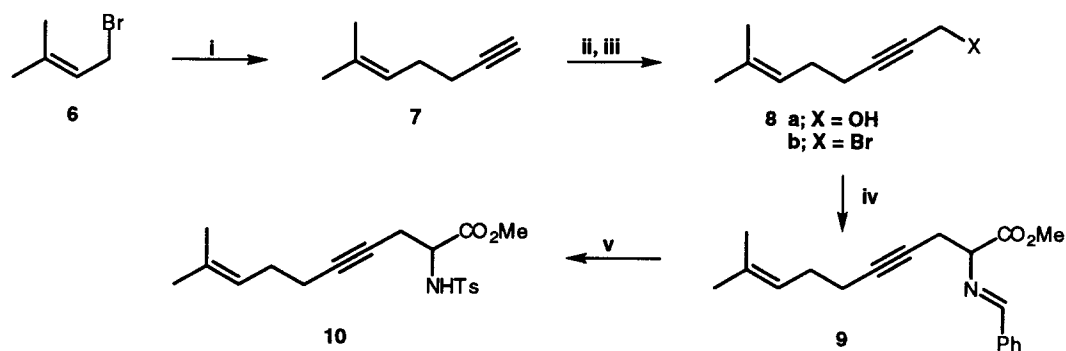


The same group then went on to prepare the tricyclic core of the compound, using a Grubbs ring closure metathesis reaction to establish the eight carbon bridge.⁴ More recently, the Hiemstra-Speckamp group have accessed an intermediate related to bicycle **2** using a combination of Michael addition and acyliminium chemistry,⁵ while the Terashima group⁶ have also succeeded in preparing the macrotricyclic core, using an intramolecular malonate alkylation to form the eight carbon bridge. The same group have already developed potentially suitable methodology for the incorporation of the pyrrolofuran appendage in roseophilin **1** by nucleophilic addition of the former to ketones related to the key intermediate **2**.⁷

We have recently discovered that β -iodopyrroles **5** can be efficiently generated by sequential 5-*endo*-dig iodocyclisation of propargyl glycine derivatives **3** and elimination of sulfinic acid from the resulting iodo-dihydropyrroles **4**.⁸ We reasoned that this could form the basis of a new approach to annulated pyrroles, given that a suitably positioned alkene function could be carried through this sequence, which was by no means certain at the outset, and that a final radical cyclisation, initiated by homolysis of the carbon-iodine bond in pyrroles **5**, was possible. Herein, we report that this sequence is indeed viable and can be applied to a synthesis of the core bicyclic ketopyrrole unit **2** of roseophilin **1**.



Our starting point (Scheme 1) was coupling of prenyl bromide **6** with propargylmagnesium bromide in the presence of mercury(II) chloride and copper(I) chloride.⁹ The resulting enyne **7** was homologated to the corresponding propargylic alcohol **8a**¹⁰ which was then brominated and the resulting bromide **8b**¹¹ used to monoalkylate the lithium enolate of methyl *N*-benzylideneglycinate¹² leading to the desired homologue **9** in good overall yield. Finally, protecting group exchange provided the key starting material **10**.



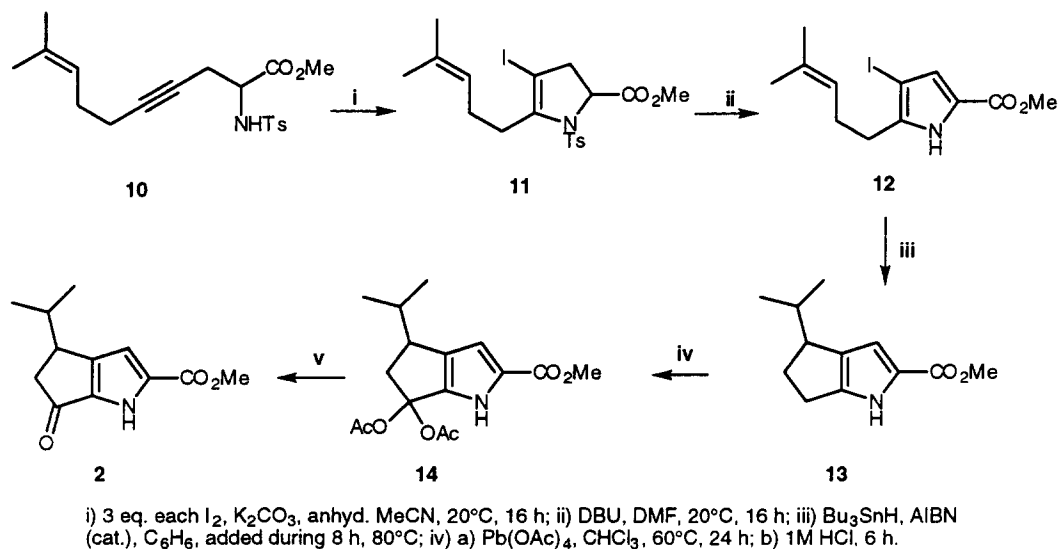
i) $\text{HCCCH}_2\text{MgBr}$, HgCl_2 , CuCl , Et_2O , 20°C , 16 h; ii) BuLi , THF , -78°C then add $(\text{CH}_2\text{O})_n$, warm to 20°C , 16 h; iii) NBS , PPh_3 , DMF , -30°C ; iv) *N*-benzylideneglycine methyl ester, LDA , THF , -78°C then add bromide **8b** and slowly warm to 20°C ; v) a) 1M HCl , Et_2O , 20°C , 1 h; b) TsCl , Et_3N , DMAP , CH_2Cl_2 , 20°C , 16h.

Scheme 1

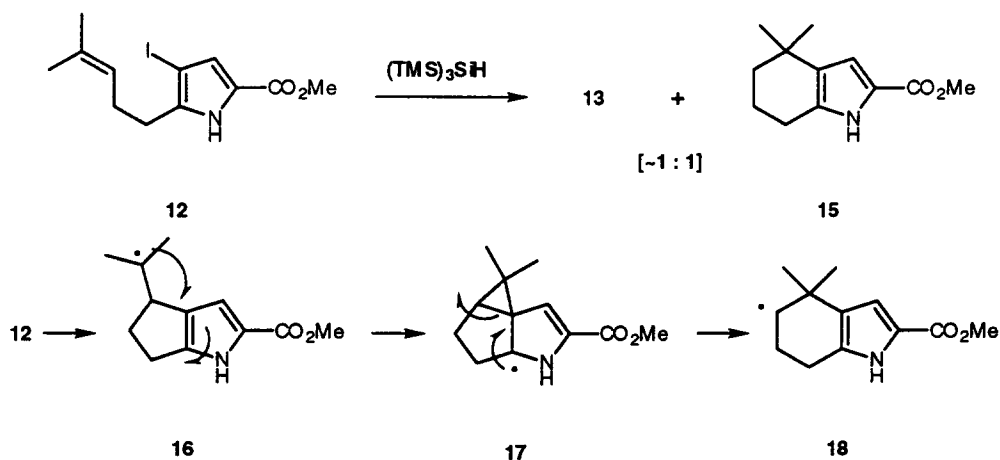
We were delighted to find that treatment of this enynoate with iodine in dry acetonitrile in the presence of sodium hydrogen carbonate⁸ gave 50–60% isolated yields of the hoped-for iodo-dihydropyrrole **11** (Scheme 2). It was essential that this step was carried out under strictly anhydrous conditions, otherwise hydration of the distal terpenoid alkene, to give the corresponding tertiary alcohol, became the main reaction. Base treatment of the dihydropyrrole **11**, as previously reported,⁸ then led smoothly to the related iodopyrrole **2** in 90% isolated yield. Reaction of this, under the now standard conditions for radical generation¹³ of slow addition of tributyltin hydride and AIBN to a refluxing benzene solution of the iodopyrrole **12**, gave a 65% isolated yield of the annulated pyrrole **13** from the anticipated 5-*exo*-trig radical cyclisation. Finally, the required ketone function was introduced by a very efficient oxidation using lead(IV) acetate in refluxing chloroform.¹⁴ The intermediate *bis*-acetoxy species **14** was isolated in 95% yield and readily hydrolysed to the target ketone **2**.

When we examined an alternative method for radical generation using the more environmentally benign

tris-(trimethylsilyl)silane,¹⁵ we were surprised to find that, while a good yield of cyclized material was obtained, this consisted of an approximately 1:1 mixture of the desired compound **13** and the product **15** formally of a 6-*endo* cyclisation. An explanation for this may be that, as the silane quenches the final radical species **16** at a slower rate (*ca.* 10 x) than the tin hydride, this can cyclize by attack onto the pyrrole nucleus. The resulting radical **17** can then open in two ways, one which simply reverses the process back to the tertiary radical **16** while the other leads to the secondary radical **18**. Subsequent quenching then leads to the observed product mixture. Results reported by the Beckwith group and others^{13,16} give ample precedent for this mechanism.

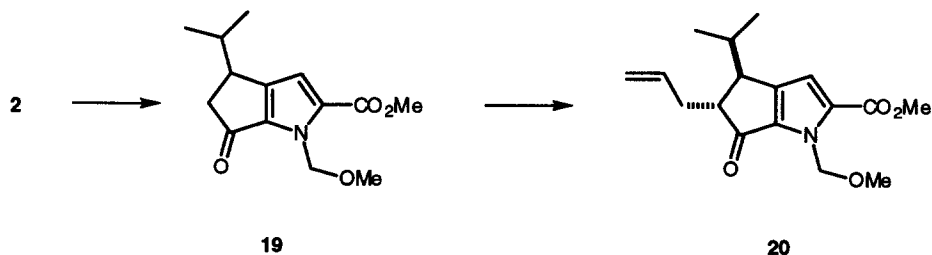


Scheme 2



In a trial reaction, we have also found that the ketopyrrole **2**, after protection as its *N*-methoxymethyl derivative **19**, undergoes smooth enolization upon exposure to lithium diisopropylamide and that the resulting enolate can be trapped by allyl bromide to give the *trans*-homologue **20**. This now sets the stage for a total synthesis of roseophilin based upon this strategy which we are actively pursuing and also indicates that such

sequential cyclisations could represent a generally useful method for the elaboration of annulated pyrroles. Aspects of this feature are also under investigation.¹⁷



Acknowledgements

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References

1. Hayakawa, Y.; Kawakima, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.*, **1992**, *33*, 2701.
2. Furstner, A.; Weintritt, H. *J. Am. Chem. Soc.*, **1998**, *120*, 2817; **1997**, *119*, 2944; Furstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.*, **1999**, *64*, 2361.
3. Kim, S. H.; Fuchs, P. L. *Tetrahedron Lett.*, **1996**, *37*, 2545.
4. Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.*, **1997**, *38*, 2601.
5. Luker, T.; Koot, W. J.; Hiemstra H.; Speckamp, W. N. *J. Org. Chem.*, **1998**, *63*, 220.
6. Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.*, **1998**, *39*, 6911.
7. Nakatani, S.; Kirihara, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.*, **1995**, *36*, 8461.
8. Knight, D. W.; Redfern, A. L.; Gilmore, J. *Chem. Commun.*, **1998**, 2207.
9. Sondheimer, F.; Wolovsky, R.; Ben-Efraim, D. A. *J. Am. Chem. Soc.*, **1961**, *83*, 1686.
10. Williams, R. M.; Sabol, M. R.; Kim, H.; Kwast, A. *J. Am. Chem. Soc.*, **1991**, *113*, 6630.
11. Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoulos, H. *J. Am. Chem. Soc.*, **1985**, *107*, 7515.
12. Stork, G.; Leong, A. Y. M.; Touzin, A.-M. *J. Org. Chem.*, **1976**, *41*, 3491.
13. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, **1991**.
14. Montforts, F.-P.; Schwarts, U. M. *Annalen*, **1985**, 2301.
15. Chatgililoglu, C. *Acc. Chem. Res.*, **1992**, *25*, 188.
16. Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.*, **1987**, *52*, 4072.
17. Satisfactory analytical and spectroscopic data were obtained for all compounds reported herein.