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Formal synthesis of roseophilin

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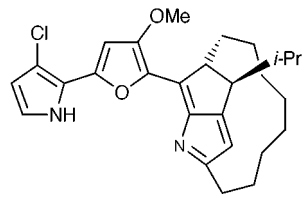
A thirteen step route to the tricyclic ketopyrrole core of roseophilin is presented in which the final step consists of a Paal–Knorr pyrrole synthesis that proceeds with *in situ* oxidation.

The intriguing structure of roseophilin, a cytotoxic antibiotic isolated from *Streptomyces griseoviridis* as disclosed by Seto in 1992,[1] has stimulated significant synthetic interest[2] culminating in Fürstner's elegant total synthesis of the racemate[3] and its analogues.[4] Our group has also been active in this area[5] and in this communication we outline a concise synthesis of the tricyclic ketopyrrole right hand half (±)-**10**. This route was

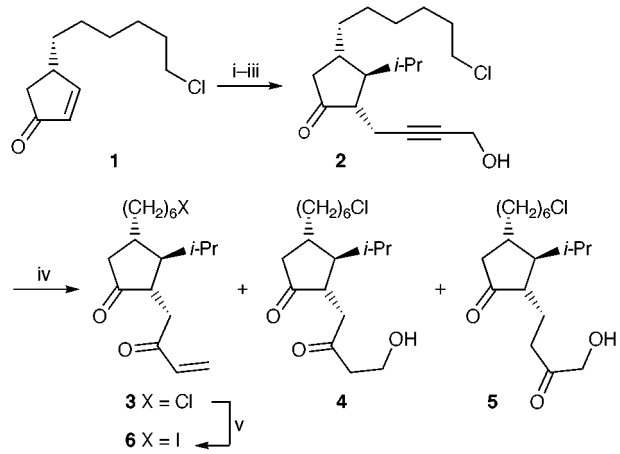


Roseophilin

designed to be easily tailored to provide access to either enantiomer of roseophilin as well as being sufficiently flexible that a range of roseophilin analogues could be prepared for biological evaluation.

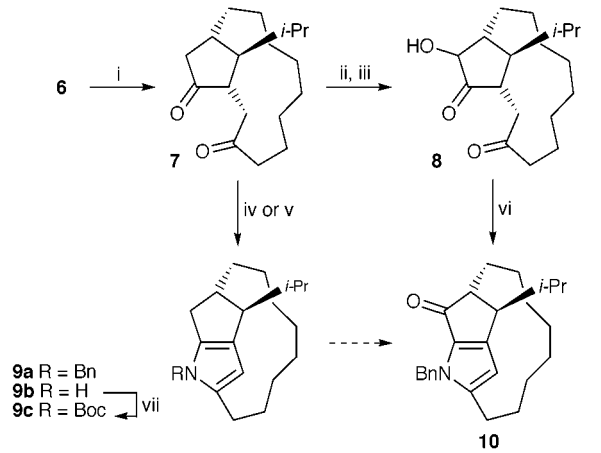
At the outset of our investigations towards tricycles such as **10** we elected to form the pyrrole ring in the final step so that the energetic drive towards aromaticity would serve to override the adverse strain inherent in these molecules. In this respect our synthetic concept differs fundamentally from those of Fürstner,[2d,3,4] Fuchs,[2b,c] and Terashima.[2f] Our second guiding principle was to construct the thirteen membered ring by a free radical macrocyclisation[6] since our own studies[5a] had shown that bicyclo[10.2.1]pentadecenones could be obtained by this method.

Radical macrocyclisation precursor **6** was constructed in five steps from cyclopentenone derivative (±)-**1**[7] (Scheme 1) starting with conjugate addition[8] of *i*-PrMgCl which proceeded in essentially quantitative yield provided excess TMSCl (4.0 equiv.) was used to trap the enolate and Et_3N was added to the reaction mixture prior to aqueous work-up. Generation of the lithium enolate from the intermediate silyl enol ether, trapping with propargylic iodide (propargyl = prop-2-ynyl) **11**[9] and desilylation with fluorosilicic acid[10] afforded 1°-alcohol **2**. Yadav's procedure for converting 1°-propargyl alcohols into vinyl ketones[11] was unsuccessful when applied to this substrate as the hydrogen sulfide used in the work-up led to thiol adducts that could not be processed further. Eventually we found that treatment of alcohol **2** with $Hg(OAc)_2$ in acetic acid containing water (1.0 equiv.) then work-up after 30 min with dilute hydrochloric acid gave much improved results, a mixture being obtained consisting of the desired enone **3**, β-hydroxy ketone **4**, and the regioisomeric hydrolysis product **5** (4.5:1:1.5 respectively). These compounds were readily separable and the 1,4-adduct **4** could be dehydrated efficiently (MsCl, Et_3N, cat. DMAP; 93%) to give an acceptable overall yield of the radical precursor **6** after Finkelstein reaction.



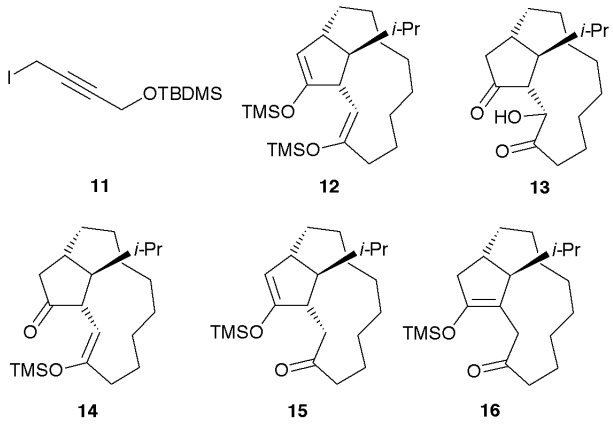
Scheme 1 *Reagents:* i. *i*-PrMgCl, CuI, LiCl, TMSCl, THF (96–99%); ii. MeLi then DMPU, **11**, THF (62%); iii. H_2SiF_6, aq. CH_3CN (96%); iv. $Hg(OAc)_2$, H_2O, AcOH then 5% aq. HCl (59% → **3**); v. NaI, butanone (88%).

The radical macrocyclisation required high dilution (2.5 mM) and slow addition (7 h) of the tin hydride in order to minimise direct reduction but enone hydrostannylation products could not be avoided. Work-up with thiophenol[12] facilitated isolation of the crystalline macrocyclic diketone **7** (Scheme 2) whose identity was confirmed by X-ray crystallography.[13] The *N*-benzyl pyrrole **9a** was formed straightforwardly but direct access to the *N*-unsubstituted analogue **9b** gave an indication of the strain in this system and forcing conditions were required (*cf.* ref. 14). Unfortunately we were unable to effect direct α-oxidation of either **9a** or the *N*-Boc analogue **9c** even though studies on compounds lacking the macrocyclic linking chain gave promising results.[15]



Scheme 2 *Reagents:* i. Bu_3SnH, AIBN, PhH (35–50%); ii. LDA, THF, −50 → 0 °C then TMSCl (55%, partial hydrolysis on SiO_2); iii. dimethyldioxirane (0.1 M in acetone), CH_2Cl_2 then aq. H_2SiF_6, CH_3CN (80%); iv. $BnNH_2$, AcOH, EtOH, 50 °C (60%); v. $(Me_3Si)_2NH$, Al_2O_3, 150 °C (sealed tube) (86%); vi. $BnNH_2$, AcOH, EtOH, 55 °C then 2 M aq. HCl, MeOH (25%); vii. KH, Boc_2O, THF (75%).

This problem proved insurmountable therefore we embarked on an attempt to effect oxidation prior to pyrrole formation which required a method for discriminating between the two carbonyl groups in diketone **7**. Treatment with LDA (1.1 equiv.) at −78 °C with an *in situ* TMSCl quench resulted in the sole formation of the doubly silylated compound **12** with a



11 **12** **13**

14 **15** **16**

corresponding recovery of starting material. Furthermore, oxidation of bis-silyl enol ether **12** by MCPBA was selective for the macrocyclic position giving α-hydroxy ketone **13** in 70% isolated yield. An attempt to effect selective mono-desilylation[16] of **12** merely returned starting material.

Selective mono-silylation in the five-membered ring proved to be a challenging task as kinetic enolate formation with an *external* TMSCl quench led predominantly to silyl enol ether **14**. However a reasonable product ratio in favour of silyl enol ether **15** could be attained under equilibrating conditions although this compound could not be obtained free of the regioisomer **16** (3–4 : 1 ratio). This mixture was treated with dimethyldioxirane[17] to give, after desilylation, α-hydroxy ketone **8** (containing *ca*. 20% of the inseparable regioisomer). Overall yields for **7** → **8** were generally around 45% either with or without purification of the intermediate silyl enol ether mixture.

The final step, Paal–Knorr pyrrole synthesis from a 1,4-diketone bearing an unprotected α-hydroxy substituent, had no immediate precedent. Heating compound **8** with benzylamine in ethanolic acetic acid proved insufficient to drive the reaction to completion but, after consumption of the starting material, addition of 2.0 M hydrochloric acid in methanol was effective in delivering a pyrrole product. However this product did not contain a hydroxy group; in fact the ring closure was accompanied by an unexpected oxidation to afford a compound with spectroscopic data exactly matching those reported by Fürstner for the ketopyrrole **10**.

This route to ketopyrrole **10** not only stands as a formal total synthesis of (±)-roseophilin but opens the way to an enantiospecific synthesis because treatment of commercially available (4*R*)-(*tert*-butyldimethylsilyl)oxycyclopentenone[18] with 6-chlorohexylcuprate[5*a*] followed by elimination of the silyloxy group is expected to yield (*R*)-**1** from which a single enantiomer of roseophilin would follow. Currently we are optimising a new synthesis of the pyrrolylfuran left hand half and will report on this and our progress towards an enantiospecific total synthesis of roseophilin in due course.

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