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Enantioselective Formal Total Synthesis of Roseophilin

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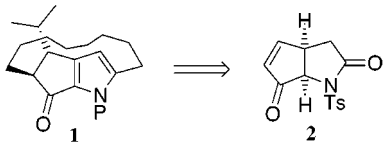
ABSTRACT



An enantioselective formal total synthesis of roseophilin 3 is presented. The 13-membered ring of macrotricycle 1 was formed via an efficient ring-closing metathesis reaction of bicycle 4. A palladium-catalyzed methoxycarbonylation reaction of enol triflate 5 was utilized to functionalize the right-hand ring of bicycle 2. The allyl substituent was introduced by a radical allylation of α-bromoketone 17.

Roseophilin **3** possesses a unique pentacyclic structure, consisting of a substituted pyrroylfuran unit attached to an *ansa*-bridged azafulvene core. This novel antibiotic was isolated from the culture broth of *Streptomyces griseoviridis* and was shown to exhibit submicromolar cytotoxicity against several human cancer cell lines.[1] Since its isolation in 1992, roseophilin **3** has attracted considerable synthetic attention, resulting in a total synthesis by Fürstner et al. and several syntheses of the macrotricyclic core **1**.[2] However, all the reported approaches toward roseophilin **3** as yet have been racemic. Herein we wish to describe our enantioselective route to the macrotricyclic core **1**.

The work of Fürstner et al. has demonstrated the viability of the initial disconnection in our retrosynthetic analysis, and as such a synthesis of macrotricycle **1** constitutes a formal total synthesis of roseophilin **3** (Scheme 1). We planned to form the 13-membered ring by a ring-closing metathesis (RCM) reaction of triene **4**, as we had obtained encouraging results in forming medium-size bridged ring systems using RCM in our model studies.[3] Specifically, we had found that the presence of a phenyl sulfone directing group provided good results in obtaining even relatively strained ring systems. RCM has been employed in several appoaches to **1**.[2d,2g,2i,4]

Lactam-derived enol triflate **5** would be employed to functionalize the right-hand ring of the chiral nonracemic bicyclic unit. Previous work in our group has described the synthesis of bicycle **2** from (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one **6**.[5] Following a recently reported procedure, we can now readily obtain multigram quantities of this chiral building block.[6] (*S*)-1-Acetyl-5-isopropoxy-3-pyrrolin-2-one is also readily available and would allow the synthesis of the enantiomer of **3**.

Initially, we wished to functionalize the right-hand ring of bicycle **2**, and this was accomplished using methodology previously developed in our group, namely, the use of lactam-

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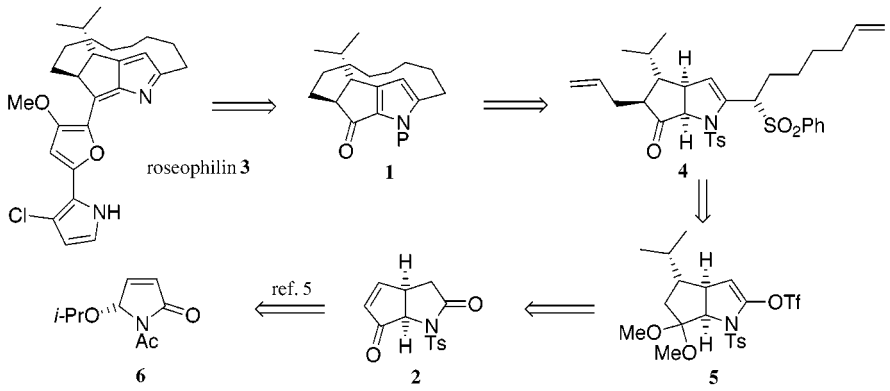
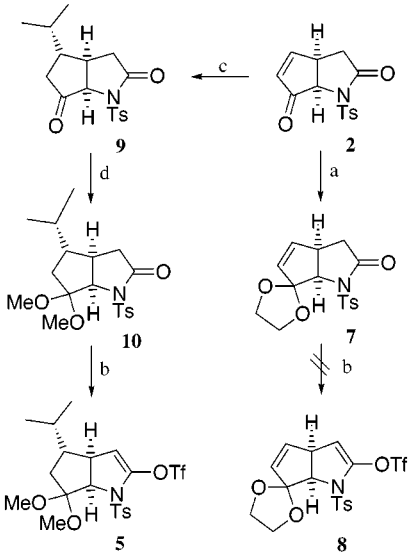
Scheme 1. Retrosynthetic Analysis of Roseophilin **3**



derived enol triflates.[7] 1,3-Dioxolane protection of α,*β*-unsaturated ketone **2**, followed by deprotonation and reaction with 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent), gave none of the desired triflate **8** (Scheme 2).[8] Interestingly, the diphenylenolphosphate of **7** could be readily formed, but attempts to perform a palladium-catalyzed methoxycarbonylation reaction on this enolphosphate, under a range of conditions, were unsuccessful.[9] However, if the 1,4-isopropylcuprate addition was first performed, followed by protection of the ketone, then triflate **5** could be formed in excellent yield and with full conversion. Protection of ketone **9** as a 1,3-dioxolane and subjection to the triflation conditions also gave the corresponding triflate, but subsequent problems were encountered on attempting to remove this protecting group.

Scheme 2. Formation of Enol Triflate **5**[a]



[a] Key: (a) $(TMSOCH_2)_2$, TMSOTf, DCM, −20 °C, 16 h, 88%; (b) KHMDS, THF, HMPA, −78 °C; Comins' reagent; (c) CuI, $BF_3.Et_2O$, *i*-PrMgCl, THF, −78 °C, 83%; (d) $HC(OMe)_3$, MeOH, TsOH, 98%.

Palladium-catalyzed methoxycarbonylation of triflate **5** gave ester **11** in good yield (Scheme 3). To achieve full conversion of the triflate to ester **11** during the carbonylation reaction, thus preventing recovery of lactam **10** and subsequent separation problems, this reaction was carried out under 20 atm of carbon monoxide. Standard conditions were then used to convert ester **11** into sulfone **14** (mp = 122 °C; $[\alpha]_D$ +131.5, *c* 1.3, $CHCl_3$). Alkylation of sulfone **14** led to the isolation of a single diastereomer. The stereochemistry of the alkylation product is assigned on the basis that a "chiral relay effect" is operating, as was encountered in our model studies.[3,10] These studies also demonstrated that this configuration was essential in bringing about a successful RCM reaction.

Removal of the dimethylacetal protecting gave ketone **16**, which then had to be allylated to form the RCM substrate. Attempts to deprotonate **16** and alkylate with allyl bromide or allyl iodide were unsuccessful and led to pyrrole formation via elimination of the *p*-toluenesulfonyl group (see below) and to epimerization at the carbon bearing the phenylsulfonyl group. Also, attempts to form the silyl enol ether at the least hindered side of the ketone met with failure. Gratifyingly, α-bromination of ketone **16** using copper(II) bromide gave a good yield of α-bromoketone **17**, as a 1:1 mixture of diastereomers at the bromine-bearing carbon, which we planned to use in a radical reaction to introduce the allyl group.[11] Indeed, radical allylation of **17** at 100 °C provided a moderate yield of the RCM precursor **4** ($[\alpha]_D$ +36.9, *c* 0.65, $CHCl_3$) as a single diastereomer possessing the desired trans relationship between the allyl and isopropyl substituents of the five-membered ring.[12] The trans stereochemistry was established by an NOE experiment performed on the

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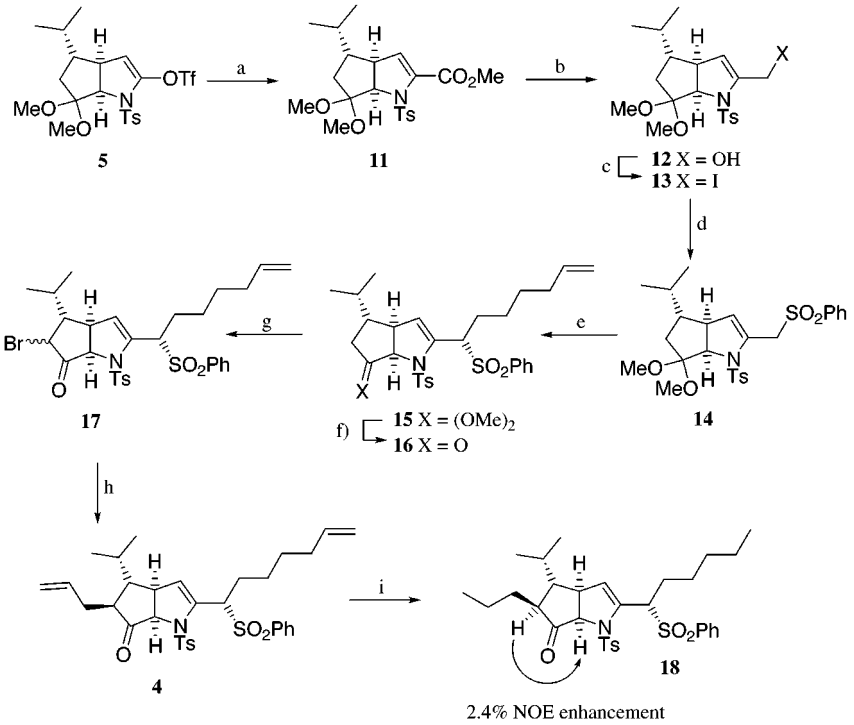
Scheme 3. Attachment of Substituents to Left-and Right-Hand Ring of Bicycle[a]

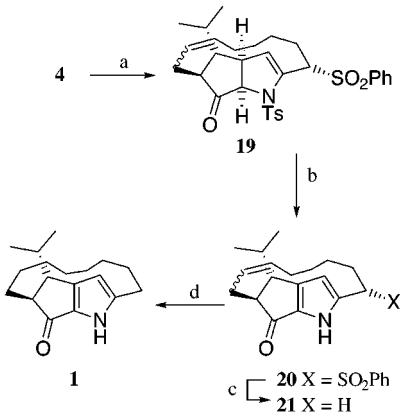


[a] Key: (a) $Pd_2(dba)_3$, $AsPh_3$, CO (20 atm), LiCl, Et_3N, MeCN, 50 °C, 71% over two steps; (b) DIBALH, THF, 78%; (c) PPh_3, imidazole, I_2, Et_2O, MeCN, 96%; (d) $PhSO_2Na$, DMF, HMPA, 95%; (e) *n*-BuLi, HMPA, THF, −78 °C; 1-bromohex-5-ene, 65%; (f) HCl (2 M), acetone, 60 °C, 99%; (g) $CuBr_2$, EtOAc, 50 °C, 92%; (h) allyltributyltin, AIBN, toluene, 100 °C, 52%; (i) H_2, PtO_2, EtOAc, 75%.

hydrogenated compound **18**, in which a 2.4% NOE enhancement was observed between the protons adjacent to the ketone functionality, illustrating their cis relationship in the five-membered ring (Scheme 3).

Triene **4** was treated with 10 mol % of Grubbs' catalyst in dichloromethane at 40 °C for 16 h, at a concentration of 1 mM (Scheme 4).[4a] This provided an excellent yield of the macrocyclic product **19**, as a 3:1 mixture of double bond isomers. The RCM reaction is particularly favorable due to the conformationally biasing effect of the sulfone substituent and the rigid concave shape of the bicyclic core, both factors which operate to bring the reacting terminal diene moieties into close proximity.[2d,3] Surprisingly, hydrogenation of the RCM product **19** gave rise to a compound which was unstable and could not be further transformed to **1**. Reaction of **19** with oxidizing agents such as *N*-iodosuccinimide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone failed to provide the protected pyrrole. However, on treatment of the RCM product **19** with sodium bis(trimethylsilyl)amide α-keto deprotonation took place, with subsequent elimination of the *p*-toluenesulfonyl group and rearrangement to pyrrole **20**.[13] Removal of the sulfone group with sodium amalgam and hydrogenation with a platinum(IV) oxide catalyst gave the ketopyrrole macrotricycle (−)-**1** ($[\alpha]_D$ −32.0, *c* 1.0, $CHCl_3$). The spectroscopic data for (−)-**1** match those previously reported in the literature for the racemic compound.[2]

Scheme 4. Ring-Closing Metathesis and Formation of **1**[a]



[a] Key: (a) 10 mol % $(Cy_3P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, 16 h, 91%; (b) NaHMDS, THF, −78 °C, 71%; (c) 6% Na(Hg), Na_2HPO_4, THF, MeOH, 0 °C, 90%; (d) PtO_2, H_2, EtOAc, 99%.

In summary, we have completed an enantioselective formal total synthesis of roseophilin **3**, which can be used to form either enantiomer of the natural product. The versatile synthesis could be readily adapted to produce analogues of

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the natural product, particularly in modifying the length of the *ansa*-bridge by alkylation of sulfone **14** with various alkyl halides.

Conversion of macrotricycle **1** to the roseophilin structure and comparison of synthetic material with the natural product will allow the determination of the absolute configuration of naturally occurring roseophilin **3**, which has yet to be illucidated. Details of these studies will be reported at a later date.

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Supporting Information Available: Experimental procedures and full characterization data for all new compounds are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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