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Application of the Grubbs Ring-Closing Metathesis for the Construction of a Macrocyclic Ansa-Bridge. Synthesis of the Tricyclic Core of Roseophilin.[1]

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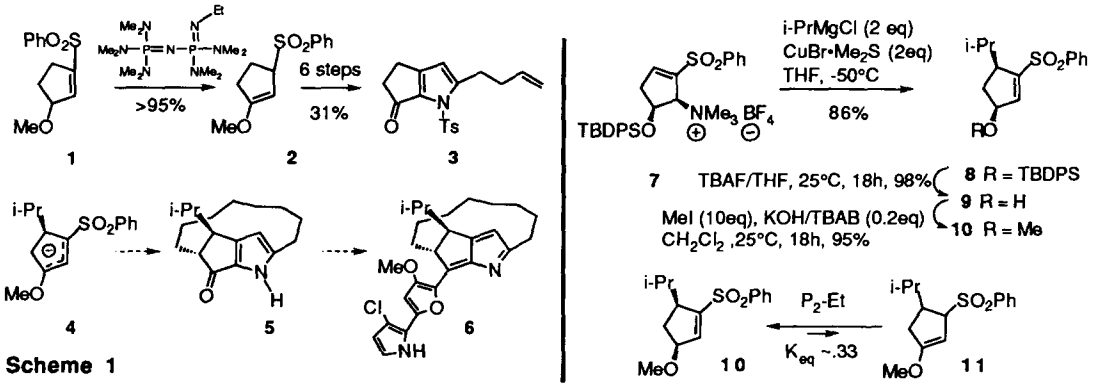
Abstract: Metalation/alkylation of the pyrrole-fused 10π anion **15** regiospecifically yields the β-alkylated ketones **16,17.** Conversion of **17** to diene **24** followed by Grubbs ring-closing metathesis provides **29** which is transformed to the roseophilin tricyclic core structure **5.**

Roseophilin **6** is a topographically interesting ansa-bridged 1-azafulvene which exhibits submicromolar cytotoxicity against several human cancer cell lines.[2] In 1995, Terashima disclosed the synthesis of the roseophilin heterobiaryl moiety,[3] followed shortly thereafter by our report on the use of metalated γ-methoxyallyl sulfone **2**[4] for the construction of bicyclic ketopyrroles, including model compound **3**.[5] We next turned to the synthesis of isopropyl-substituted γ-methoxyallyl sulfonyl anion **4**, with a view to employing the symchiral[6] version of this material to ansa-bridged tricyclic ketopyrrole **5** via a Grubbs ring-closing metathesis strategy. Initial experiments were conducted on *dl*-**7**,[7] but previously established chemistry[7,8] enables access to both enantiopodes of **7**, an attractive prospect since the absolute configuration of **6** remains yet to be established.

In the event, treatment of ammonium salt **7** with i-PrMgCl in the presence of CuBr•Me_2S stereospecifically afforded *cis*-adduct **8** in high yield. Desilylation followed by methylation gave isopropyl-substituted vinylsulfone **10**. Unfortunately, in stark contrast to compound **1** which undergoes quantitative isomerization to allylic isomer **2** upon treatment with the Schwesinger P_2-Et phosphazene base,[4,9] similar reaction of **10** only generates a 3:1 equilibrium mixture in which the (labile and inseparable) allyl sulfone **11** constitutes the minor component as a single (unassigned) stereoisomer (Scheme 1).

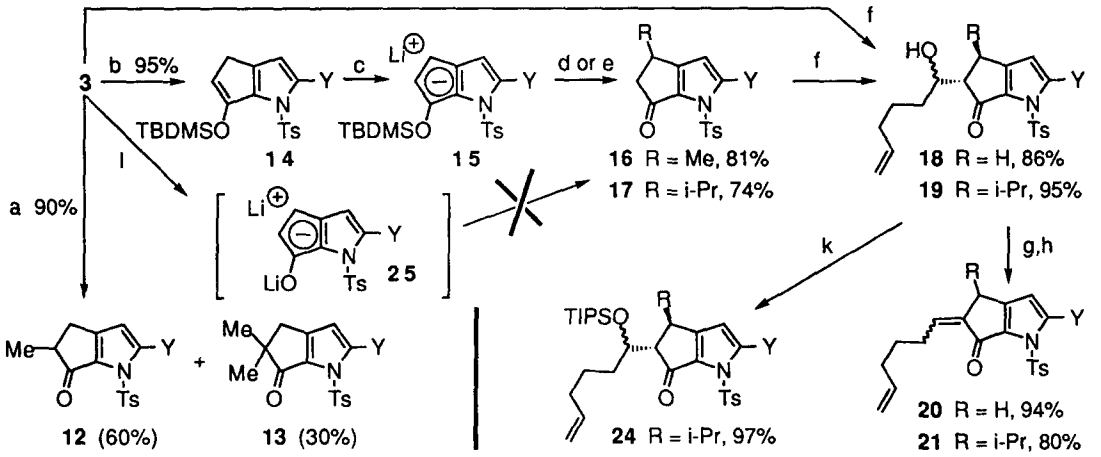


Scheme 1

Faced with the prospect of a long-term study to remediate the above problem, we shifted our attention to an alternative preparation of an appropriate substrate in order to test the feasibility of effecting closure of the crucial ansa-bridge via Grubbs ring-closing metathesis. The regiochemistry of alkylation of keto-pyrrole **3** was first determined by reaction of **3** with potassium hexamethyldisilazide followed by addition of excess methyl iodide to produce a 2:1 mixture of mono and dimethylation products **12** and **13** (90%). Alkylation in the β-position could be regiospecifically secured by conversion of ketone **3** to silylenol ether **14** followed by low temperature metalation with t-butyllithium to generate intermediate 10π anion **15**. Alkylation of **15** with methyl iodide followed by hydrolysis of the resultant silylenol ether during work-up affords **16** to the complete exclusion of regioisomer **12**. Conformation of the regiochemical assignment of **16** was secured by observation of a methyl-pyrrole-H nOe interaction, a feature absent from the spectrum of keto-pyrrole **12**. Similar alkylation of intermediate **15** with isopropyl iodide afforded the isopropyl-substituted keto-pyrrole **17**, which also demonstrated the appropriate isopropyl methine-pyrrole-H nOe interaction.

Although metalation of the cross-conjugated silyldienylether of cyclopentenone is known to afford the silyloxycyclopentadienyl anion (cf. **15**) which has been used as an organometallic ligand, no alkylation chemistry of this species has been reported.[10] A related strategy using the dianion of 1-indanone for β-alkylation reported by Trost and Latimer[11] encouraged us to also examine the intermolecular alkylation chemistry of dianion **25**. Unfortunately, dianion **25** is apparently unstable at ca. -30°C and does not survive long enough to yield **16** or **17** upon addition of alkylating agent.

Scheme 2 Y = $CH_2CH_2CH{=}CH_2$



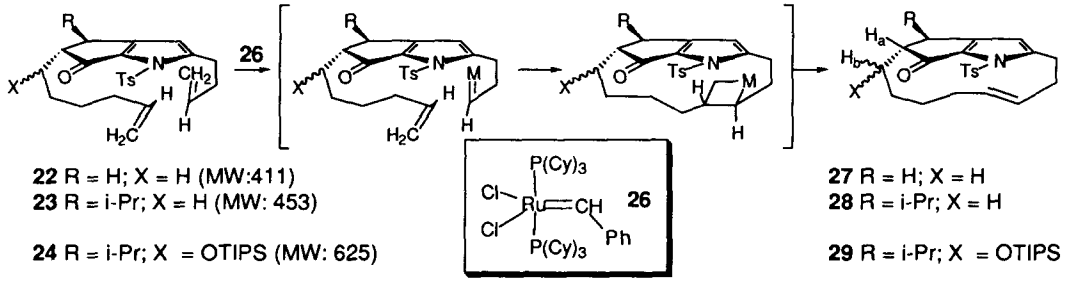
a) i. KHMDS (1.5eq); ii. MeI (xs), -60°C; b) TBDMSOTf, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0°C to 25°C; c) t-BuLi, THF -78°C; d) add MeI to (c), add aq. NH_4Cl, warm to 25°C; e) add i-PrI/HMPA to (c), add aq. NH_4Cl, warm to 25°C; f) LiHMDS (1.1 eq), THF -60°C, add 1.5 eq $CH_2{=}CH(CH_2)_3CHO$, warm to -45°C, quench NH_4Cl; g) MsCl, Et_3N, THF, 0°C to 25°C, 1h; h) DBU (2eq), THF, 18h, 25°C (**20** Z:E >99:1; **21** Z:E = 3:1); i) L-Selectride, THF, -78°C, 4h (**23** t/c=1:1); j) KOt-Bu, t-BuOH, 25°C, 5h (**23** t/c >99:1); k) TIPS-Cl, $AgNO_3$, DMF, 25°C, 15h; l) LiHMDS (2.2 eq), THF -78°C to -30°C, add MeI or i-PrI.

Reaction of the enolates of **3** or **17** with 6-iodo-hex-1-ene in an attempt to generate **22** or **23** was unrewarding, so we treated the lithium enolates with 5-hexenal[12] to give a high yield of aldol adducts **18** and **19** as a 2-3:1 mixture of unassigned diastereomers. Mesylation followed by DBU gave enones **20,21** which were smoothly converted to the keto-pyrroles **22,23** via selectride-mediated conjugate reduction[13] followed by base-catalyzed side-chain equilibration. Preparation of the final substrate for evaluation simply involved silylation of **19** with $AgNO_3$/TIPS-Cl[14] to afford silyl ether **24** as a 3:1 mixture of diastereomers which was carried further without separation (Scheme 2).

The Grubbs ring-closing metathesis reaction is rapidly becoming exploited in the setting of total synthesis, and has already been used for cyclizations of 12, 13, 14, 16, and 17-membered rings,[15] *including those where the olefins are not conformationally restrained to be in reasonable proximity.* An open question is whether moderately strained systems such as **27-29** can be accessed without unwanted polymerization becoming the preferred process. Treatment of deoxydienes **22** or **23** at 0.002M in CH_2Cl_2 or benzene at 25°C with the functional-group tolerant Grubbs Ruthenium benzylidene carbene **26** (30 mol%) revealed our fears were well-founded. In the former instance, the MS of the major product exhibited an ion at m/e 611, consistent with a macrocyclic dimeric structure, less the Ts group and two moles of ethylene. This same reaction also produced, in addition to recovered **22**, a species whose MS at m/e 639 was consistent with intermolecular metathesis followed by ionization of the Ts group. The chemistry of **23** at either 0.002M or 0.0005M was similar, giving starting material along with another macrocyclic dimer (m/e 850).

Molecular mechanics of **24**-β (OTIPS β) revealed that the global minimum had the hexenyl side chain in much closer proximity to the requisite butenyl moiety. This is in strong contrast to calculations on **22,23** which preferred the side chains orientated far apart. In the event, treatment of a 0.0005M solution in CH_2Cl_2 of the two diastereomers (3:1) of **24** with 30% of catalyst **26** at 40°C for 25h afforded the ansa-bridged silylether **29** *as a single diastereomer* in 60% yield in addition to a small amount of dimerized products and the *minor diastereomer* of starting material **24**. The NMR of compound **29** reveals the new olefin to be trans (J=15.6Hz), and is suggestive of having the silyloxy moiety in the beta-configuration (J_{ab}=4.4Hz), an assignment which must be regarded tentative until a suitable X-ray derivative can be secured.

Scheme 3



22 R = H; X = H (MW:411)
23 R = i-Pr; X = H (MW: 453)

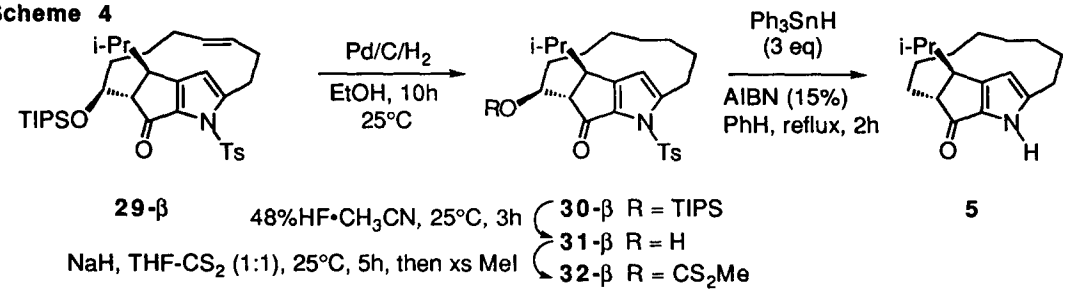
24 R = i-Pr; X = OTIPS (MW: 625)

27 R = H; X = H
28 R = i-Pr; X = H

29 R = i-Pr; X = OTIPS

Completion of the synthesis of the roseophilin core tricyclic **5** involved hydrogenation of olefin **29**–β to **30**–β which was desilylated using 48% HF to alcohol **31**–β (J_{ab}=6.2Hz; 85% overall from **29**), followed by conversion to xanthate **32**–β (J_{ab}=6.7Hz; 77%). Triphenyl tinhydride treatment of **32**–β effected concomitant deoxygenation and cleavage of the tosyl moiety providing tricyclic **5** in 90% yield (Scheme 4).

Scheme 4



29-β 48%HF•CH_3CN, 25°C, 3h → **30-β** R = TIPS; **31-β** R = H

NaH, THF-CS_2 (1:1), 25°C, 5h, then xs MeI → **32-β** R = CS_2Me

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