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Synthesis of the Spiroketal Segment (C19-C34) of the Rutamycins, Antifungal Metabolites of *Streptomyces* Species

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Abstract: A convergent synthesis of the spiroketal subunit of rutamycins A and B has been devised via Julia coupling of sulfone **14** with aldehyde **23**; the pentahydroxy ketone **3** derived from **25** underwent spontaneous cyclization to spiroketal **4**.
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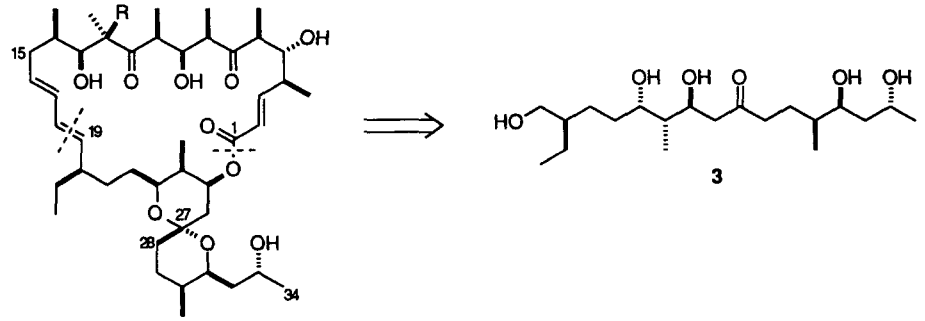
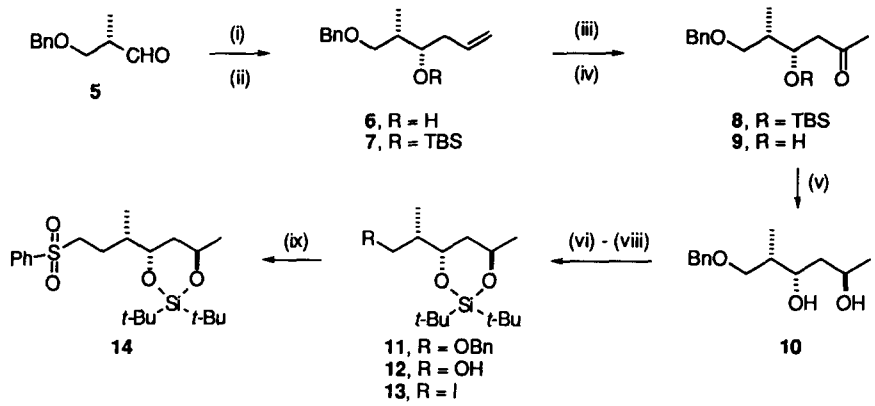
Rutamycins A (**1**)[1] and B (**2**)[2] are metabolites of *Streptomyces griseus* and *S. aureofaciens*, respectively, which exhibit potent antifungal activity. The structures of these macrolides embody a 1,7-dioxaspiro[5.5]undecanyl moiety that is found, with minor variation, in phthoramycin,[3] cytovaricin,[4] and the oligomycins.[5] Our plan for a synthetic assault on **1** and **2**[6] required the "southern" component in the form of a preassembled spiroketal, and an approach to this subunit was conceived which hinged upon spirocyclization of the acyclic precursor **3**.[7] We describe the successful implementation of a scheme in which spiroketal **4**, comprising C19-34 of the rutamycins and incorporating eight of their 17 stereogenic centers, is assembled from two fragments representing C19-27 and C28-C34.



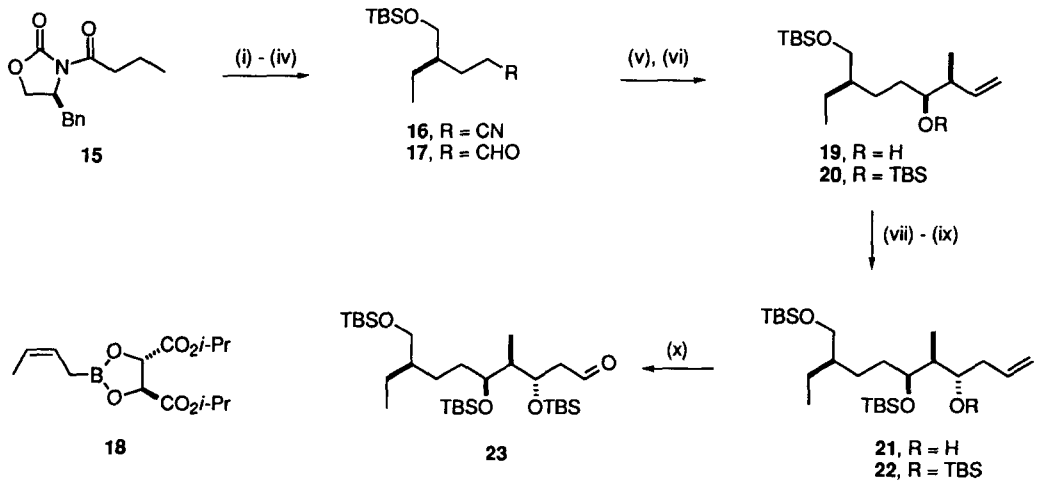
Rutamycin A, **1**, R = OH
Rutamycin B, **2**, R = H

The first of these segments was prepared from aldehyde **5**,[8] which was reacted with the borane obtained *in situ* from allylmagnesium bromide and (-)-diisopinylcampheylmethoxyborane.[9] The resultant *syn* homoallylic alcohol **6**[8,9] was protected as its silyl ether **7**, and the terminal alkene was subjected to a Wacker oxidation[10] that afforded ketone **8** in excellent yield. After removing the silyl protecting group, the β-hydroxy ketone **9** was reduced with tetramethylammonium triacetoxyborohydride[11] to furnish the *anti* diol **10**. The



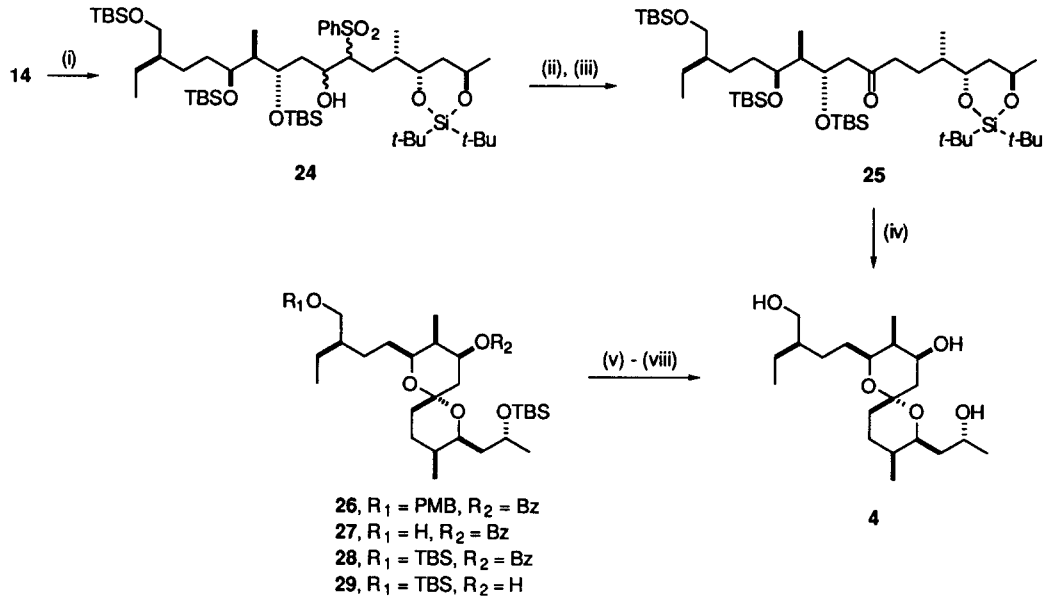
(i) Ref 9; (ii) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 90%; (iii) $PdCl_2$, CuCl, O_2, DMF-H_2O, rt, 85%; (iv) HF-pyr, THF, rt, 78%; (v) $Me_4NBH(OAc)_3$, MeCN-AcOH, -30 °C, 82%; (vi) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 0 °C, 92%; (vii) H_2, 3% Pt/C, EtOH, 96%; (viii) I_2, Ph_3P, imidazole, C_6H_6, Δ, 96% (ix) *n*-BuLi, $PhSO_2CH_3$, HMPA-THF, -78 °C → rt, 85%.

1,3-diol was protected as its di-*tert*-butylsilylene derivative **11**,[12] and the benzyl ether was cleaved by hydrogenolysis to yield alcohol **12**. The latter was converted to its iodo derivative **13**[13] which was reacted with the anion of methyl phenyl sulfone to provide sulfone **14**.



(i) $TiCl_4$, $Ti(Oi\text{-}Pr)_4$, *i*-Pr_2NEt, then CH_2=CHCN, CH_2Cl_2, 0 °C, 85%; (ii) $LiBH_4$, THF, rt, 67%; (iii) TBSCl, imidazole, DMF, rt, 91%; (iv) *i*-Bu_2AlH, hexane, -78 °C, 93% (v) **18**, 4 Å mol sieve, toluene, -78 °C, 85%; (vi) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 97%; (vii) O_3, CH_2Cl_2–MeOH, -78 °C, then Me_2S, 96%; (viii) CH_2=$CHCH_2MgBr$, (-)-$(Ipc)_2$ BOMe, Et_2O, -78 °C, 92%; (ix) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 93%; (x) O_3, CH_2Cl_2–MeOH, -78 °C, then Me_2S, 88%.

Synthesis of the C19-C27 subunit required for coupling with **14** began from (*S*)-(-)-3-butyryl-4-benzyloxazolidin-2-one (**15**).[7,14] The titanium enolate of **15**[15] underwent highly stereoselective Michael addition with acrylonitrile to furnish **16** as the only detectable stereoisomer, and the latter after removal of the chiral auxiliary was reduced to aldehyde **17**. Reaction of **17** with the (*Z*)-crotylboronate **18**,[16] prepared from diisopropyl (*S*, *S*)-tartrate, afforded the *syn* homoallylic alcohol **19** in excellent yield. After protection of **19** as its silyl ether **20**, the vinyl group was cleaved by ozonolysis to an aldehyde which was reacted with the same chiral allylborane[9] used to prepare **6**. The resulting homoallylic alcohol **21** was converted to the trisilyl ether **22** before ozonolytic cleavage to aldehyde **23**.



26, R_1 = PMB, R_2 = Bz
27, R_1 = H, R_2 = Bz
28, R_1 = TBS, R_2 = Bz
29, R_1 = TBS, R_2 = H

(i) *n*-BuLi, $BF_3.Et_2O$, THF, then **23**, -78 °C → rt, 86%; (ii) TPAP, NMO, 4 Å mol sieve, CH_2Cl_2, rt, 86%; (iii) SmI_2, THF–MeOH, -78 °C, 89%; (iv) HF–MeCN, rt, 82%; (v) H_2, 20% $Pd(OH)_2$/C, EtOH, rt, 97%; (vi) TBSOTf, Et_3N, CH_2Cl_2, O °C, 98%; (vii) LiOH, MeOH, rt, 100%; (viii) TBAF, THF, rt, 98%.

Julia coupling[17] of the lithio anion of **14** with **23** proceeded smoothly in the presence of boron trifluoride etherate to give hydroxy sulfone **24** as a mixture of all four stereoisomers. This mixture was oxidized with perruthenate[18] to the keto sulfone (two stereoisomers), which upon reductive desulfonylation with samarium diiodide[19] produced a single ketone **25**. Exposure of **25** to hydrogen fluoride in acetonitrile simultaneously removed all of the silyl blocking groups and resulted in spontaneous spirocyclization. The structure of the resulting trihydroxy spiroketal **4** was confirmed by chemical correlation with a substance **26** previously prepared by Evans.[7]

Thus, the *p*-methoxybenzyl (PMB) ether of **26** was first removed by hydrogenolysis, and the primary alcohol **27** was silylated to yield **28**. The benzoate of **28** was next removed by saponification, and both silyl ethers were then cleaved from **29** to give **1**. This material was identical in all respects with the substance obtained by spirocyclization of **25**.

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