Ripostatin B (1)

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Access to Skipped Polyene Macrolides through Ring-Closing Metathesis: Total Synthesis of the RNA Polymerase Inhibitor Ripostatin B[**]

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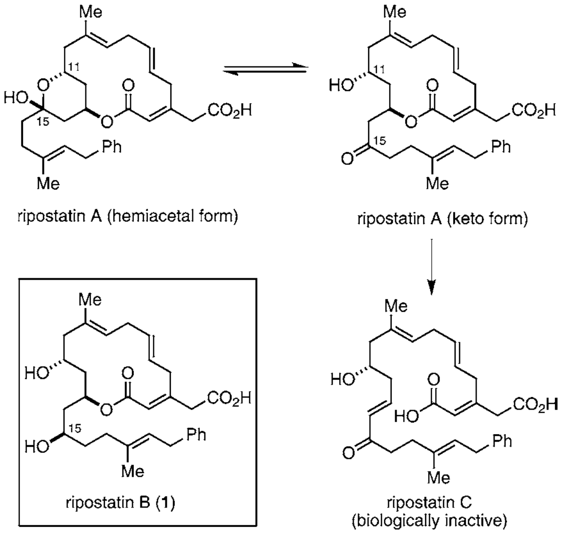
Dedicated to Professor Ernst Schaumann

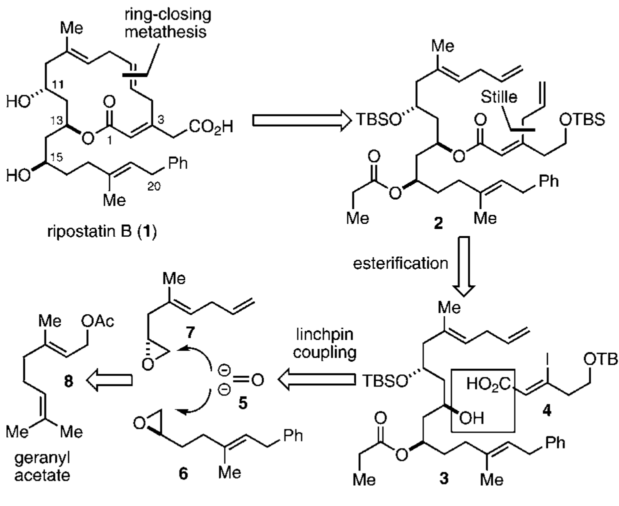
An increasing number of reports on drug-insensitive bacterial strains have revived public awareness towards the importance of antibiotics research. The emergence of multiresistant variants of *Mycobacterium tuberculosis* poses a deadly threat that is not limited to developing countries.[1] Similarly methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a deadly pathogen among hospitalized patients. One of the clinically validated approaches for the treatment of bacterial infections—often applied in a combination therapy with other antibiotics—involves the inhibition of eubacterial RNA polymerase.[2] The rifamycins are currently the only approved class of RNA polymerase inhibitors. As a result of increasing rifamycin resistance, the development of new cross-resistant RNA polymerase inhibitors is necessary.



Scheme 1. The ripostatins A–C.

In 1995, Reichenbach, Höfle, and co-worker reported the isolation of ripostatins A and B (**1**; Scheme 1) as the active principle agent of the myxobacterium *Sorangium cellulosum* (strain So ce 377) from a soil sample collected in 1989 from Kenya.[3] Both compounds display activity across a narrow antibiotic spectrum[4] against some strains of *Staphylococcus aureus* with MIC values of 1 $\mu g\,mL^{-1}$. Moreover, there is no cross-resistance with rifampin, thus suggesting a different binding mode.[5] The ripostatins differ only in the oxidation state at C15. Ripostatin A exists in an approximate 1:1 ratio of the hemiacetal/keto form (Scheme 1), and the latter can undergo facile eliminative lactone opening to form the biologically inactive ripostatin C. Because of the reported sensitivity of ripostatin A towards acid and base, we selected **1** as the primary target of our study with the aim of fully exploring the structural space accessible by means of chemical synthesis. From a structural point of view, **1** features a stereotriad (C11–C15) partially embedded into a polyunsaturated 14-membered macrolide. The stereocontrolled synthesis of such methylene interrupted ("skipped") polyene[6] motifs requires careful synthetic design.[7]

In our retrosynthetic analysis (Scheme 2), the sensitive triene moiety and the carboxylic acid would be introduced at a late stage of the synthesis using a ring-closing metathesis (RCM) reaction[8]/oxidation sequence. To the best of our



Scheme 2. Retrosynthesis. TBS = *tert*-butyldimethylsilyl.

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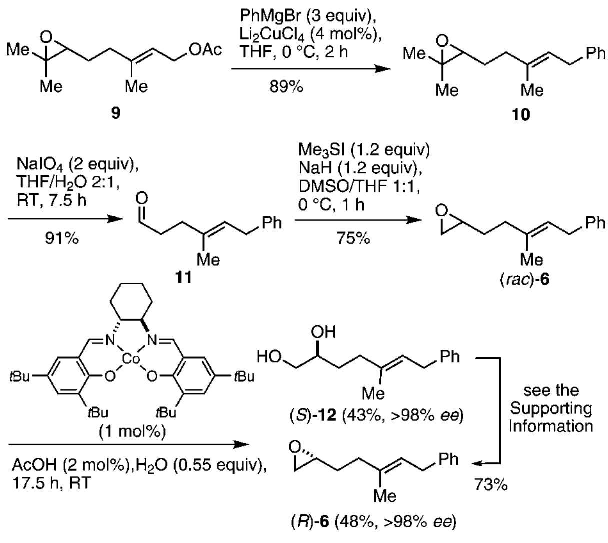
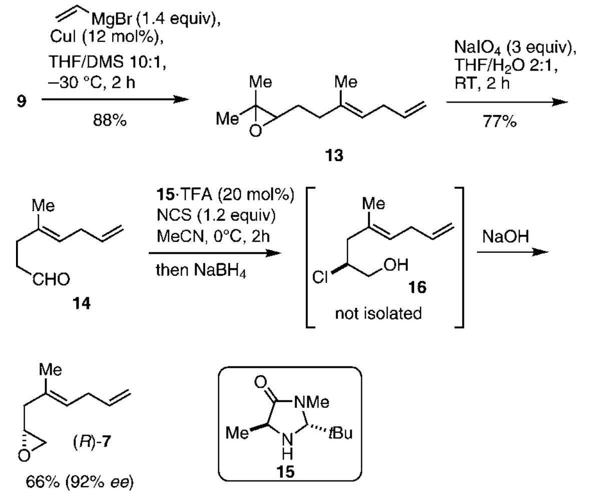
knowledge, this would constitute the first RCM of two 1,4-dienes.[9] Previous synthetic studies[10] indicated that the ester side chain of **2** is prone to double bond isomerization under esterification conditions. We therefore decided to establish the C2–C7 diene of **2** after coupling of the fragments **3** and **4** using a Stille reaction with an allylstannane. The stereotriad within **3** should be accessible by opening of the two epoxides **6** and **7** with a suitable formyl dianion equivalent (**5**),[11] and subsequent diastereoselective reduction.

To minimize the number of C–C bond-forming steps within the synthesis, we developed chemistry that is enabling in the utilization of readily available monoterpenoids for the synthesis of higher terpenoids or polyketides by selective functionalization reactions. A close inspection of the epoxides **6** and **7** reveals that both compounds can be derived from geranyl acetate (**8**) by simple displacement of the allyl acetate with either vinyl- or phenylmagnesium nucleophiles. Subsequent transformation of the other termini would then establish the requisite epoxide coupling partners. The synthesis of epoxide **6** (Scheme 3) commenced with a copper-catalyzed substitution[12] of *rac*-6,7-epoxygeranyl acetate **9**[13] with phenylmagnesium bromide (89 % yield). The epoxide **10** was cleaved with sodium periodate[14] to give aldehyde **11** in 91 % yield. A Corey–Chaykovsky reaction afforded the epoxide *rac*-**6** in 75 % yield on a 20 g scale. This material was subjected to a Jacobsen hydrolytic kinetic resolution (HKR)[15] reaction to give the desired epoxide (*R*)-**6** in 48 % yield and greater than 98 % *ee*, along with 43 % of the diol (*S*)-**12** (> 98 % *ee*). Following a known[16] procedure, the diol (*S*)-**12** could be converted into the desired epoxide (*R*)-**6** in 73 % yield in three steps (see the Supporting Information for details), thus raising the overall yield of (*R*)-**6** to 79 % (starting from *rac*-**6**).



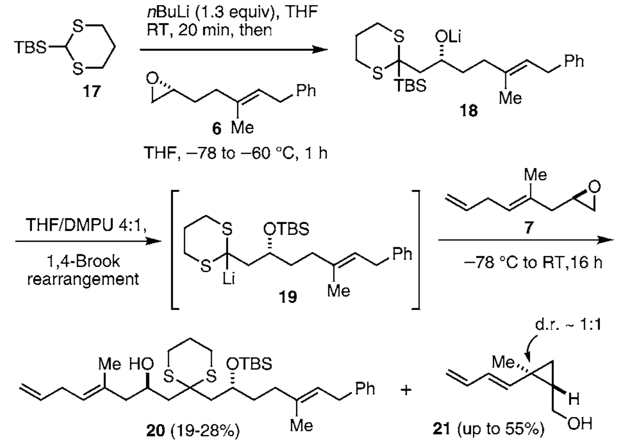
Scheme 3. Synthesis of epoxide (*R*)-**6**. DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

The synthesis of the epoxide **13** (Scheme 4) required intensive optimization, which resulted in the discovery of an efficient procedure[17] for the synthesis of 1,4-dienes from allylic acetates and vinylmagnesium bromide. Application of this protocol to 6,7-epoxgeranyl acetate **9** smoothly yielded epoxide **13** in 88 % yield. Epoxide cleavage ($NaIO_4$) liberated aldehyde **14** in 77 % yield, and was in turn subjected to a merged[18] Jørgensen[19]/MacMillan[20] chlorination protocol. In situ reduction with sodium borohydride gave the intermediate alcohol **16** which was treated directly with NaOH to furnish the epoxide (*R*)-**7** in 66 % yield and 92 % *ee*. The synthesis of fragment **6** and **7** demonstrates how oxidative functionalizations of simple terpene raw materials and their transformation into suitable polyketide building blocks provide a shortcut for the expeditious synthesis of polyketide scaffolds.



Scheme 4. Synthesis of epoxide (*R*)-**7**. DMS = dimethylsulfide, TFA = trifluoroacetate.

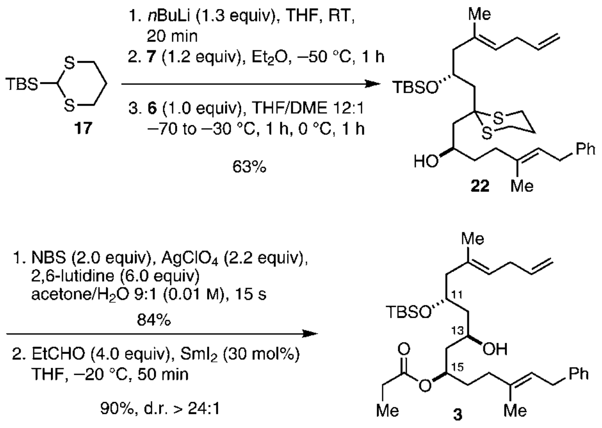
With the two epoxides **6** and **7** in hand, we turned our attention to the crucial one-pot[21] dithiane linchpin coupling (Scheme 5) using dithiane **17** as a formyl dianion synthon (see **5**, Scheme 1). This powerful multicomponent reaction,[22] based on a concept[23] put forward by Schaumann and coworkers, was extended to the coupling of identical epoxides by Tietze et al.[24] The important finding of Smith and



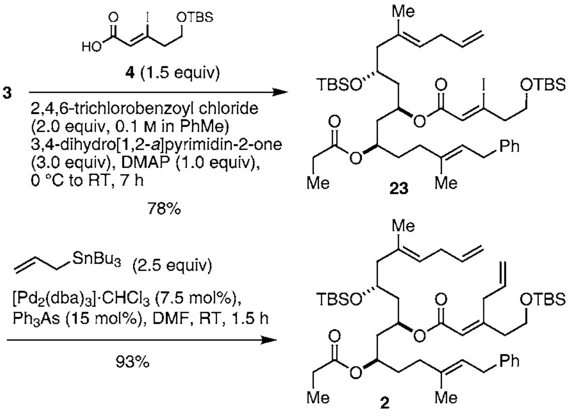
Scheme 5. First-generation dithiane linchpin coupling. DMPU = 1,3-dimethylpropyleneurea.

Pitram[25] that either HMPA (HMPA = hexamethylphosphoramide) or DMPU accelerate the 1,4-Brook rearrangement added great value to this strategy, thus enabling the sequential coupling of two different epoxides. While the order of addition of the two epoxides appears to be inconsequential, in our first trials, the epoxide **6** was added to a lithium anion of dithiane **17**. Solvent-induced Brook rearrangement of the intermediate alkoxide **18** and subsequent addition of the corresponding lithiated dithiane **19** to epoxide **7** gave **20** in surprisingly low yields (19–28 %). The major products upon isolation were the cyclopropane **21** along with protonated **19**, both resulting from **19** acting as a strong base that is capable of deprotonating **7** in the doubly allylic position, thus leading to intramolecular epoxide opening by the anion.

At this point, we reasoned that changing the order of addition would result in a more favorable outcome. In our rationale, the less basic lithiated derivative of **17** (resulting from the α effect of the TBS group) would cleanly open the epoxide **7**, thereby avoiding the base-induced rearrangement to the cyclopropane **21**. Gratifyingly, in an optimized protocol using 1,2-dimethoxyethane (DME)[26] to induce the Brook rearrangement, we were able to obtain the desired coupling product **22** in a respectable 63 % yield (Scheme 6). The dithiane was removed using a protocol from Corey and Erickson,[27] and the resulting hydroxyketone was subjected to an Evans–Tishchenko reduction[28] leading to the differentially protected triol **3** having a free hydroxy group at C13. The relative configuration of the C11–C15 stereotriad was established by orthogonal removal of the C11 and C15 protecting groups, and conversion of the resulting diols into their respective acetonides.[29]



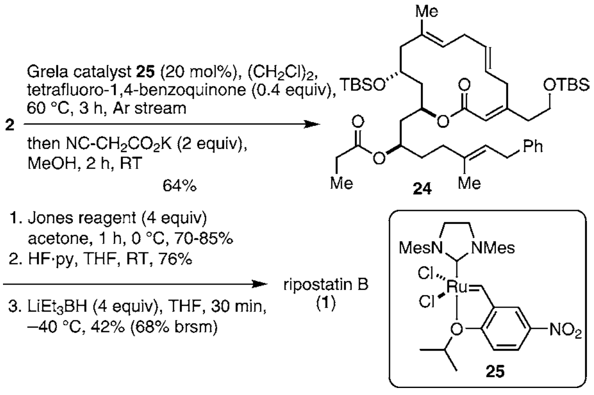
Scheme 6. Second-generation coupling and dithiane removal/reduction. DME = dimethylether, NBS = *N*-bromosuccinimide.



Scheme 7. Esterification and Stille coupling. dba = dibenzylideneacetone, DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N'*-dimethylformamide.

The yields for the Yamaguchi esterification[30] step (Scheme 7) to give the 3-iodoalkenonic ester **23** initially suffered from significant elimination of hydrogen iodide (HI); up to 21 % when amine-based proton scavengers like Et$_3$N were used. This problem was solved by using 3,4-dihydro[1,2-a]pyrimidin-2-one[31] as the base. The synthesis of the two skipped dienes for the RCM was completed with a Stille coupling[32] to smoothly deliver **2** in 93 % yield without any isomerization.

The stage was now set for the crucial metathesis event (Scheme 8). After considerable experimentation, we found that using Grela's catalyst[33] (**25**) with tetrafluoro-1,4-benzoquinone as an additive[34] and purging with argon minimizes the problems encountered with other catalysts. Grubbs I and II, Hoveyda–Grubbs, and other catalysts resulted in loss of the *E*/*Z* selectivity, cross-metathesis with ethylene, or sluggish reactions.



Scheme 8. Ring-closing metathesis and endgame.

Interestingly, the argon purge was mandatory to suppress the truncation of the carbon skeleton by means of a cross-

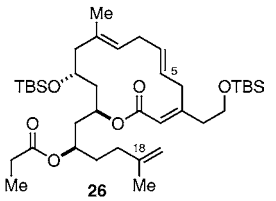


Figure 1. The truncated metathesis product **26**.

metathesis reaction with ethylene (**26**; Figure 1). When using the Grubbs II catalyst[35] without an argon purge (20 mol% catalyst, 40 mol% 1,4-benzoquinone, toluene (1 mM), 90 °C, 1.5 h), we observed the desired products **24** and **26** in an approximately 1:1 ratio. Dorta's catalyst[36] (10 mol% catalyst, 20 mol% tetrafluoro-1,4-benzoquinone, toluene (1 mM), 2 h, 50 °C), gave **26** as the major product. We speculate that a relay-type mechanism[37] might be operative in transferring the catalyst to the trisubstituted C18 double bond instead of cycloreversion of the metallacyclobutane and dissociation of the catalyst. Moreover, the truncation appears to be interconnected with the configuration of the double bond at C5. Compound **26** was always isolated as a clean $5E$ isomer even when **24** was a mixture of $5E$ and $5Z$ isomers.

By using Jones oxidation conditions (excess Jones-reagent diluted in acetone, 0 °C)[38] the TBS ether on the primary alcohol of **24** was cleaved and effected rapid oxidation to the carboxylic acid in 70–85% yield, thereby avoiding double-bond isomerization and decomposition observed upon isolation of aldehyde intermediates (e.g., TEMPO-based oxidations). The C11 TBS ether was removed by using HF·py (76%), and finally selective reductive cleavage of the propionate ester[39] in presence of the α,β-unsaturated lactone and the carboxylic acid moiety afforded ripostatin B (**1**) in 42% yield (68% based on unreacted starting material). The spectroscopic data including the optical rotation ($[\alpha]_D^{20} = +26$ ($c = 5$, MeOH), published $+35.7$ ($c = 1$, MeOH)) was in good[40] agreement with that reported in the literature.

In conclusion, we describe herein an efficient total synthesis[41] of the RNA polymerase inhibitor ripostatin B. By using a ring-closing metathesis reaction as the key step we were able to establish the sensitive 14-membered macrolactone featuring the unusual doubly skipped triene moiety. The acyclic precursors were joined in a one-pot linchpin coupling of two terminal epoxides derived from cheap monoterpene raw materials. Our route involves 14 steps in the longest linear sequence (4% overall yield from geranyl acetate) and nicely showcases the powerful interplay of modern organocatalytic (epoxide **7**) and transition metal catalyzed transformations (Cu, Co, Pd, Ru). Future work from our laboratories will concern the synthesis of analogues and their biological evaluation.

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