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(+)-Rimocidin Synthetic Studies. Construction of an Advanced C(1–18) Polyol Fragment

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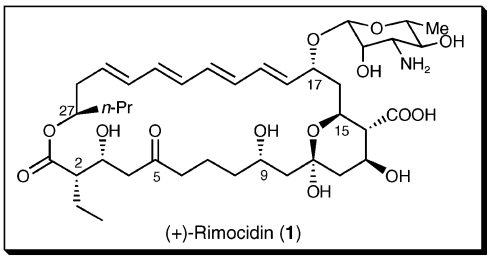
ABSTRACT



(+)-Rimocidin (**1**)

The synthesis of an appropriately functionalized advanced C(1–18) polyol fragment of the mycosamine-glycosylated polyene macrolide, (+)-rimocidin (1), has been achieved in a highly efficient manner. Highlights of the strategy include the S_N2/S_N2' addition of dithiane anions to vinyl epoxides and the multicomponent linchpin union of 2-TBS-1,3-dithiane with two advanced epoxides.

Rimocidin (**1**), an architecturally interesting antifungal polyene macrolide glycosylated at C(17) with (−)-mycosamine, was isolated from *Streptomyces rimosus* in 1951.[1] Early structural analysis by Cope and co-workers[2a] led to the assignment of the absolute configuration of the C(27) stereocenter. However, it was not until 1995 that the complete stereostructure was shown to comprise a 28-membered aglycon, termed rimocidinolide, possessing an all-trans tetraene system and nine stereogenic centers.[2f] Importantly, the C(9−18) segment is common to a number of clinically effective antifungal agents, including (+)-amphotericin B and (+)-nystatin A_1.[3]

In this Letter, we report an efficient, stereocontrolled synthesis of an advanced C(1−18) polyol fragment for (+)-rimocidin (**1**), appropriately functionalized for future incorporation into the macrolide skeleton. The synthetic strategy calls upon both our one-flask, multicomponent linchpin union of silyl dithianes with epoxides,[4] employed to great advantage in our recent spongistatin syntheses,[5] and the highly chemoselective S_N2 and S_N2' reactions of simple and sterically encumbered dithianes with vinyl epoxides, also recently disclosed by our laboratory.[6] The overall strategy is outlined in Scheme 1.

Final assembly of the advanced C(1−18) fragment **2** was envisioned to involve union of epoxides **3** and **5** with the anion derived from 2-TBS-1,3-dithiane (**4**) via the three-

(1) Davisson, J. W.; Tanner, F. W., Jr.; Finlay, A. C.; Solomons, I. A. *Antibiot. Chemother.* **1951**, *1*, 289−290.

(2) (a) Cope, A. C.; Axen, U.; Burrows, E. P. *J. Am. Chem. Soc.* **1966**, *87*, 4221−4227. (b) Cope, A. C.; Burrows, E. P.; Derieg, M. E.; Moon, S.; Wirth, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 5452−5460. (c) Falkowski, L.; Golik, J.; Zielinski, J.; Borowski, E. *J. Antibiot.* **1976**, *29*, 197−198. (d) Falkowski, L.; Zielinski, J.; Golik, J.; Bylec, E.; Borowski, E. *J. Antibiot.* **1978**, *31*, 742−749; (e) Pandey, R. C.; Rinehart, K. L., Jr. *J. Antibiot.* **1977**, *30*, 146−157. (f) Sowinski, P.; Pawlak, J.; Borowski, E.; Gariboldi, P. *J. Antibiot.* **1995**, *48*, 1288−1291.

(3) Omura, S. *Macrolide Antibiotics: Chemistry, Biology, Practice*; Academic Press: New York, 1984.

(4) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925−6926.

(5) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783−786.

(6) Smith, A. B., III; Pitram, S. M.; Gaunt, M. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 14516−14517.

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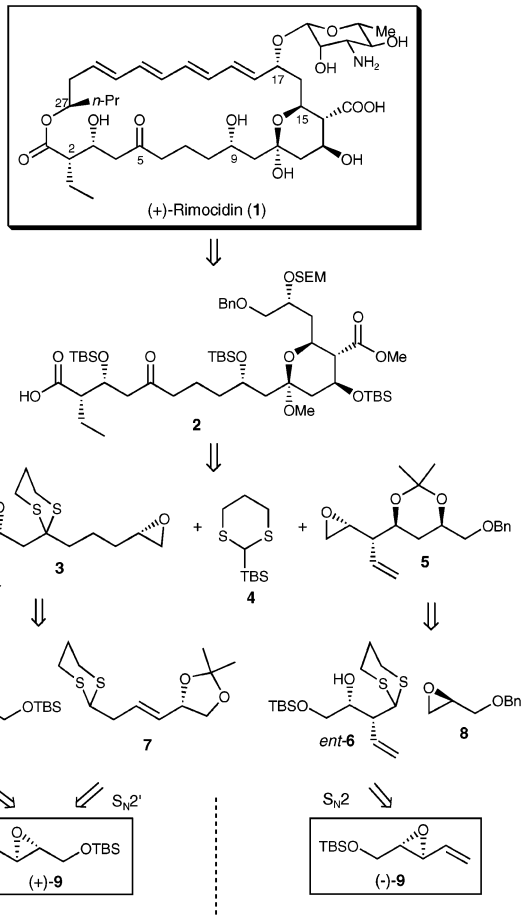
Scheme 1

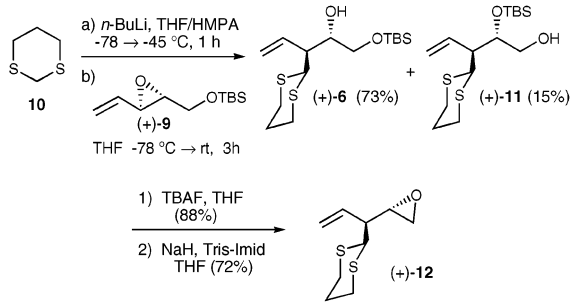


component coupling protocol.[4] Epoxide **3**, possessing two dithiane moieties, in turn, would arise via dithiane coupling of **7** with an epoxide derived from **6**, followed by conversion of the acetonide to the terminal epoxide and hydrogenation of the two olefins. Importantly, both **6** and **7** can be assembled from vinyl epoxide (+)-**9** exploiting, respectively, the S_N2 and S_N2' reaction manifolds observed upon the addition of the lithium anions of 1,3-dithiane and 2-TIPS-1,3-dithiane, while advanced epoxide **5** would arise from the union of the similarly prepared *ent*-**6** and (*R*)-benzyl glycidyl ether (**8**). Finally, both antipodes of **9** were anticipated to be readily available in three steps from commercial 1,4-pentadien-3-ol.[7]

We began the synthesis with the construction of **3**. Addition of the lithium anion of 1,3-dithiane (**10**) to vinyl epoxide (+)-**9**[7] proceeded as expected, with high selectivity, via the S_N2 manifold (Scheme 2) to furnish (+)-**6** in 73% yield, along with a minor amount (15%) of (+)-**11**, the product of silyl migration. Removal of the silyl groups in both adducts and one-step Fraser−Reid epoxide formation[8] [NaH, trisylimidazole (Tris-Imid), THF, 72%] then furnished (+)-**12**.

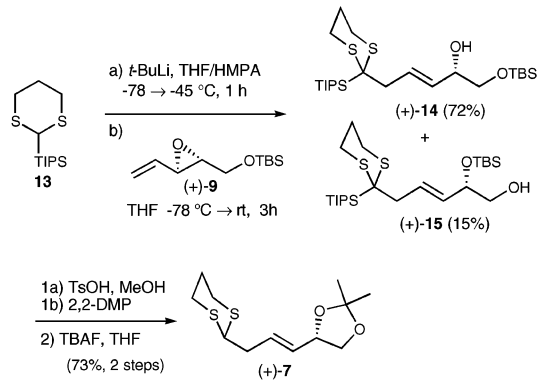
To construct dithiane (+)-**7** (Scheme 3), we turned to the S_N2' manifold of vinyl epoxides, reacting lithiated 2-TIPS-1,3-dithiane (**13**) with (+)-**9**. Adduct (+)-**14** and a modest

Scheme 2



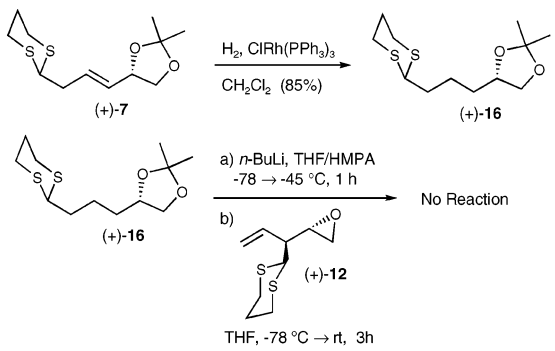
amount of silyl migration product (+)-**15** were obtained in a combined yield of 87%. Without separation, removal of the TBS groups with TsOH, acetonide formation, and treatment with TBAF to remove the TIPS group furnished (+)-**7** in 73% yield.

Scheme 3



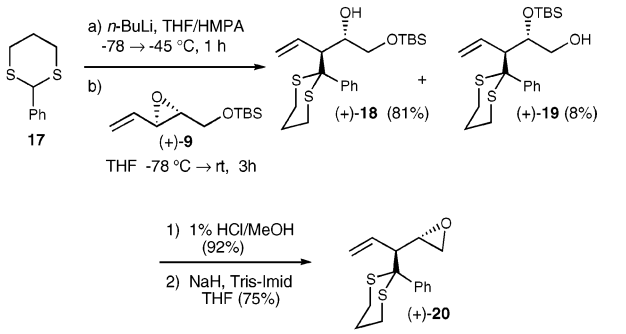
From the outset, we had planned to reduce the olefins present in both (+)-**7** and (+)-**12** after their union. Unfortunately, the adjacent allylic system in (+)-**7** destabilized the dithiane anion, preventing union with epoxide (+)-**12**.[9] To circumvent this event, (+)-**7** was hydrogenated (Wilkinson's catalyst; 85%) to furnish (+)-**16** (Scheme 4), which in turn could be readily lithiated, as determined by deuterium

Scheme 4



incorporation. Coupling with epoxide (+)-**12**, however, again proved unsuccessful. We reasoned that the dithiane in (+)-**12** undergoes competitive deprotonation leading to complex mixtures. To test this hypothesis, a "capped" dithiane was sought. Ideal for this purpose appeared to be the phenyl moiety [e.g., **20**; Scheme 5], as earlier studies[6] had revealed that the lithium anion of 2-phenyl-1,3-dithiane (**17**) also furnishes only S_N2 adducts with simple vinyl epoxides. Equally important, removal of the dithiane at an advanced stage in the synthesis would afford the phenyl ketone, a reasonable surrogate for the required carboxyl group, requiring only regioselective Baeyer−Villager oxidation.[10]

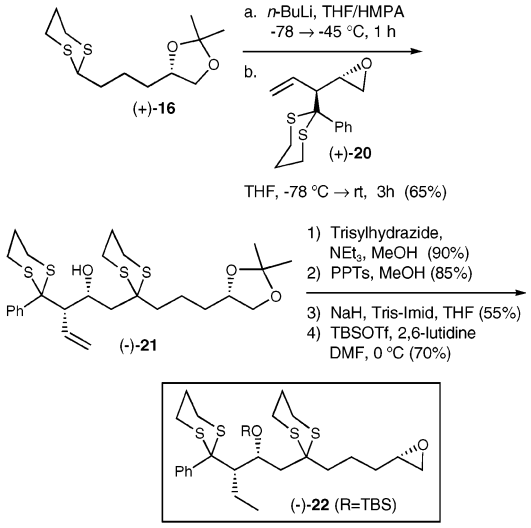
Scheme 5



Toward this end, addition of lithiated 2-phenyl-1,3-dithiane (**17**) to vinyl epoxide (+)-**9** led efficiently to S_N2 adduct (+)-**18** (Scheme 5), again with a minor amount of (+)-**19** derived by silyl migration. Removal of the TBS groups in both alcohols was achieved under acidic conditions (1% HCl/MeOH, 92%); one-step Fraser−Reid epoxide formation[8] (NaH, trisylimidazole, THF, 75%) then furnished (+)-**20**. The overall yield for the three-step sequence was 61%.

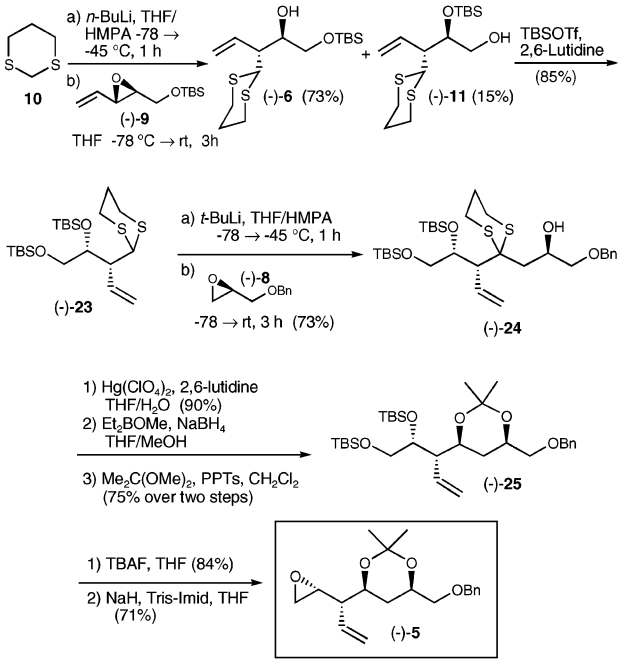
Union of (+)-**16**, via the lithium anion, with epoxide (+)-**20** also proceeded in good yield to furnish (−)-**21** (Scheme 6). Diimide reduction of the alkene, a process known to proceed in the presence of dithianes,[11] was then followed by removal of the acetonide, epoxide formation,[8] and protection of the resulting hydroxyl as the TBS ether (TBSOTf, 2,6-lutidine). The result was bis-dithiane (−)-**22**, available in four steps and 30% overall yield.

Scheme 6



For advanced epoxide **5**, we began with the enantiomers of dithianes (+)-**6** and (+)-**11** prepared from (−)-**9** (Scheme 7). Without separation, protection of the hydroxy functionality in both alcohols as the TBS ethers and union of the derived lithium anion with (−)-**8** provided (−)-**24**. Removal of the dithiane [$Hg(ClO_4)_2$, 2,6-lutidine, THF/H_2O], followed in turn by hydroxyl-directed reduction of the resulting ketone [$NaBH_4$, Et_2BOMe],[12] acetonide formation (75% over two steps), treatment with TBAF to remove the silyl groups (84%), and epoxide formation[8] (NaH, trisylimidazole, THF, 71%) completed construction of (−)-**5**. The overall yield for this eight-step sequence was 21%. With epoxides (−)-**5** and (−)-**22** in hand, we explored the key multicomponent coupling.

Scheme 7



(7) See Supporting Information for preparation of vinyl epoxides (+)- and (−)-**9**.

(8) (a) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439−1441. (b) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, *3*, 203.

(9) On the basis of previous work from our laboratory, we reasoned that union of (+)-**7** and (+)-**12** would be feasible. Unfortunately, quenching experiments with MeOH-d_4 revealed that lithiation of (+)-**7** under numerous conditions led primarily to decomposition; see: Smith, A. B., III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35−46.

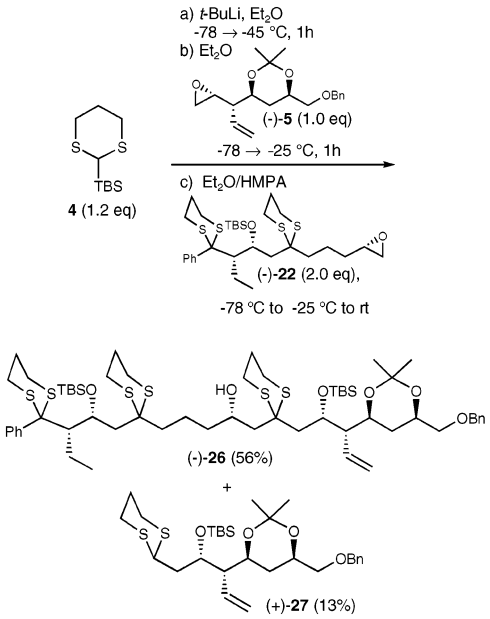
(10) Hawthorne, M. F.; Emmons, W. D.; McCallum, K. S. *J. Am. Chem. Soc.* **1958**, *80*, 6393−6398.

(11) (a) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157−2162. (b) Yamaguchi, Y.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1987**, *7*, 515−516.

(12) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.

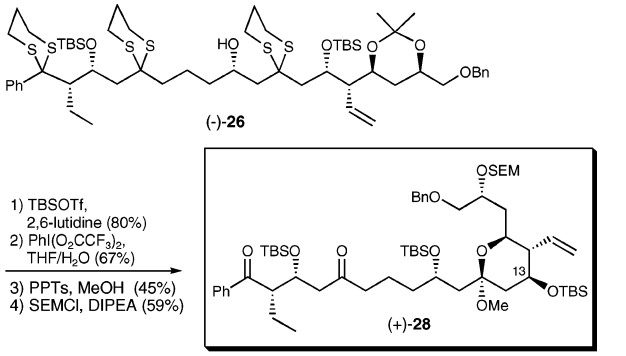
Pleasingly, lithiation of 2-TBS-1,3-dithiane (**4**) in Et_2O at −78 °C (Scheme 8), followed by addition of epoxide (−)-**5** (1.0 equiv, −78 °C), warming to −25 °C over a 1 h period, and then addition of epoxide (−)-**22** (2 equiv) in Et_2O containing HMPA (2−3 equiv) furnished (−)-**26** in 56% yield, accompanied by a minor amount of dithiane (+)-**27** (13%).[13]

Scheme 8



Having achieved construction of the complete C(1−18) carbon backbone, we now faced the task of removing three dithianes. To this end, silylation of the C(9) hydroxyl (Scheme 9), followed by application of the Stork conditions [$PhI(O_2CCF_3)_2$, 2,6-lutidine, THF/H_2O],[14] removed the dithianes with an overall efficiency of 67%. Acetonide removal was then achieved under mild acidic conditions to furnish the mixed methyl acetal, along with modest loss of the C(13) TBS ether. Protection of the C(17) hydroxyl as the SEM ether (59%) completed construction of subtarget (+)-**28**. Studies to effect conversion of (+)-**28** to the C(1−18) polyol fragment **2** of (+)-rimocidin are ongoing in our laboratory.

Scheme 9



In summary, we have achieved an effective, convergent synthesis of (+)-**28**, an advanced C(1−18) polyol fragment for the construction of (+)-rimocidin (**1**). Highlights of the synthesis include the S_N2/S_N2' addition of dithiane anions to vinyl epoxides and the multicomponent linchpin union of 2-TBS-1,3-dithiane with two advanced epoxides. The longest linear sequence from vinyl epoxide (+)-**9** to (+)-**28** is 13 steps and currently proceeds in 2% overall yield. Progress toward the total synthesis of (+)-rimocidin (**1**) will be reported in due course.

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Supporting Information Available: Spectroscopic and analytical data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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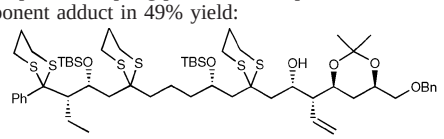
(13) Reversing the order of addition of epoxides (−)-**5** and (−)-**22** in the multicomponent coupling procedure also proved successful, yielding a three-component adduct in 49% yield:



(14) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287−290.