ORGANIC LETTERS

1999
Vol. 1, No. 12
2001−2004

Multicomponent Linchpin Couplings of Silyl Dithianes: Synthesis of the Schreiber C(16–28) Trisacetonide Subtarget for Mycoticins A and B

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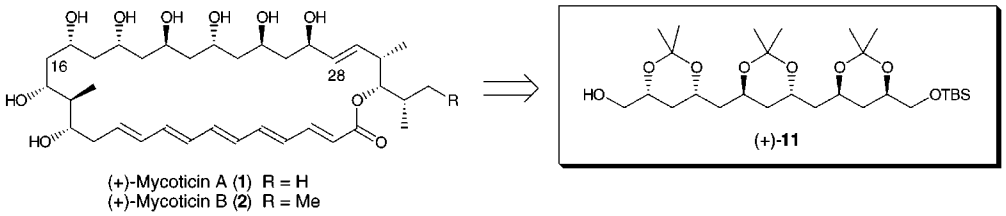
Received October 19, 1999

ABSTRACT



An efficient synthesis of trisacetonide (+)-11, the Schreiber C(16–28) subtarget for mycoticins A and B, is described. The key synthetic transformation entails a one-flask, *five-component* linchpin coupling tactic.

Extended 1,3-hydroxylated chains constitute a central architectural feature of the polyene class of macrolide antibiotics.[1] Some members, such as roxaticin,[2] the dermostatins,[3] and the mycoticins[4] (Figure 1), vary in ring size but share a common polyol structural motif possessing the same relative and absolute stereochemistries. Concise stereocontrolled routes to such structural elements thus represent a significant synthetic goal. Although the asymmetric aldol reaction has proven to be a viable means of accessing 1,3-polyols, the tactic suffers from the iterative nature required to set correctly each stereogenic center. Alternatives to the aldol approach are therefore finding increasing use.[5] Rychnovsky and coworkers employed the cyanohydrin acetonide strategy in their elegant construction of the polyol moieties of roxaticin,[2b] roflamycoin,[6] and filipin.[7]

Recently, we described a one-flask, multicomponent linchpin coupling of silyl dithianes with epoxides, exploiting a solvent-controlled Brook rearrangement (Scheme 1).[8] The protocol, based on the work by Tietze,[9] Oshima, and Utimoto,[10] involves lithiation of 2-*tert*-(butyldimethylsilyl)-1,3-dithiane (**6**), followed in turn by addition of an epoxide

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(2) Structure determination: (a) Maehr, H.; Yang, R.; Hong, L.-N.; Liu, C.-M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1992**, *57*, 4793. Syntheses: (b) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753. (c) Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299. (d) Mori, Y.; Asai, M.; Kawade, J.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315.

(3) Rychnovsky, S. D.; Richardson, T. I.; Rogers, B. N. *J. Org. Chem.* **1997**, *62*, 2925.

(4) Structure determination: (a) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 6001. (b) Schreiber, S. L.; Goulet, M. T.; Sammakia, T. *Tetrahedron Lett.* **1987**, *29*, 6005. (c) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. Synthesis: (d) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360.

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10.1021/ol991166b CCC: $18.00
Published on Web 11/09/1999

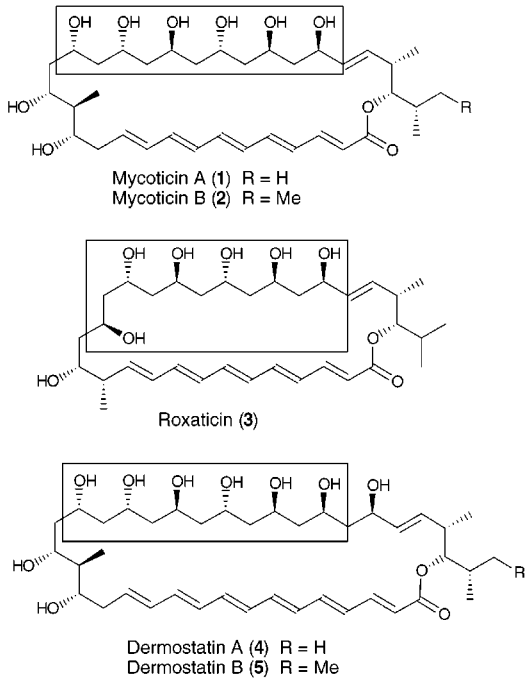
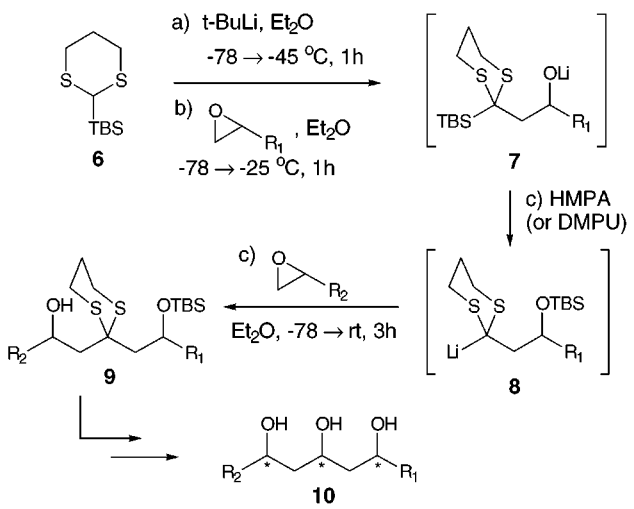


Figure 1.

to generate alkoxy dithiane **7**, Brook rearrangement triggered by HMPA or DMPU to afford anion **8**, and alkylation with a second epoxide to provide the unsymmetrical adduct **9**. Ether rather than THF is required as solvent for the *initial* alkylation to suppress premature silyl migration leading to the formation of symmetric adducts. Altering the absolute configuration of the epoxides followed by removal of the dithiane and stereocontrolled reduction of the derived ketone provides access to all possible diastereomers of the 1,3-polyol fragment (**10**). From the synthetic perspective, this tactic efficiently furnishes the polyol chain with both full stereochemical control and differentiation between hydroxyl

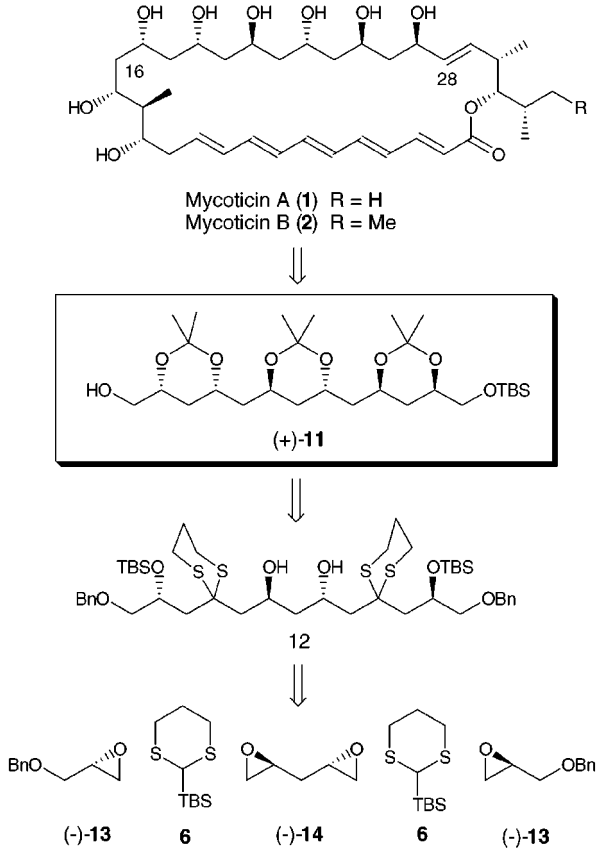
Scheme 1



groups. This strategy was exploited to good advantage in our recently reported syntheses of the spiroketal segments of the spongistatin antitumor agents.[11] We also demonstrated the feasibility of a five-component coupling process.[8]

Herein, we report application of this tactic for the economic (i.e., short) construction of the pseudo-C_2-symmetric trisacetonide subtarget (+)-**11** (Scheme 2), employed

Scheme 2



by Schreiber et al. in their synthesis of (+)-mycoticin A (**1**).[4d] Importantly, fragment (+)-**11** also holds promise as an effective building block for the synthesis of roxaticin and the dermostatins.

Trisacetonide (+)-**11** can be envisioned to arise from the C_2 symmetric diol **12**, an adduct potentially available from a one-flask, five-component linchpin coupling (Scheme 2). A key constituent of this procedure would be (−)-(*S*,*S*)-1,2:4,5-diepoxypentane (**14**), prepared via the Rychnovsky protocol.[12]

Toward this end, lithiation of dithiane **6** (2.5 equiv; Scheme 3), followed by alkylation with (−)-benzyl glycidyl

(10) (a) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503. (b) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951.

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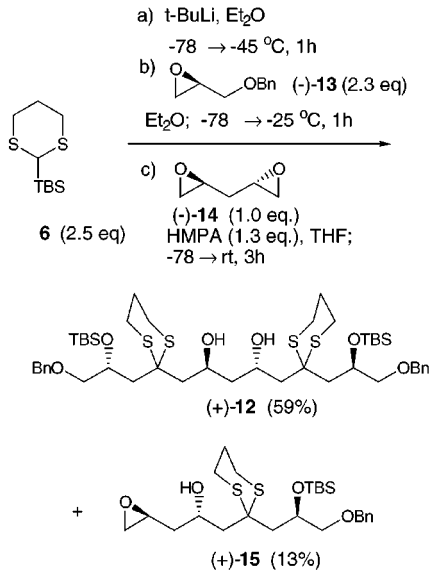
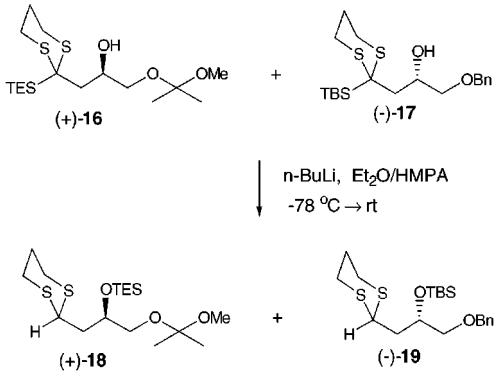
Scheme 3



ether (**13**), addition of a mixture of diepoxypentane (−)-**14** (1.0 equiv) and HMPA (1.3 equiv) in THF, furnished the predicted diol (+)-**12**[13] in 59% yield, accompanied by a minor amount of epoxide (+)-**15** (ca. 13%).[13] Notably, use of THF as cosolvent with HMPA in the second alkylation resulted in higher yields compared to Et_2O (17%). Alternatively, when DMPU was employed as the additive, diol (+)-**12** was obtained in comparable yield (55%), also accompanied by epoxide (+)-**15** (18%). Thus, in a single flask, we generate four carbon−carbon bonds, constructing the carbon skeleton of the desired polyol fragment in an efficient, stereocontrolled fashion.

During analysis of this multicomponent, linchpin coupling we conducted mechanistic studies to determine whether silyl migration preceded via an intra- or intermolecular process (Scheme 4). Lithiation of a mixture of silyl dithianes (+)-**16**[13,14] and (−)-**17**[13,14] (1:1) at −78 °C in the presence of HMPA, followed by warming to ambient temperature, resulted in rearranged products (+)-**18**[13] and (−)-**19**.[13] No

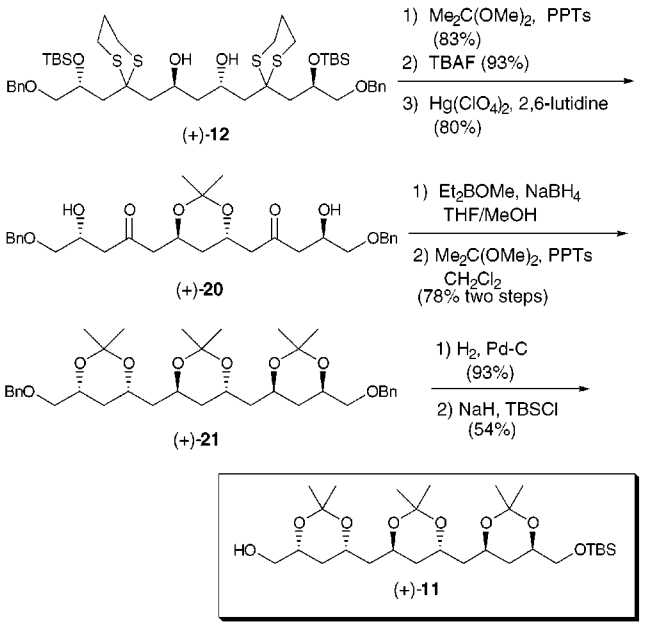
Scheme 4



crossover products were observed; thus silyl migration is intramolecular.

Elaboration of diol (+)-**12** to the Schreiber subtarget [(+)-**11**; Scheme 5] began with protection to form the acetonide

Scheme 5

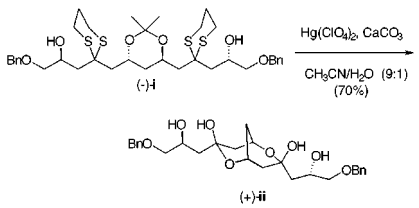


(83%), followed by removal of the silyl groups with TBAF (93%) and hydrolysis of the dithiane with mercuric perchlorate and 2,6-lutidine in aqueous THF, to provide the bis(*β*-hydroxy) C_2 symmetric ketone (+)-**20**[13] in 80% yield.[15] Hydroxyl-directed syn-reduction of both ketones with $NaBH_4$ in the presence of Et_2BOMe (Scheme 5)[16] and trisacetonide formation yielded exclusively (+)-**21**,[13] as determined by NMR analysis (78%, two steps).[17] Hydrogenolysis (93%) and monosilylation[18] (54%) completed construction of the desired subtarget (+)-**11**.

(13) The structural assignment to each new compound is in accord with its IR, ^1H and ^{13}C NMR, and high-resolution mass spectra.

(14) These compounds were prepared via addition of the corresponding silyl dithiane to the requisite epoxide (see ref 8).

(15) In our initial studies with the enatiomeric series of compounds, calcium carbonate proved insufficient as a base. The result was removal of the isopropylidene group and formation of the bicyclic compound (+)-**ii**.



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In summary, synthesis of (+)-**11**, the Schreiber C(16−28) subtarget for mycoticins A and B, has been achieved by exploiting a one-flask, five component, linchpin coupling tactic. The highly convergent synthesis proceeded in eight steps, five fewer than the previously reported route, and in 17% overall yield from diepoxypentane (−)-**14**. Importantly, this multicomponent linchpin coupling protocol should provide ready access to a wide variety of polyene macrolide antibiotic analogues.

Acknowledgment. Financial support was provided by the National Institutes of Health (National Institute of General Medical Sciences) through Grant GM 29028.

Supporting Information Available: Spectroscopic and analytical data for **11**, **12**, **20**, and **21** as well as a representative experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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