ORGANIC LETTERS

2000
Vol. 2, No. 20
3127−3129

Efficient Asymmetric Synthesis of Radicicol Dimethyl Ether: A Novel Application of Ring-Forming Olefin Metathesis

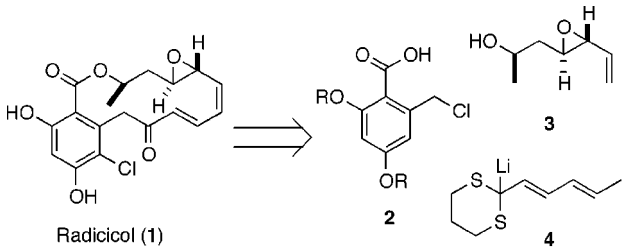
Robert M. Garbaccio[†] and Samuel J. Danishefsky*[,†,‡]

The Laboratory for Bioorganic Chemistry, The Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021, and The Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

s-danishefsky@ski.mskcc.org

Received July 12, 2000

ABSTRACT



A concise, stereospecific synthesis of radicicol dimethyl ether is presented. The strategy relies on a convergent three-stage assembly of the 14-membered lactone which has, as a key transformation, a novel ring-forming metathesis reaction utilizing a vinyl epoxide.

Radicicol (**1**), a metabolite of *Monocillium nordinii*,[1] is an antitumor antibiotic which has the ability to morphologically revert the tumor phenotype of *src*[2] and *ras*[3] transformed cell lines back to normal tissue (Figure 1). While the origins of this property had remained unclear, recent efforts[4] have demonstrated that radicicol binds with nanomolar affinity to the Hsp90 molecular chaperone and inhibits its ATPase activity. This inhibition, in turn, disrupts the ability of Hsp90 to participate in signal transduction pathways that are important for tumor cell growth and leads to proteasomal degradation of oncogenic proteins and apoptosis.[5] Importantly, while radicicol displays this and other activities in vitro, the compound per se has not yet shown in vivo antitumor activity in animal models.[6]

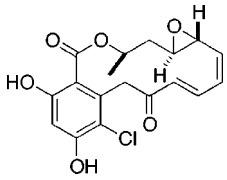


Figure 1. Structure of radicicol.

Isolation of radicicol from natural sources has been characterized as difficult. Some congeners of radicicol obtained from chemistry starting with the natural product have overcome limitations to its in vivo activity.[7] We took note of the improved prognosis for obtaining useful in vivo agents in the radicicol series in the context of our recent efforts involving geldanamycin,[8] an antitumor antibiotic also

[†] The Sloan-Kettering Institute for Cancer Research.
[‡] Columbia University.

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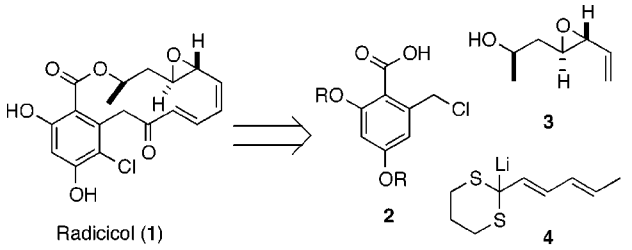
10.1021/ol0063252 CCC: $19.00
Published on Web 08/31/2000

shown to bind to Hsp90. Given these considerations, and given some interesting structural issues which we hoped to address, we identified radicicol as an appropriate focusing target for a program in total synthesis.

To date, only one synthesis of radicicol has been recorded,[9] by a route which is distinct from that practiced here. In this Letter, we describe the results of research which has led to a rather concise and stereoselective entry to the radicicol series. Our interim report contains several instances of differential chemoselectivity successes which could not have been anticipated with confidence in advance of experiment.

The strategy employed relied on a highly convergent three-stage coupling for macrolide formation (Scheme 1). The first

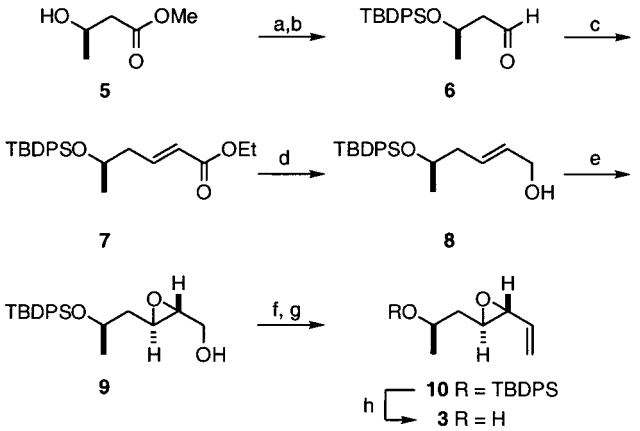
Scheme 1. Three-Stage Strategy for Macrolide Formation



stage would entail esterification of an appropriately substituted benzoic acid (**2**) with an enanatiomerically defined chiral secondary alcohol (**3**), which contains all three stereocenters of radicicol. The second stage requires chemo- and regioselective alkylation of an allylic dithiane (**4**) by the resulting benzylic chloride of **2** + **3**. Last, stereospecific ring-closing metathesis of an olefin with a vinyl epoxide in place would give the desired 14-membered novel lactone cyclization.

The synthesis commenced with construction of the homochiral allylic alcohol (**3**) via a procedure that closely follows that described by Waldmann and co-workers.[10] Thus, methyl (*R*)-3-hydroxybutyric acid (**5**) was silylated (TBDPSCl, imidazole, 95%) and the product reduced at low temperature (DIBAL-H, −78 °C, 92%) to provide directly the desired aldehyde (**6**) (Scheme 2). Wadsworth−Horner−Emmons homologation of **6** under Roush−Masamune condi-

Scheme 2. Synthesis of **2** and **3**[a]



[a] (a) TBDPSCl, imid., >95%; (b) DIBAL-H, −78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL-H, −20 °C, 96%; (e) (+)-DET, $Ti(OiPr_4)$, TBHP, 90%, >95% ee; (f) SO_3•pyridine, Et_3N, DMSO, 90%; (g) Ph_3PCH_3Br, NaHMDS, 0 °C, 82%; (h) TBAF, 89%.

tions[11] (LiCl, DIPEA, 95%) followed by a second reduction (DIBAL-H, 96%) yielded the desired *trans*-allylic alcohol (**8**). Sharpless asymmetric epoxidation ((−)-DET, $Ti(OiPr)_4$, TBHP, 90%) gave the desired epoxyalcohol (**9**) with excellent (>20:1) selectivity. The resulting epoxyalcohol was then oxidized (SO_3•pyridine, Et_3N, DMSO, 90%) and the product aldehyde was converted to the vinyl epoxide (**10**) via Wittig olefination (PPh_3CH_3Br, NaHMDS, 82%). Fluoride-catalyzed removal of the TBDPS group proceeded smoothly (nBu_4NF, 89%) to yield the desired secondary alcohol (**3**). The latter, in principle, contains the sp^3 stereochemical network appropriate for reaching radicicol.

The remaining two building blocks were then synthesized. The allylic dithiane (**4**) was secured in one step from commercially available 2,4-hexadienal (**11**) ($MgClO_4$, H_2SO_4, $H_2S(CH_2)_3SH_2$, 64%).[12] The substituted benzoic acid

(**2**) was synthesized in two steps from commercially available 3,5-dimethoxybenzyl alcohol (**12**) (Scheme 3). Concomitant formylation and conversion of the alcohol to the chloride was effected[13] ($POCl_3$, DMF, 93%) to give the desired aldehyde (**13**). Careful oxidation of this aldehyde ($NaClO_2$, sulfamic acid, 85%) yielded the desired benzoic acid (**2**) with no observed cyclization and tolerably minimal[14] aromatic ring chlorination (<15%).

Assembly of the fragments could then be initiated. Esterification of the benzoic acid (**2**) proceeded smoothly via the acid chloride ($COCl_2$, DMF, Et_3N, **3**, 80%) to provide the benzoic ester (**14**). Addition of the lithiated dithiane (*n*BuLi, −30 °C) to **14** at −78 °C gave chemoselective addition[15] at the benzylic center to give **15** (60% yield).

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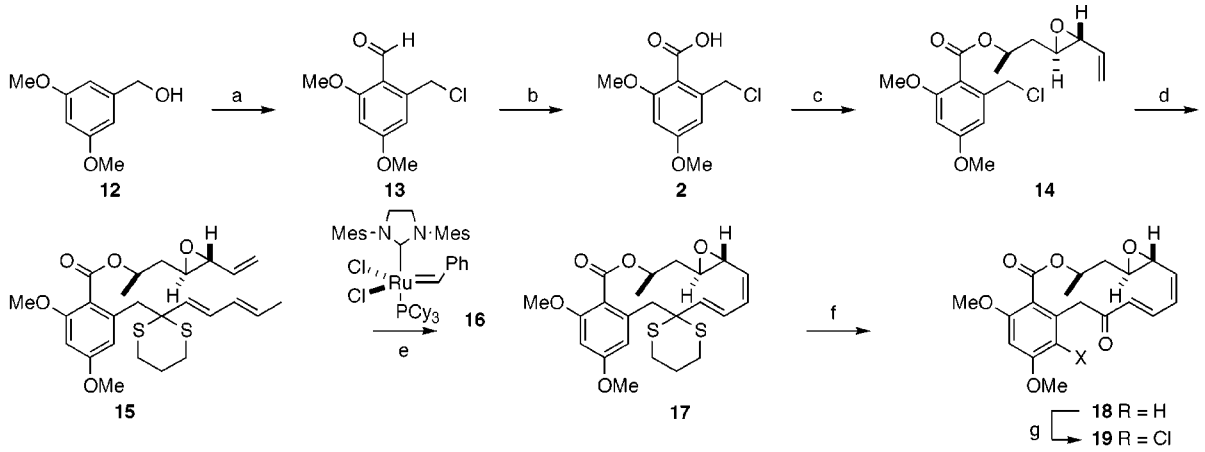
Scheme 3. Synthesis of Radicicol Dimethyl Ether[a]



[a] (a) $POCl_3$, DMF, 75 °C, 93%; (b) $NaClO_2$, 85%; (c) $(COCl)_2$, Et_3N, **3**, 80%; (d) *n*-BuLi, **4**, 60%; (e) 45 °C, 55%; (f) mCPBA; Et_3N, Ac_2O, H_2O, 70%; (g) $Ca(OCl)_2$, 80%

For achieving macrolide formation, we chanced an unprecedented ring-closing metathesis of an olefin and a vinyl epoxide. Other resorcylic acid type macrolides have been elegantly reached by Fürstner and co-workers[16] utilizing olefin metathesis, although not with vinyl epoxide precursors. In the case of **15**, commercially available Grubbs catalyst, $(PCy)_3Cl_2Ru{=}CHPh$, gave only trace amounts of the desired product. We took note that, in a recent communication,[17] Grubbs and co-workers reported the successful intermolecular cross-coupling of a vinyl epoxide utilizing a new-generation and highly active ruthenium-based olefin metathesis catalyst (**16**).[18] Synthesis of this catalyst, and its application to **15** (CH_2Cl_2, 45 °C), gave the desired 14-membered lactone (**17**) stereospecifically in 55% yield. Notably, this transformation was also successful in the presence of two sulfur atoms. Previously, sulfur-containing substrates had been identified as deactivating ligands for ruthenium in unsuccessful ring-closing metathesis.[16,19] Thus, the radicicol-like macrolide was formed from three similarly sized components in a highly convergent fashion.

There remained the need to retrieve the ketone from the dithiane, to regioselectively chlorinate the aromatic ring, and to remove the methyl ethers for completion of the natural product synthesis. Initial efforts to expose the ketone led to gross decomposition, and it was surmised that the allylic nature of the epoxide in **17** was complicating the deprotection. Fortunately, a two-step intramolecular Pummerer-based protocol[20] was successful. The dithiane was oxidized to the monosulfoxide (*m*CPBA, 0 °C), and the crude monosulfoxide was exposed to the action of Ac_2O, Et_3N, and H_2O to give the desired ketone (**18**, 70%), also known as dimethyl monocillin I. Regiospecific chlorination of the aromatic ring ($Ca(OCl)_2$, 80%)[9] produced radicicol dimethyl ether (**19**).[21]

Removal of the phenolic methyl ethers in the presence of the sensitive epoxide and lactonic functions has not been accomplished thus far. Preliminary results have indicated that the epoxide is the first site of vulnerability to Lewis acids (BBr, BCl_3). Opening of the epoxide is soon followed by cleavage of the methyl ether ortho to the benzoic ester.

Efforts are underway to complete the synthesis of the natural product, as well as to apply this concise strategy to generate structural analogues of radicicol with useful in vivo activity.

Acknowledgment. The research was supported by the National Institutes of Health (CA-28824 and HL25848). Postdoctoral Fellowship support is gratefully acknowledged by R.M.G. (NIH, 1 F32 CA85894-01). Dr. George Sukenick (NMR Core Facility, Sloan-Kettering Institute, CA-02848) is acknowledged for mass spectral analyses. We acknowledge the invaluable help of Dr. Hyunjin Kim, currently in the laboratory for Dr. Robert Grubbs at Caltech, for information regarding the catalyst preparation as well as Ms. Phieng Siliphaivanh for her initial efforts at Columbia on alternative routes to radicicol.

Supporting Information Available: Detailed descriptions of experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Chemoselective addition of the dithiane at the benzylic center occurred with predominant α (**15**) vs γ (**15a**) regioselectivity (4:1, 60% yield isolated **15**). These regioisomers were separable by HPLC. For a report on vinyl dithiane regioselectivity, see: Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2678−2682.

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