Concise Asymmetric Syntheses of Radicicol and Monocillin I

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Abstract: Radicicol (**1**) exhibits potent anticancer properties in vitro, which are likely to be mediated through its high affinity (20 nM) for the molecular chaperone Hsp90. Recently, we reported the results of a synthetic program targeting radicicol (**1**) and monocillin I (**2**), highlighted by the application of ring-closing metathesis to macrolide formation. These efforts resulted in a highly convergent synthesis of radicicol dimethyl ether but failed in the removal of the two aryl methyl ethers. Simple exchange of these methyl ethers with more labile functionalities disabled a key esterification in the initial route. Through extended experimentation, a successful route to both natural products was secured, along with some intriguing results that emphasize the implications of this design on a broad range of fused benzoaliphatic targets, including analogues of these natural products.

Introduction

Radicicol[1,2] (**1**) and monocillin I[2] (**2**) are resorcylic macrolides which can both be isolated from *Monocillium nordinii*[2] (Figure 1). While the skeletal structure of radicicol was determined in 1964,[3] its relative and absolute stereochemical configuration was not unambiguously established until 1987.[4] The structure of monocillin I (**2**) was confirmed by its direct conversion into radicicol (**1**).[4] Affirmation of these structures was achieved by their only total synthesis accomplished by Lett and Lampilas.[5]

Both radicicol (**1**) and monocillin I (**2**) exhibit a variety of antifungal and antibiotic properties not shared by other members of this class of natural products. Recently, the antitumor properties of radicicol have come into focus. Its ability to suppress the transformed phenotype caused by various oncogenes such as *src*, *ras*, and *raf* has been linked to its high affinity binding (20 nM) and inhibition of the Hsp90 molecular chaperone.[6] This "anti-chaperone" activity may stimulate depletion of oncogenic proteins and could therefore be of clinical interest. Importantly, while radicicol displays this and other activities in vitro, the compound has not yet exhibited in vivo antitumor activity in animal models,[7] though some derivatives do manifest in vivo efficacy.[8] In addition, recent reports on the neurotrophic ability of geldanamycin (**3**) and radicicol (**1**) have merited attention.[9]

Our interest in inhibitors of Hsp90 began with efforts involving geldanamycin (**3**),[10] an antitumor antibiotic also shown to bind to Hsp90 (1.2 μM). In addition, a novel class of synthetic nucleotide analogues were shown to bind to Hsp90 (15−20 μM) and inhibit the proliferation of cancer cells.[11] Hence, the combination of growing interest in anticancer activity mediated by Hsp90 inhibition, the high affinity of radicicol (**1**) for this chaperone, and the absence of an efficient synthetic route prompted our total synthesis efforts. Through these efforts, we hoped to gain access to the radicicol system and thereby gain the opportunity to address various biological issues starting with SAR analysis. These efforts could also enable the design of bifunctional agents by linking radicicol (**1**) with other ligands, as has been done with geldanamycin (**3**),[10] thus expanding our portfolio of selective Hsp90 inhibitors.

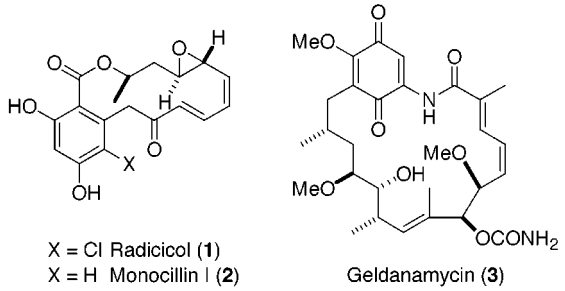

Figure 1. Structures of radicicol, monocillin I, and geldanamycin.

Synthesis of Radicicol Dimethyl Ether. We focused on a modular route to monocillin I (**2**) as well as radicicol (**1**) that would be favorable for analogue production. A strategy was devised utilizing a highly convergent coupling sequence for three key intermediates (**4**−**6**) (Scheme 1).[12]

(1) Delmotte, P.; Delmotte-Plaquée, J. *Nature* **1953**, *171*, 344.
(2) Ayer, W. A.; Lee, S. P.; Tsuneda, A.; Hiratsuka, Y. *Can. J. Microbiol.* **1980**, *26*, 766.
(3) Two independent efforts confirmed the structures of monorden and radicicol and found them to be identical. McCapra, F.; Scott, A. I.; Delmotte, P.; Delmotte-Plaquée, J.; Bhacca, N. S. *Tetrahedron Lett.* **1964**, 869. Mirrington, R. N.; Ritchie, E.; Shoppee, C. W.; Taylor, W. C.; Sternhell, S. *Tetrahedron Lett.* **1964**, 365.
(4) Cutler, H. G.; Arrendale, R. F.; Springer, J. P.; Cole, P. D.; Roberts, R. G.; Hanlin, R. T. *Agric. Biol. Chem.* **1987**, *51*, 3331.
(5) Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 773 and 777.
(6) Roe, S. M.; Prodromou, C.; O'Brien, R.; Ladbury, J. E.; Piper, P. W.; Pearl, L. H. *J. Med. Chem.* **1999**, *42*, 260.
(7) Kwon, H. J.; Yoshida, M.; Nagaoka, R.; Obinata, T.; Beppu, T.; Horinouti, S. *Oncogene* **1997**, *15*, 2625.
(8) Soga, S.; Neckers, L. M.; Schulte, T. W.; Shiotsu, Y.; Akasaka, K.; Narumi, H.; Agatsuma, T.; Ikuina, Y.; Murakata, C.; Tamaoki, T.; Akinaga, S. *Cancer Res.* **1999**, *59*, 2931.
(9) Gold, B. G.; Densmore, V.; Shou, W.; Matzuk, M. M.; Gordon, H. S. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1202. Gold, B. G. Compositions and Methods for Promoting Nerve Regeneration by Disrupting the Steroid Receptor Complex and Stimulating MAP Kinase/Kinase Activity. Patent WO 2001003692, Jan 2001.
(10) Kuduk, S. D.; Zheng, F. F.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *Biorg. Med. Chem. Lett.* **1999**, *9*, 1233. Kuduk, S. D.; Harris, C. R.; Zheng, F. F.; Sepp-Lorenzino, L.; Ouerfelli, Q.; Rosen, N.; Danishefsky, S. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 4325.
(11) Chiosis, G.; Timaul, M. N.; Lucas, B.; Munster, P. N.; Zhewng, F. F.; Sepp-Lorenzino, L.; Rosen, N. *Chem. Biol.* **2001**, *8*, 289.
(12) Garbaccio, R. M.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3127.

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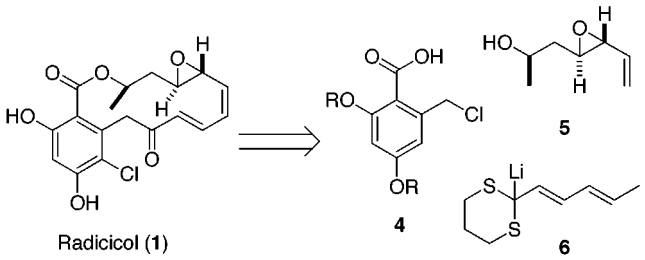
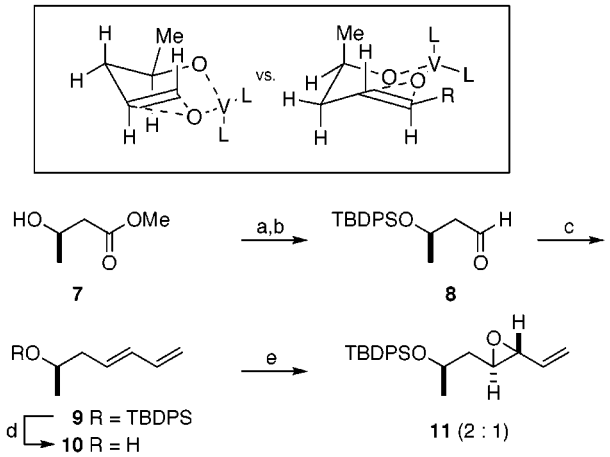
Scheme 1



The first coupling would entail esterification of an appropriately substituted benzoic acid (**4**) with an optically pure secondary alcohol (**5**) containing all three stereogenic centers of radicicol. The second coupling requires chemo- and regioselective addition of a masked acyl anion equivalent (such as **6)** to the benzyl chloride carbon in the presence of a vinyl epoxide. In the concluding phase, stereospecific ring-closing metathesis of a diene with a vinyl epoxide would lead to the desired 14-membered lactone containing the cis−trans diene. This route would lead to monocillin I (**2**), which can subsequently be converted to radicicol (**1**) by aromatic chlorination.[4]

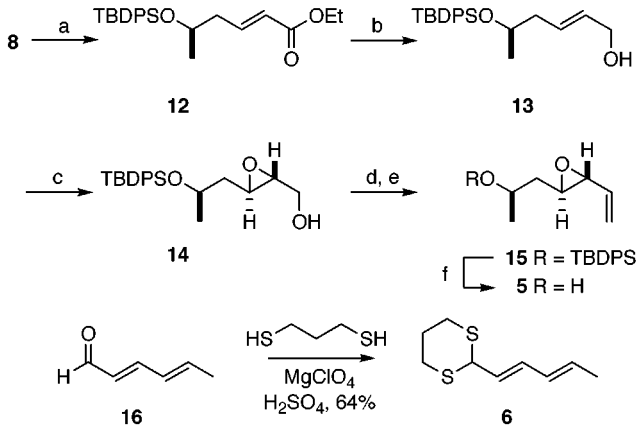
Scheme 2[a]



[a] (a) TBDPSCl, imidazole, >95%; (b) DIBALH, −78 °C, 92%; (c) allyl diethyl phosphonate, 80%, 8:1; (d) TBAF, 85%; (e) $VO(acac)_2$, CH_2Cl_2, −30 °C, 2:1.

The first and most complex coupling partner needed for this synthetic plan was the enantiomerically homogeneous vinyl epoxide **5**. A short substrate-directed approach was devised. The route relies on directed epoxidation of a homoallylic alcohol (Scheme 2). It was hoped that the orientation of the methyl group (equatorial versus axial) in the chairlike transition state would direct the epoxidation to afford the desired vinyl epoxide. In the event, (*R*)-3-hydroxybutyric acid methyl ester (**7**) was protected (TBDPSCl, imidazole, >95%), and the product was reduced at low temperature (DIBALH, −78 °C, 92%) to provide aldehyde (**8**). Chain extension of this aldehyde with allyl diethyl phosphonate (*n*-BuLi, 80%, 8:1 trans:cis) followed by removal of the TBDPS protecting group (*n*-Bu_4NF, 85%) gave the required homoallylic alcohol **10**. $VO(acac)_2$-catalyzed epoxidation of **10** at 0 °C (TBHP, CH_2Cl_2, 12 h) afforded desired epoxide **11** only in a 3:2 ratio. Conduct of the reaction at −30 °C (5 days) gave only minor improvement (2:1). Varying solvent had little effect on the outcome of this transformation. One potential shortcoming of this route was that it would require hydroxyl *R* stereochemistry in order to produce the all *R* vinyl epoxide, thus eliminating the Mitsunobu reaction as a method for subsequent esterification with the aromatic fragment. It will become evident later that this was a significant limitation. This route was left unoptimized in favor of a more general and selective route.

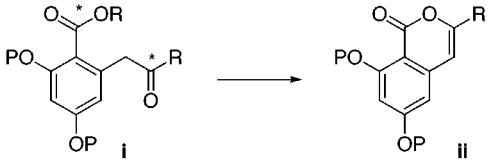
Scheme 3[a]



[a] (a) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (b) DIBALH, −20 °C, 96%; (c) (+)-DET, $Ti(OiPr)_4$, TBHP, 90%, >95% ee; (d) SO_3·pyridine, Et_3N, DMSO, 90%; (e) Ph_3PCH_3Br, NaHMDS, 0 °C, 82%; (f) TBAF, 89%.

Given the low diasteroselectivity of the homoallylic epoxidation and the relative inflexibility of this approach to the generation of analogous fragments, an alternate sequence was explored. This route closely follows that described by Waldmann and co-workers[13] (Scheme 3) and initiates with aldehyde (**8**). Wadsworth−Horner−Emmons homologation of **8** under Roush−Masamune conditions[14] (LiCl, DIPEA, 95%) followed by reduction (DIBALH, 96%) yielded *trans*-allylic alcohol (**13**). Sharpless asymmetric epoxidation ((−)-DET, $Ti(OiPr)_4$, TBHP, 90%) gave the desired epoxyalcohol (**14**) with excellent (>20:1) selectivity. Epoxyalcohol **14** was then subjected to Parikh−Doering oxidation (SO_3·pyridine, Et_3N, DMSO, 90%)[15] and the resultant aldehyde converted to the vinyl epoxide (**15**) (PPh_3-CH_3Br, NaHMDS, 82%). Removal of the TBDPS group proceeded smoothly (*n*-Bu_4NF, 89%) to yield the secondary alcohol (**5**), which carried all three stereocenters appropriate for reaching radicicol (**1**).

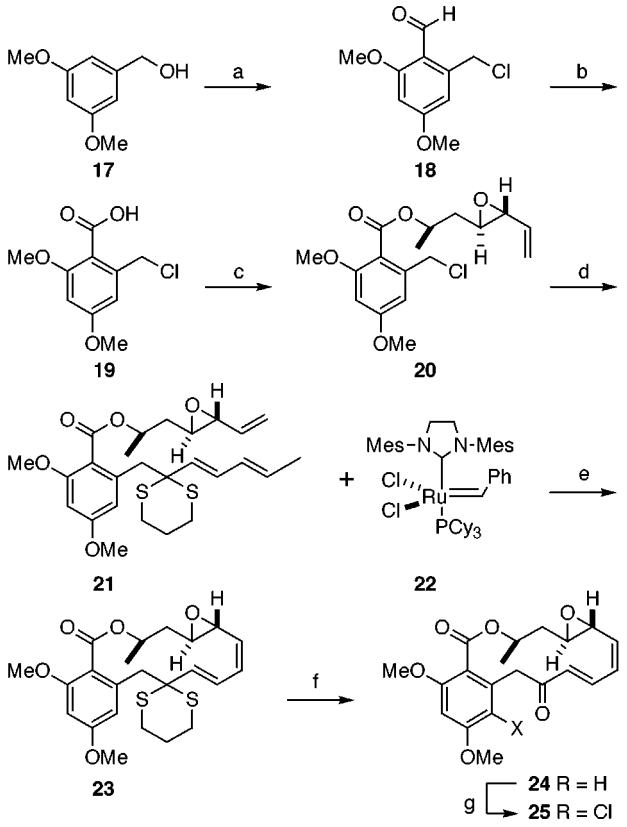
The second required coupling partner for this design was an appropriate acyl anion equivalent. Dienyl dithiane (**6**) was envisaged to be the optimal choice. This building block could serve two critical functions. First, it would allow for nucleophilic introduction of the required diene. Second, it was hoped that the dithiane function would mask the latent ketone. Previous work in our laboratory as well as others revealed that the combination of the free ketone and ester (see asterisks in **i**, eq 1) before the macrocyclic ring has been established possesses a high propensity to cyclize to a coumarin (**ii**). Ring opening of such a structure such as **ii** to gain access to substances useful for macrocyclization can become problematic.



(1)

(13) Schlede, U.; Nazaré, M.; Waldmann, H. *Tetrahedron Lett.* **1998**, *39*, 1143.
(14) Masamune, S.; Roush, W. R. *Tetrahedron Lett.* **1984**, *25*, 2183.
(15) Parikh, V. E., Jr.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

Scheme 4[a]



[a] (a) $POCl_3$, DMF, 75 °C, 93%; (b) $NaClO_2$, 85%; (c) $(COCl)_2$, Et_3N, **5**, 80%; (d) *n*-BuLi, **6**, 60%; (e) 45 °C, 55%; (f) mCPBA; Et_3N, Ac_2O, H_2O, 60 °C, 70%; (g) $Ca(OCl)_2$, 80%.

In the event, the allylic dithiane (**6**), was secured in one step from commercially available 2,4-hexadienal (sorbaldehyde, **16**) ($MgClO_4$, H_2SO_4, $H_2S(CH_2)_3SH_2$, 64%, Scheme 3).[16]

The third coupling partner required for the synthetic plan was a protected benzoic acid **4**. It was synthesized in two steps from commercially available 3,5-dimethoxybenzyl alcohol (**17**) (Scheme 4). Formylation and concomitant conversion of the alcohol to the chloride was effected in excellent yield[17] ($POCl_3$, DMF, 93%) to give the desired aldehyde (**18**). Careful oxidation of this aldehyde ($NaClO_2$, sulfamic acid, 85%) yielded the desired benzoic acid (**19**) with no observed cyclization and minimal[18] aromatic ring chlorination (<5%). Here, the methyl groups were retained for phenolic protection because of their stability. It was hoped that demethylation could be accomplished at a late stage in the synthesis.

With the three coupling partners in hand, assembly anticipating macrolide formation could then be initiated. Esterification of the benzoic acid (**19**) proceeded smoothly via its acid chloride ($COCl_2$, DMF, Et_3N, **5**, 80%) to provide the benzoic ester (**20**). It is important to note that esterifications using either carbodiimide or Mitsunobu-based conditions were unsuccessful because of intervening cyclization to 2,4-dimethoxy phthalide. These limitations foreshadowed difficulties we would encounter with differentially protected benzoic acid systems. Addition of the lithiated dithiane (*n*-BuLi, −20 °C) to **20** chemoselectively gave **21** (−78 °C, 60% yield), although only with 4:1 α:γ regioselectivity.[19] Attempts to run the addition at higher temperatures or stoichiometry resulted in undesired addition of the dithiane anion to the vinyl epoxide.

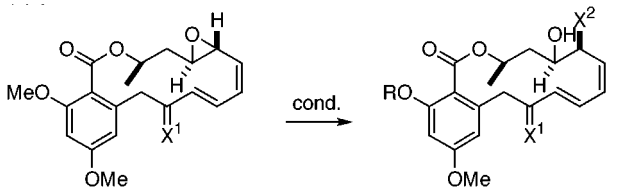
For achieving macrolide formation, we envisaged an unprecedented ring closing metathesis of a diene and a vinyl epoxide. Other resorcylic acid type macrolides have been elegantly reached by Fürstner and co-workers[20] utilizing olefin metathesis, although not with vinyl epoxides, nor with this degree of functionality. In our case, the reaction of **21** with commercially available catalyst $(PCy)_3Cl_2Ru{=}CHPh$,[21] resulted in only trace amounts of the desired product. In a recent communication,[21] Grubbs and co-workers reported the successful intermolecular cross-metathesis of a vinyl epoxide with a new generation, and highly active, ruthenium-based olefin metathesis catalyst (**22**).[22] Application of this second generation catalyst to **21** (CH_2Cl_2, 45 °C) gave the desired *Z*−*E* 14-membered lactone (**23**) in a gratifying 55% yield. Notably, this transformation was accomplished in the presence of two sulfur atoms. Previously, sulfur-containing substrates were implicated as deactivating ligands in unsuccessful ring-closing metatheses.[23] Thus, the radicicol-like macrolide **23** was assembled in three sequential steps.

For completion of the synthesis, there remained only removal of the dithiane, cleavage of the methyl ethers, and regioselective aromatic chlorination. Initial efforts to liberate the ketone from its dithiane protection moiety led to gross decomposition. These attempts at deprotection ($Th(NO_3)_3$, $PhI(OCOCF_3)_2$)[24,25] were directed to the generation of a version of a "thionium moiety" en route to the hydrolytic deprotection. Not surprisingly, the dienyl epoxide was vulnerable when exposed to these Lewis acids. To circumvent generation of a thionium intermediate, a two-step Pummerer-like deprotection[26] was enlisted. This protocol served well in this case, as the dithiane was oxidized to the monosulfoxide (*m*CPBA, 0 °C) and the crude monosulfoxide was exposed to Pummerer-like conditions (Ac_2O, Et_3N, H_2O, 60 °C) to give the desired ketone (**24**, 70%), also known as dimethyl monocillin I. Regiospecific chlorination of the aromatic ring ($Ca(OCl)_2$, 80%)[5] produced radicicol dimethyl ether (**25**) without complication. The structure of **25** was confirmed by comparison of its spectral data with those of commercial radicicol following methylation (MeI, K_2CO_3, acetone, 95%) of both free phenols.

Unfortunately, we were unable to cleave the two methyl ethers of **24** required to reach fully synthetic monocillin I (**2**). This finding was not wholly unexpected in the light of the highly sensitive functional core. Representative conditions for accomplishing deprotections are depicted below (Table 1). Lewis-acid promoted deprotections result in the opening of the epoxide at −78 °C, and only later result in deprotection of the *ortho*-

(16) Fang, J.-M.; Liao, L.-F.; Hong, B.-C. *J. Org. Chem.* **1986**, *51*, 2828.
(17) Makara, G. M.; Klubek, K.; Anderson, W. K. *Synth. Commun.* **1996**, *26*, 1935.
(18) The chlorinated benzoic acid did not participate in esterification and, thus, easily dropped out of the sequence following purification of **20**.
(19) Chemoselective addition of the dithiane at the benzylic center occurred with predominant α (**21**) vs γ (**21a**) regioselectivity (4:1, 60% yield isolated **21**). These regioisomers were separable by HPLC. For a report on vinyl dithiane regioselectivity and similar reactions, see: Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2678. Colombo, L.; Gennari, C.; Santandrea, M.; Narisano, E.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 136.
(20) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.
(21) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
(22) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(23) Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett.* **1996**, *37*, 9373.
(24) Ho., T.-L.; Wong, C. M. *Can. J. Chem.* **1972**, *50*, 3740.
(25) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
(26) Kishi, Y.; Fukuyama, T.; Natatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490. Fukuyama, T.; Natatsuka, S.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045. Wu, Z.; Williams, L. J.; Danishefsky, S. J. *Angew. Chem.* **2000**, *39*, 3866.

Table 1



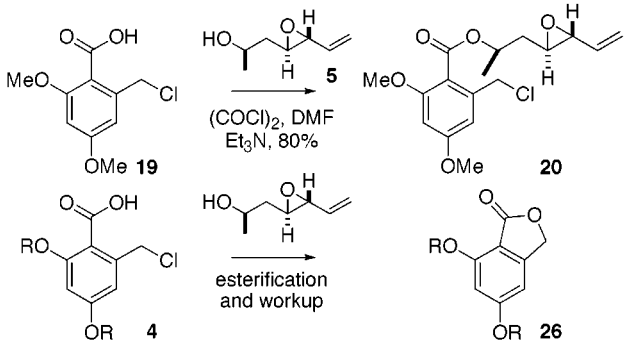
X^1	Reagent	Solvent	Temp.	R	X^2
O	BBr_3	CH_2Cl_2	– 78 °C	Me	Br
O	BCl_3	CH_2Cl_2	– 78 °C	Me	Cl
O	BCl_3	CH_2Cl_2	– 30 °C	H	Cl
O	BCl_3	CH_2Cl_2	40 °C	decomposition	–
$S(CH_2)_3S$	NaSEt	DMF	80 °C	no reaction	–
$S(CH_2)_3S$	NaSEt	DMF	140 °C	decomposition	–

methyl ether. Retreating a step in the synthesis, thiolate-promoted deprotections were attempted on the dithiane-protected macrolide (in order to avoid Michael-like degradation pathways). Again, the methyl ethers were resistant to cleavage, and no reaction occurred at 80 °C. Higher temperatures led to extensive decomposition.[27]

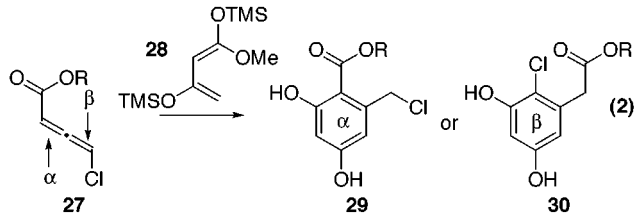
The difficulties with methyl ether deprotection clearly called for a minimally modified follow-up synthesis with more labile phenolic protecting groups. Indeed, schemes to this end were initiated. However, an unexpected difficulty frustrated these initiatives.

A key enabling reaction in our previous route was the esterification of benzoic acid **19** with alcohol **5** to produce benzyl ester **20**. Unfortunately, all attempts (including Mitsunobu, carbodiimide, and acid chloride) to conduct this reaction on systems such as **4**, where R is more complex than methyl, were unsuccessful. Such initiatives led, instead, to phthalide formation (**26**) (Scheme 5).

Scheme 5



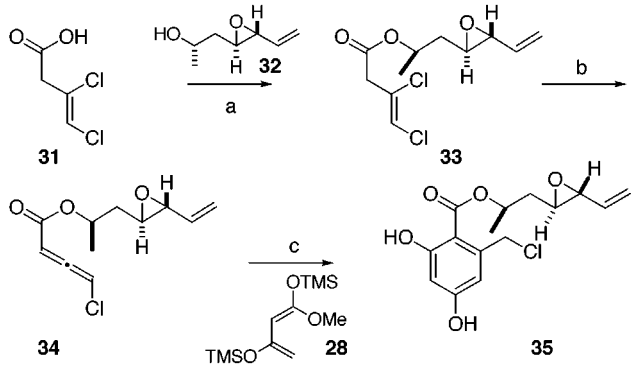
An interesting possibility for circumventing this nonachievable esterification of the relevant hindered benzoic acids (cf., **4**) presented itself. This approach anticipated a Diels−Alder reaction of 1,3 asymmetrically disubstituted allene[28] **27**, where the ester was preintroduced in the dienophile. (Equation 2). Hence, the product from the cycloaddition reaction of allene type **27** with a diene (cf., **28**) would directly be **29**, en route to **1** and **2**. It was expected that this cycloaddition should be selective for the α-double bond. Of course, we recognized that an alternative aromatic system (**30**) could arise from reaction with the *β*-double bond. However, perhaps naively, we dissected allene **27** into two potentially competitive dienophile moieties; one, an α,*β*-unsaturated ester, and the other, a chloro-olefin. The sense that acrylates are much more reactive dienophiles than are vinyl chlorides supported our optimism.



Application of this concept to the synthesis of monocillin I (**2**) and radicicol (**1**) required presentation of the vinyl epoxide fragment containing all three stereocenters at the stage of the allene prior to formation of the aromatic system. This subgoal was accomplished as shown in Scheme 6, using the C-5 epimeric alcohol (**32**, see Supporting Information for synthetic details), which was obtained via the same route alternatively employing the commercially available (*S*)-3-hydroxybutyric acid. Mitsunobu esterification of acid **31**[29] with alcohol **32** (DEAD, PPh_3, 70%) afforded allenic ester (**34**) after elimination using Hünig's base (70%).

In the critical Diels−Alder cycloaddition between **34** and diene **28**, the desired resorcinylic chloride (**35**) was obtained as the major product (50%). Surprisingly, considerable amounts (15%) of the alternative cycloaddition product **35a** (not pictured, see **30**) were observed. Thus, the goal of high convergence leading to **35** had indeed been realized. However, the modest yield and regioselectivity of the allene Diels−Alder sequence were disappointing. Efforts are underway to determine the scope of this transformation, the origin of this unusual regioselectivity outcome, and the value of the allene Diels−Alder cycloaddition concept for the construction of highly functionalized aromatic systems.

Scheme 6[a]



(a) DEAD, PPh_3, 70%; (b) *i*-Pr_2NEt, 70%; (c) 50% (4:1).

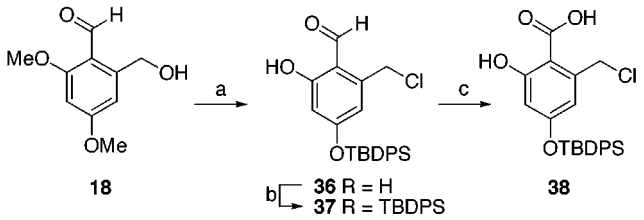
Given the importance of the radicicol program and our problems with the allene route, the possibility of direct esterification of a hindered benzoic acid was revisited (cf., Scheme 5). After much experimentation and fine tuning, it was found that esterification *was possible with the* ortho*-phenol unprotected*. The salicylic acid system **38** was constructed starting

(27) Whether or not the presence of the aromatic chloride could positively impact these efforts remains uninvestigated.

(28) Diels−Alder reactions of allenic esters have been used to establish the orsellinic motif (first in 1978 by our laboratory). Danishefsky, S. J.; Singh, R. K.; Gammill, R. B. *J. Org. Chem.* **1978**, *43*, 379. Roush, W. R.; Murphy, J. *J. Org. Chem.* **1992**, *57*, 6622. Fink, M.; Gaier, H.; Gerlach, H. *Helv. Chim. Acta* **1982**, *65*, 2563.

(29) See Supporting Information.

Scheme 7[a]

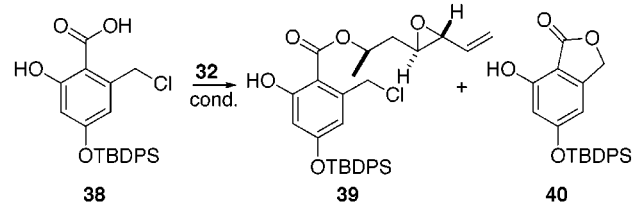


(a) BBr_3, 85%; (b) TBDPSCl, 95%; (c) $NaOCl_2$, 95%.

with **18** (Scheme 7), which was available in one step from commercially available **17** (Scheme 4). Removal of both methyl ether groups (**36**, BBr_3, 85%, 25 °C, 24 h) was accomplished without effect on the benzyl chloride. Selective protection of the *para*-phenol (TBDPSCl, imidazole, 95%) provided monophenol benzaldehyde **37**. Oxidation to benzoic acid **38** ($NaOCl_2$, 95%) occurred without undesired chlorination or cyclization, thus completing a short, high yielding route to the aromatic core of monocillin I (**2**).

We returned to the Mitsunobu reaction for esterification of salicylic acid system **38**. It was hoped that the hydrogen bonding of the free phenol with the adjacent carboxylic acid would suppress phthalide formation during the course of the esterification. It was pleasing to find that this was the case. Mitsunobu esterification did indeed occur in THF, albeit in low yield (Table 2). Reducing the polarity of the solvent by switching from THF to benzene improved the yield significantly (15% to 40%, entries 1−4),[30] but large quantities of phthalide **40** were still recovered. A survey of tertiary phosphines revealed the suprising observation that $P(fur)_3$ gave a slow, but highly efficient, esterification reaction (75%, entry 7) with no competing cyclization. That the expected inversion of the chiral center did indeed occur was confirmed by synthesis of the identical product via the allene Diels−Alder route (vide supra). The combination of a less polar solvent with a less nucleophilic phosphine served to enhance the quality of the transformation. The generality of this finding as it pertains to other difficult systems has yet to be explored. This solution to the construction of key benzoic ester **39** has a distinct advantage for analogue synthesis, as it introduces the most complex fragment, namely the vinyl epoxide, at the latest stage possible.

Table 2



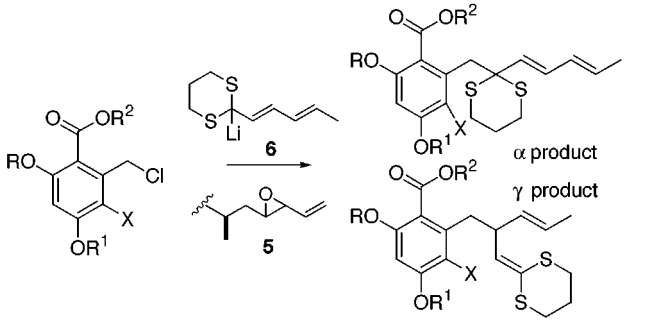
	Solvent	Phosphine	Reagent	Time	Yield **39**	Yield **40**
1	CH_3CN	PPh_3	DIAD	1 h	0 %	90 %
2	THF	PPh_3	DIAD	1 h	15 %	65 %
3	CH_2Cl_2	PPh_3	DIAD	1 h	15 %	60 %
4	benzene	PPh_3	DIAD	1 h	40 %	40 %
5	benzene	PPh_3	DEAD	1 h	40 %	40 %
6	benzene	$P(butyl)_3$	DIAD	1 h	10 %	70 %
7	benzene	$P(fur)_3$	DIAD	24 h	75 %	0 %

(30) Benzoic acids are not particularly good coupling partners in the Mitsunobu reaction, and solvent can have a dramatic effect. See: Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933.

Continuing with the synthesis, we were now prepared to introduce the acyl anion equivalent in preparation for ring-closing metathesis. Initially, addition of lithiated dithiane **6** to protected variants of benzyl chloride **39** was discouraging. While the α:γ selectivity for the addition to the dimethyl ether system **20** (entry 2, Table 3) gave a 4:1 (α:γ) selectivity for the synthesis of radicicol dimethyl ether, when the same conditions were applied to the bissilylated variant (entry 3), no selectivity (1:1) was realized.

An attempt was made to define the parameters which direct the regiochemical outcome of this reaction. Prior work describes a "hard−soft" component underlying α:γ selectivity.[19] More specifically, it was observed that hard electrophiles preferably combined with the harder α-dithiane anion. It should be noted that from the outset a benzyl chloride was chosen because of its hardness relative to the corresponding benzyl bromide or iodide. The experiments in this table clearly show a conformational (steric) influence on this specific transformation as well. Steric bulk contained in the ester (entry 1 vs entry 2) favors the desired α-alkylation product. Sterically demanding protection at the phenol has the opposite effect and favors γ-alkylation (entry 2 vs entry 3). It was observed that the presence of the aromatic chloride (required for radicicol) was especially deleterious to the α:γ ratio, giving only the γ-alkylated product (entry 4). A key experiment showed that having the *ortho*-phenol free (as a lithium salt) appeared to increase the amount of the desired α-product (entry 3 vs entry 5). Following further experimentation, free *ortho*-phenol **39** emerged as a remarkably selective substrate for the dithiane alkylation (entry 6). Addition of **6** to the lithium salt of benzyl chloride (**39**) proceeded with good (6:1) α:γ regioselectivity. Alternative acyl anion equivalents were also explored to circumvent the problem of allylic dithiane regioselectivity. Notably, the TMS ether of the corresponding cyanohydrin[31] gave only α-alkylation selectivity when applied to simple model systems. Unfortunately, because of the reduced nucleophilicity of this carbanion, no alkylation product was produced when applied to the more complex and sterically hindered system **39**.

Table 3

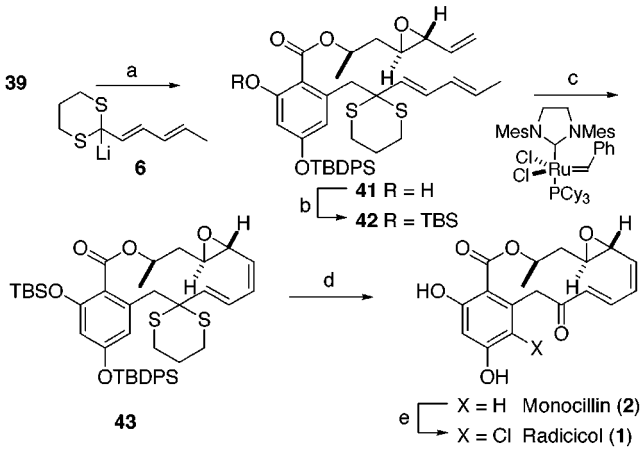


	R	R^1	R^2	X	ratio [α : γ]	combined yield
1	Me	Me	Me	H	3 : 2	90%
2	Me	Me	**5**	H	4 : 1	80%
3	TBS	TBDPS	**5**	H	1 : 1	70%
4	TBS	TBDPS	**5**	Cl	<1 : 10	50%
5	H	TBDPS	Me	H	2 : 1	70%
6	H	TBDPS	**5**	H	6 : 1	50%

With the dithiane alkylation issue resolved (if imperfectly), ring closing metathesis was attempted. Protection of the *ortho*-

(31) Allylic TMS cyanohydrins have been noted to give high α:γ ratios. Hertenstein, U.; Hünig, S.; Oller, M. *Chem. Ber.* **1980**, *113*, 3783.

Scheme 8[a]



[a] (a) *n*-BuLi, −78 °C, 50% (6:1); (b) TBSCl, 88%; (c) 42 °C, 60%; (d) (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60 °C, (iii) $NaHCO_3$, MeOH, 60%; (e) SO_2Cl_2, 58%.

phenol of **41** (**42**, TBSCl, 88%, Scheme 8) was necessary to facilitate ring closing metathesis. Despite the presence of the dithiane, and the choice of a vinyl epoxide and a conjugated diene as coupling partners, the new generation Grubbs catalyst[32] again closed to the 14-membered ring **43** in 60% yield. When this same type of transformation was attempted on free *ortho*-phenol **41**, both the yield and rate of closure decreased. In addition, the metathesis reaction of **43** proceeded more rapidly and in higher yield than that for dimethyl ether substrate **21**. Pummerer-like dispatch of the dithiane, vide supra, followed by hydrolysis of the resulting phenolic acetates, resulted in global deprotection and afforded monocillin I (**2**) in 60% yield.

(32) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

Finally, a regioselective chlorination was accomplished using SO_2Cl_2 in Et_2O (58%), thereby converting monocillin I into radicicol (**1**).[33] This chlorination represents a significant improvement over the literature method (NCS, DMF, 15%) for this same transformation.[4]

Conclusions

In summary, our totally synthetic route to radicicol comprises 6 steps from the three fragments (**6**, **32**, **38**). Its longest linear sequence is 14 steps. Most importantly, chemical synthesis can now provide ample amounts of radicicol and analogues needed to launch a comprehensive Hsp90 directed drug discovery program.

While, at the moment, the allene cycloaddition route via dienophile **34** is not competitive with the route via **38**, it too merits continuing attention, given its potential for reaching complex aromatic structures in a convergent way. Studies to this effect are well in progress.

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

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(33) Synthetic radicicol was identical to commercial radicicol (Sigma) as judged by ^{1}H NMR, ^{13}C NMR, HRMS, IR, UV, and optical rotation. Spectral data for synthetic monocillin I matched that for natural monocillin I as judged by ^{1}H NMR and IR.