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Divergent Syntheses of Resorcylic Acid Lactones: L-783277, LL-Z1640-2, and Hypothemycin

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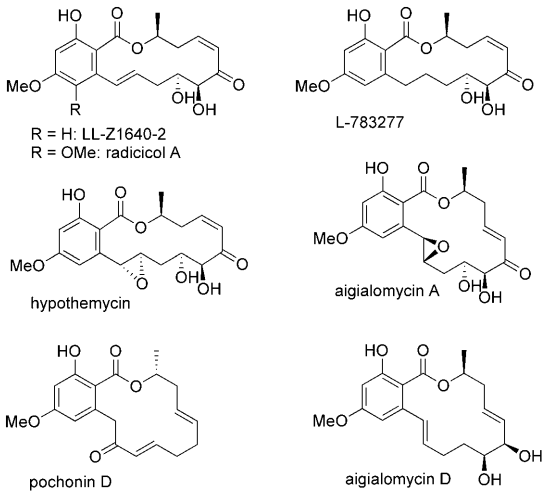
Dedicated to Professor Jean-Marie Lehn on the occasion of his 70th birthday

Abstract: The resorcylic acid lactones (RAL) are endowed with diverse biological activity ranging from transcription factor modulators (zearalenone and zearalenol) to HSP90 inhibitors (radicicol and pochonin D) and reversible (aigialomycin D) as well as irreversible kinase inhibitors (hypothemycin and other RAL containing a *cis*-enone). Our interest in broadening the diversity of this family beyond naturally occurring diversity has led us to seek a general approach that could be used to address the entire spectrum of functionalities present within this family. Herein, we present our efforts on accessing macrocycles bearing an alkane, alkene, or epoxide at the benzylic position from a common benzylic sulfide intermediate to access L-783277, LL-Z1640-2, and hypothemycin.

Keywords: kinases · lactones · resorcylic acid · solid-phase synthesis · sulfur

Introduction

While a number of resorcylic acid lactones (RAL) have been know for over 30 years, the more recent discovery that several members of this family are potent kinase and ATPase inhibitors have brought renewed attention to the chemistry of this important family of natural products (a selection of which are shown here).[1,2] Two members of this family have now been co-crystallized with a targeted protein (radicicol with HSP90[3] and LL-Z1640-2 with ERK2[4,5]) and shown to be competitive ligands for the ATP-binding pocket. We have been particularly interested in this subset of RAL as a privileged starting point for the elaboration of chemical probes based on the prevalence of ATP-binding motifs across the proteome. Furthermore, resorcylides appear to exploit a different area of chemical diversity space than heterocyclic compounds typically pursued for this purpose.[6] Thus far, over thirty natural products belonging to this family have been reported and new sources[7,8] continue to yield variants. In addition, a better understanding of the biosynthesis[9,10] enabling manipulation of the polyketide machinery will undoubtedly provide additional analogues. Nevertheless, chemical synthesis remains important in particular to access compounds that are chemically not accessible through biosynthetic pathways.[11] Our first efforts towards radicicol and pochonin C had led us to explore a sulfide linker α to a carbonyl as a convenient means of masking a sensitive conjugate alkene and providing numerous chemical opportunities to construct adjacent bonds.[12,13]



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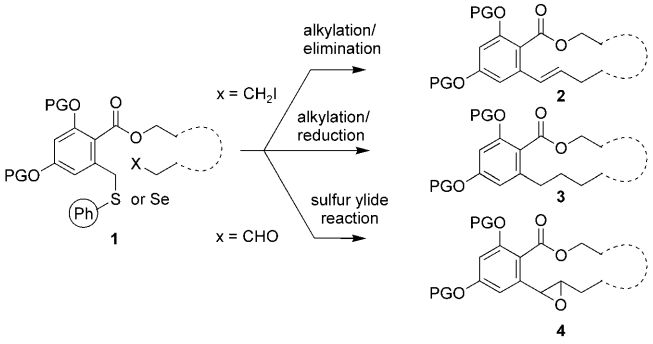
We envisioned that a sulfide at the benzylic position (Scheme 1) could indeed provide access to all the other functionalities present in the RAL family, namely, an alkane, an alkene, and an epoxide. As shown in Scheme 1,

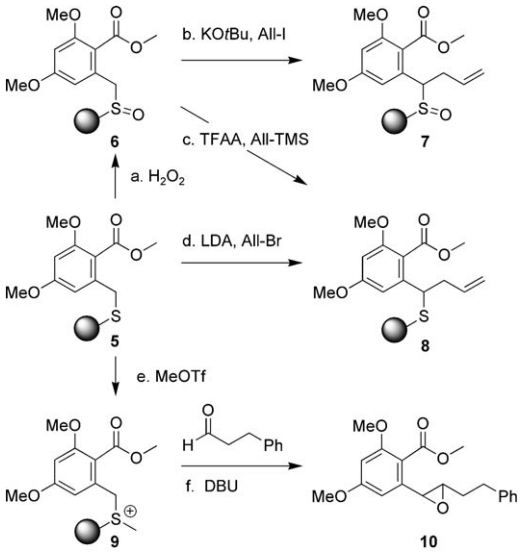


Scheme 1. Divergent synthesis of benzylic alkene **2**, alkane **3**, and epoxide **4** from common intermediate **1**.

the resorcylic ester **1** bearing a sulfide at the benzylic position could be directly alkylated following deprotonation with strong bases such as lithium diisopropylamide (LDA).[14] Conversely, oxidation of the sulfide to a sulfoxide should further acidify the benzylic position thus enabling alkylation under milder conditions. Elimination of the sulfoxide or reductive cleavage of the sulfide would afford the benzylic alkene **2** and alkane **3**, respectively. The sulfoxide moiety could also provide an entry in Pummerer reactions. On the other hand, methylation of the sulfide would yield a sulfur ylide, which are known to participate in the formation of epoxides such as **4**. Indeed, some precedents for each of these transformations existed starting with the pioneering work of Takahashi and Tsuji using an alkylation of a benzylic sulfide for the macrocyclization of zearalenone's core.[15] Gennari and co-workers had shown that stabilized sulfur ylides could be used in cyclative cleavages from solid phase[16] and the Pummerer reaction of sulfoxide had been used on solid phase.[17] Of course, these transformations could also be envisioned with the corresponding selenides and a polymer-bound version of the most popular selenium reagents[18] has been used extensively.

Results and Discussion

As shown in Scheme 2, each of these proposed transformations was evaluated starting from sulfide **5**. Thus, sulfide **5**, which was obtained from the 2-(chloromethyl)-4,6-dimethoxy benzoyl chloride[19] by esterification in methanol and loading onto a thiophenol resin, could be oxidized to the corresponding sulfoxide with H_2O_2 in hexafluoroisopropanol (HFIP)/CH_2Cl_2 to afford **6**.[20] This procedure was found to be extremely practical as it can be driven to completion with an excess of H_2O_2 (typically 4 equiv) without over oxidation to the sulfone, as was observed with other procedures (dimethyldioxirane (DMDO) or *meta*-chloroperoxybenzoic



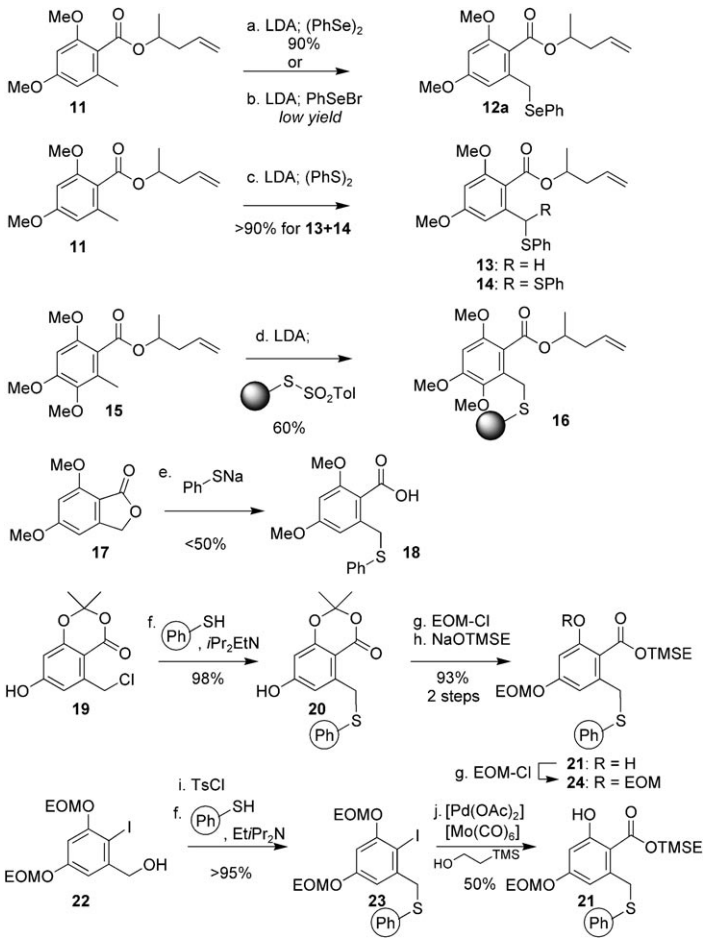
Scheme 2. a) H_2O_2 (4.0 equiv), HFIP/CH_2Cl_2 (1:1), 12 h, 23 °C, quant; b) KO*t*Bu (6.6 equiv), All-I (8.0 equiv), DMSO, 11 h, 23 °C, 60 %; c) TFAA (10 equiv), All-TMS (20 equiv), CH_2Cl_2, 12 h, −78 to 23 °C, 54 %; d) LDA (6.0 equiv), All-Br (3.0 equiv), THF/HMPA (10:1), −78 °C, 30 min, 92 %; e) Me_3OTf (1.5 equiv), CH_2Cl_2, 1.5 h, 23 °C; f) 3-phenylpropanal (3.0 equiv), DBU (10 equiv), CH_2Cl_2, 12 h, 23 °C, 24 %; All-Br = allylbromide, All-I = allyliodide, All-TMS = allyltrimethylsilane, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethylsulfoxide, HFIP = hexafluoroisopropanol, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, TFAA = trifluoro acetic anhydride, THF = tetrahydrofuran, Tf = triflate.

acid (*m*CPBA)). We had previously noted that alkylation of sulfoxide proceed in highest yield in dimethylsulfoxide (DMSO).[21] This was also the case for **6**, which could be alkylated at room temperature with allyl iodide to obtain **7** in 66 % yield (calculated based on the amount of product recovered following elimination from the resin). A similar transformation using lithium bis(trimethylsilyl)amide (LiHMDS) in THF/hexamethylphosphoramide (HMPA) was previously reported to be unsuccessful[22] attesting to the importance of the solvent in this reaction. The elimination of this sulfoxide did not proceed unless a temperature of 60–80 °C was attained and thus allowed for washing of reagents prior to elimination in a different solvent (toluene). The sulfoxide could also be allylated under Pummerer conditions (trifluoro acetic anhydride (TFAA), allyl silane) to afford **8** in moderate yield (54 % based on recovered product following oxidation/elimination). Deprotonation of sulfide **5** with an excess of LDA followed by addition of allyl bromide afforded the product **8** in excellent yield (92 % based on the amount of product recovered following elimination from the resin). Methylation of sulfide **5** with MeOTf (OTf = triflate) afforded **9** which upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and addition of an aldehyde afforded the epoxide **10** in modest yield (24 %). It should be noted that such benzylic epoxides were found to be particularly sensitive to acid and were difficult to isolate in good yield. While none of these reactions were optimized,

they provided clear indication of the versatility of benzylic sulfide.

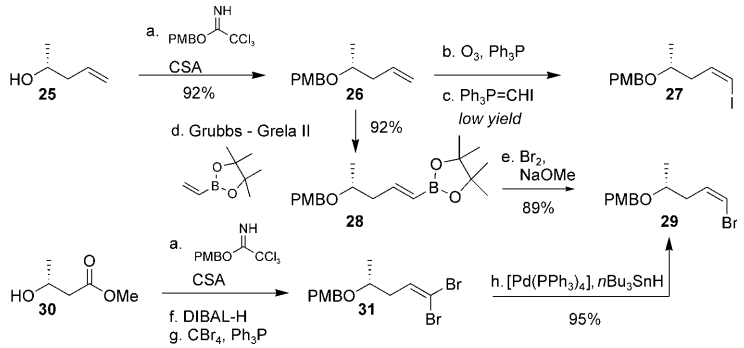
To access the required sulfide or selenoide such as **1** (Scheme 1), the sulfur or selenium can be envisioned as a nucleophile or as an electrophile. For electrophilic sulfur or selenium, the toluate position can readily be deprotonated with LDA. Treatment of **11** (Scheme 3) with LDA followed by addition of diphenyl diselenide provided the desired compound **12a** in high yield. This reaction has proven extremely reliable with a number of different substrates. However, the analogous reaction with diphenyl disulfide to obtain **13** proved to be less reliable, as it frequently was contaminated with the di-alkylated compound **14**. Reactions with different source of electrophilic selenium or sulfur that are compatible with solid-phase processes proved to be less productive. Indeed, reaction with phenyl selenium bromide provided only modest yield of **12a**, while reaction of **15** with phenyl thiotosylate[23,24] was equally modest both in solution and on solid phase (**16**). As can be expected, reaction with nucleophilic selenium or thiol were found to be high yielding (**5**, Scheme 2, was obtained quantitatively from the corresponding benzyl chloride and thiophenol resin[14] using DBU in DMF); however, access to the benzyl chloride or bromide with suitable protecting groups can be lengthy. Free-radical halogenations of the benzylic position was not reliable in our hands with the protecting-group combination sought (ethoxymethyl (EOM)-protected phenol, 2-trimethylsilylethanol (TMSE)-protected ester). We thus evaluated if the phthalide ring could be opened with thioxides as there are a number of precedents in the literature.[25] As shown in Scheme 3, reaction of **17** with sodium thioxide in solution or on a solid phase failed to provide the desired compound **18** in good yield and purity as significant level of demethylation was observed. The most convenient access to polymer-bound resorcylate with high flexibility in the choice of protecting groups on the phenol was to start from an acetonide protection of the acid and *ortho*-phenol **19**, which is obtained in three steps from the readily available 3,5-dihydroxybenzyl alcohol ($POCl_3$, DMF; $NaClO_2$; acetone, trifluoroacetic acid (TFA), TFAA).[19,26] Substitution of the benzyl chloride with a thiophenol resin afforded **20** in quantitative yield (estimated based on the mass gain of the resin and analogous reaction in solution). Protection of the *para*-phenol followed by acetonide opening in the presence of (trimethylsilyl)ethoxide afforded **21**, which was readily converted to **24**. Alternatively, we reasoned that the ester moiety could be introduced through palladium-mediated carbonylation. The corresponding aryl iodide **22** being readily available from Ipy_2BF_4 iodination[27] of 3,5-dihydroxybenzyl alcohol. Tosylation of the benzyl alcohol **22** followed by loading on the thiophenol resin afforded resin **23** in excellent yield. While the carbonylation[28,29] worked well with MeOH, it was not effective for secondary alcohols and afforded moderate yield with (trimethylsilyl)ethanol. In all reactions, partial or complete loss of the EOM group was observed leading to **21** rather than **24**. Alternatively, a Diels–Alder reaction could be envisioned to construct the desired aromatic ring from propargylic ester and dimedone diene, as has been elegantly demonstrated by Danishefsky,[30] but the high yield in the preparation of intermediate **20** and its versatility did not warrant this exploration.

A number of resorcylides of interest contain an alkene at the β-position of the lactone, which provides an evident disconnection through metathesis. Conveniently, both stereo-

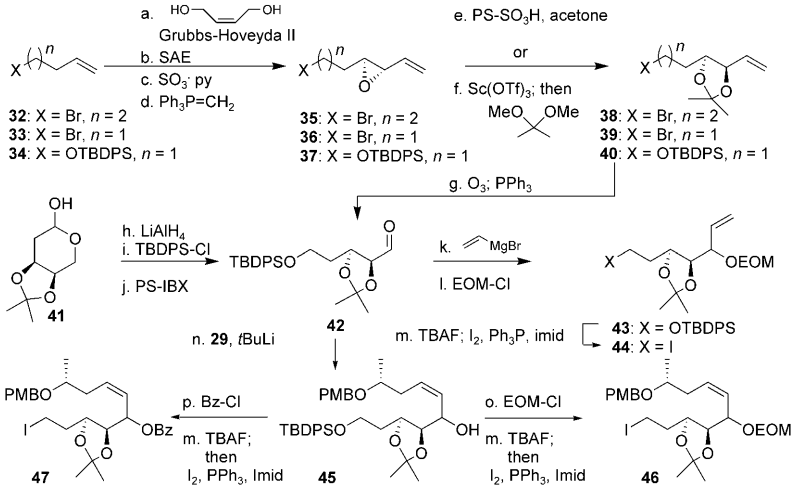


Scheme 3. a) LDA (2.0 equiv), $(PhSe)_2$ (1.0 equiv), THF, −78 °C, 45 min, 90%; b) LDA (2.0 equiv), PhSeBr (1.0 equiv), THF, −78 °C, 45 min, 48%; c) LDA (2.0 equiv), $(PhS)_2$ (1.0 equiv), THF, −78 °C, 45 min, >90% for **13**/**14** 1.8:1; d) **15** (3.0 equiv), LDA (6.0 equiv); PS-SO_2Tol (1.0 equiv), THF, −78 °C, 1 h, 60%; e) PhSH (1.0 equiv), NaH (1.0 equiv), DMF, 150 °C, 12 h, 45%; f) in solution: Ph-SH (1.0 equiv), **19** (1.0 equiv), iPr_2NEt (1.0 equiv), DMF, 60 °C, 12 h, 98%; on solid phase: PS-SH (1.0 equiv, 0.8 mmol g^{-1}), **19** (1.5 equiv), iPr_2NEt (1.0 equiv), DMF, 60 °C, 12 h, quantitative; g) in solution: EOM-Cl (2.0 equiv), iPr_2NEt (2.0 equiv), TBAI (cat), CH_2Cl_2, 23 °C, 12 h, 97%; on solid phase: EOM-Cl (2.0 equiv), DBU (2.0 equiv), TBAI (cat), DMF, 23 °C, 12 h. quantitative; h) in solution: TMSEOH (1.1 equiv), NaHMDS (1.1 equiv), THF, 0 °C, 2 h, 95%; on solid phase: TMSEOH (4.2 equiv), NaHMDS (1.1 equiv), THF, 0 to 23 °C, 12 h; i) TsCl (1.5 equiv), pyridine (2.2 equiv), CH_2Cl_2, 0 to 23 °C, 12 h, quantitative; j) In solution: [Pd(OAc)$_2$] (0.1 equiv), $[Mo(CO)_6]$ (1.0 equiv), TMSE (11.0 equiv), DMAP (2.0 equiv), iPr_2NEt (2.0 equiv), THF, 100 °C, μwave, 10 min, 50%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, EOM = ethoxymethyl, LDA = lithium diisopropylamide, PS = polystyrene, NaHMDS = sodium bis(trimethylsilyl)amide, THF = tetrahydrofuran, TBAI = tetrabutyl ammonium iodide, TMSE = 2-trimethylsilylethanol, Tol = toluene, Ts = tosyl.

chemical derivatives of 3-hydroxybutene are commercially available. However, the metathesis cannot be used in a straightforward manner to access a RAL containing a *cis*-enone (vide infra). To this end, we needed access to a *cis*-vinyl halide for transmetalation or cross-coupling reactions. As shown in Scheme 4, *p*-methoxybenzyl (PMB)-protection of 3-hydroxybutene afforded **26** in high yield, which was converted to **27** by ozonolysis followed by olefination with methyl iodide ylide. This strategy was appealing as immobilized versions of all reagents used in this sequence are available;[31,32] however, the Wittig reaction could not be performed in acceptable yield (<30%). Alternatively, cross metathesis of **26** with vinyl borolane[33] by using the Grela modification[34] of the Grubbs second-generation catalyst afforded the *trans*-vinyl borolane **28** (>20:1 *E*:*Z*), which was stereospecifically converted to the *cis*-vinyl bromide using a procedure reported by Brown[35] to obtain vinyl bromide **29** in good yield (82% for two steps). Conversely, the same vinyl bromide **29** could be obtained in four steps from the less expensive methyl 3-hydroxybutyrate (**30**), which is also available in both stereochemistries. Thus, PMB protection followed by a diisobutylaluminium hydride (DIBAL-H) reduction and Corey–Fuchs reaction afforded compound **31**, in which the more reactive *trans*-vinyl bromide was reduced with tributyltin hydride under the action of palladium tetrakis to afford **29** in excellent yield.[36]



Scheme 4. a) $PMBOCNHCCl_3$ (1.0 equiv), CSA (0.1 equiv), CH_2Cl_2, 23 °C, 12 h, 92%; b) O_3, CH_2Cl_2, −78 °C; Ph_3P (2.0 equiv), −78 to 23 °C, 2 h, 92%; c) Ph_3PCH_2I (1.25 equiv), NaHMDS (1.25 equiv), THF/HMPA (7.7:1), 23 °C, 2 h, 26%; d) vinyl borolane (1.0 equiv), Grubbs-Grella II (2.5 mol%), toluene, 80 °C, 12 h, 92%; e) Br_2 (1.0 equiv), Et_2O, −20 °C, 15 min; NaOMe, −20 °C, 30 min, 89%; f) DIBAL-H, (1.1 equiv), toluene, −78 °C, 2 h, 89%; g) CBr_4 (4.0 equiv), Ph_3P (8.0 equiv), CH_2Cl_2, 0 °C, 45 min, 90%; h) $[Pd(PPh_3)_4]$ (0.2 equiv), nBu_3SnH (5.1 equiv), benzene, 23 °C, 1.5 h, 95%. CSA = camphorsulfonic acid, DIBAL-H = diisobutylaluminium hydride, HMPA = hexamethylphosphoramide, NaHMDS = sodium bis(trimethylsilyl)amide, PMB = *p*-methoxybenzyl, THF = tetrahydrofuran.



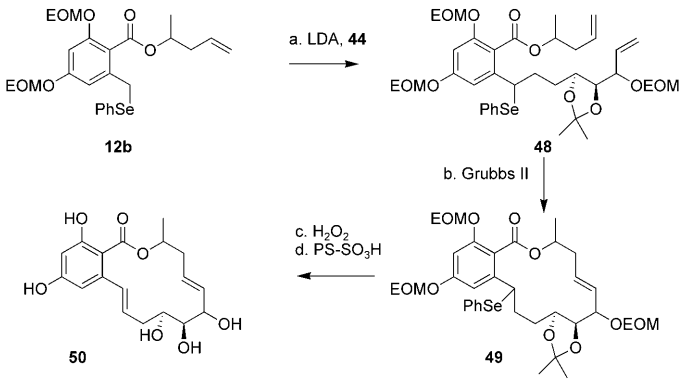
Scheme 5. a) 2-Buten-1,4-diol (2.0 equiv), Grubbs-Hoveyda II (0.01 equiv), CH_2Cl_2, 23 °C, 4 h, 85–97%; b) L-(+) diethyltartrate (0.12 equiv), $Ti(OiPr)_4$ (0.1 equiv), *t*BuOOH (1.52 equiv), CH_2Cl_2, −40 °C,12 h, 85%; c) SO_3·py (3.5 equiv), Et_3N (4.9 equiv), CH_2Cl_2/DMSO (4:1), 0 to 23 °C, 30 min; d) $Ph_3P{=}CH_2$ (1.9 equiv), NaHMDS (1.8 equiv), THF, −10 °C, 40 min, 70% (2 steps); e) PS-SO_3H (0.35 equiv), acetone, 23 °C, 12 h, 40%; f) $Sc(OTf)_3$ (0.2 equiv), THF/H_2O (10:1), 23 °C, 2.5–12 h, 50–99%; dimethoxypropane (10 equiv), TsOH·H_2O (0.05 equiv), CH_2Cl_2, 12 h, 23 °C, 70–90%; g) O_3, Ph_3P (2.0 equiv), CH_2Cl_2, −78 to 23 °C, 2 h, 92%; h) $LiAlH_4$ (1.4 equiv), THF, 0 to 23 °C, 2 h, 95%; i) TBDPSCl (1.0 equiv), imidazole (1.5 equiv), DMF, 23 °C, 2 h, 66%; j) PS-IBX (3.0 equiv), CH_2Cl_2, 23 °C, 2 h, quantitative; k) vinylMgBr (1.5 equiv), THF, 0 °C, 1 h, 92%; l) EOM-Cl (8.0 equiv), iPr_2NEt (8.0 equiv), TBAI (cat), CH_2Cl_2, 23 °C, 12 h, 99%; m) TBAF (2.0 equiv), THF, 23 °C, 6 h, quantitative; I_2 (1.5 equiv), Ph_3P (1.5 equiv), imidazole (2.5 equiv), THF, 0 °C, 30 min, 91%; n) **29** (1.0 equiv), *t*BuLi (2.0 equiv), Et_2O, −100 °C, 30 min, 88%; o) EOM-Cl (8.0 equiv), iPr_2EtN (8.0 equiv), TBAI (cat), CH_2Cl_2, 23 °C, 6 h, 98%; p) BzCl (2.5 equiv), pyridine (2.5 equiv), TBAI (cat), CH_2Cl_2, 0 to 23 °C, 6 h, 90%. Bz = benzoyl, DMF = *N*,*N*-dimethylformamide, EOM = ethoxymethyl, IBX = 2-iodobenzoicacid, Imid = imidazole, NaHMDS = sodium bis(trimethylsilyl)amide, SAE = Sharpless asymmetric epoxidation, PS = polymer supported, Py = pyridine, TBAF = tetrabutylammonium fluoride, TBAI = Tetrabutylammonium iodide, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran, Tos = Tosyl.

A number of resorcylides contain an allylic or homoallylic *anti*-diol moiety in the macrocycle. We had previously shown[37] that such acetonide-protected diols could be conveniently obtained starting from the alkene bromide **32** (Scheme 5) in six steps via allylic epoxide **35** through using a sequence involving cross metathesis with 1,4-butenediol, Sharpless epoxidation, oxidation, olefination, and stereoselective opening of the epoxide **35**.[37] This epoxide could be opened by using protic or Lewis acid conditions, such as $Sc(OTf)_3$, followed by acetonide protection to obtain **38**. Most

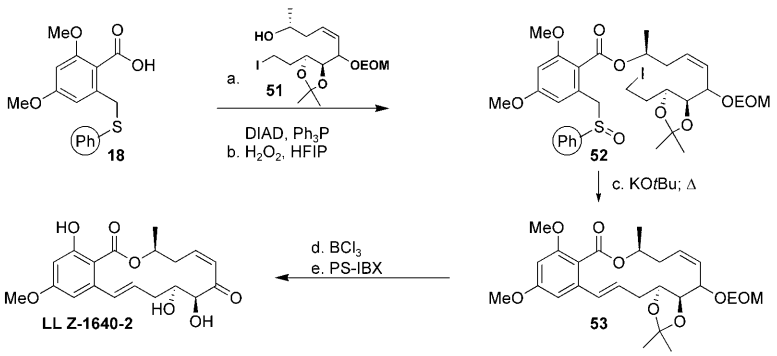
conveniently, the epoxide opening and acetonide protection can be carried out in one-pot by using sulfonic acid resin in acetone. However, using the shorter alkene chain, the chemistry proved less productive. While **36** could be obtained in good yield, its conversion to **39** was accompanied by the formation of an inseparable side product. Alternatively, the bromide could be masked in the form of a protected hydroxyl. Starting with *tert*-butyldiphenylsilyl (TBDPS)-protected butenol **34**, allylic epoxide **37** was obtained in good yield; however, its conversion to **40** was accompanied by partial desilylation under all conditions tried. Nevertheless, ozonolysis of **40** afforded aldehyde **42**, which was more conveniently obtained from the known acetonide protected deoxyribose **41** in three steps.[37] Vinyl Grignard addition onto the aldehyde **42** followed by EOM-Cl protection of the resulting alcohol afforded compound **43**, which was converted to the required iodide **44** through conventional procedure (tetrabutylammonium fluoride (TBAF) desilylation and iodination). Conversely, treatment of **42** with the vinyl lithium obtained upon treatment of **29** with *t*BuLi afforded **45** in good yield as a diastereomeric mixture. This intermediate can be converted to the fragment bearing acid labile protecting groups on the triol (**46**) or compound **47** bearing an orthogonal protecting group on the allylic alcohol (Bz).

While our experience with aigialomycin D suggested that a metathesis should provide the *trans*-alkene,[14] this speculation was assessed experimentally. Starting from readily available **12b**, deprotonation of the toluate with LDA and alkylation with **44** afforded the metathesis precursor **48** in good yield (Scheme 6). Treatment with the second-generation Grubbs catalyst[38] at 60 °C afforded a complete conversion to **49** within three hours. While the product obtained had a complex NMR spectrum due to the presence of multiple diastereoisomers, oxidation/elimination of the selenide followed by removal of the protecting groups led to compound **50**, which was assigned as the product of an *E*-selective metathesis. While a number of RAL contain a *trans*-enone system, including some aigialomycins[39] and the more recently isolated caryospomycins,[8] none of them has been reported to be potent modulators of a protein function. Of course, although introduction of conformation constrains with different protecting groups may lead to a *Z*-selective metathesis reaction (as is the case of radicicol),[12,40] the strategy was not deemed general enough for the purposes of library synthesis.

To access the *cis*-enone resorcylides with a strategy compatible with solid-phase synthesis, we envisioned starting from **18** (Scheme 7) and **51** (obtained by PMB-deprotection of **46**) through Mitsunobu reaction followed by a macrocyclization. Macrocyclization directly from the sulfide (not shown) was low yielding due to decomposition of the product over prolonged exposure to LDA; however, excellent yields were obtained using the sulfoxide **52** in DMSO. While the sulfoxide may be isolated by flash chromatography, the crude product was redissolved directly in toluene and irradiated with microwave to 120 °C to recover the desired alkene in 98 % yield (two steps). This chemistry also proved equally productive on solid phase affording macrocycle **53** in 34 % overall yield (based on the loading of thiophenol resin). Compound **53** was treated with BCl_3 to deprotect selectively the *ortho*-phenol as well as the acetonide and EOM to afford the triol, which was selectively oxidized at the allylic position to yield LL-Z1640-2. We



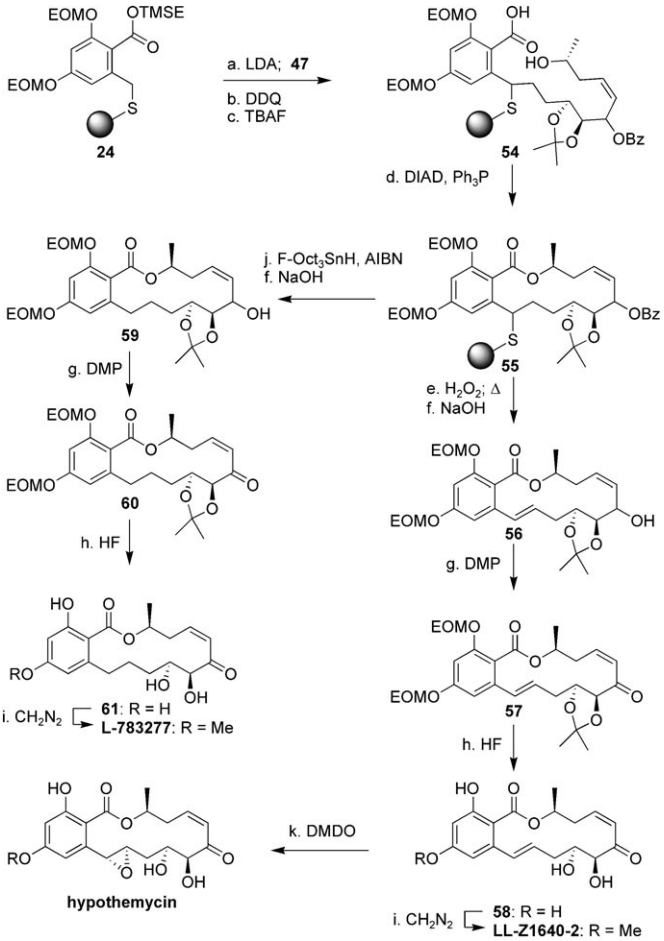
Scheme 6. a) LDA (2.0 equiv), **44** (1.0 equiv), THF/HMPA (10:1), −78 °C, 20 min, 80 %; b) Grubbs II (0.1 equiv), toluene, 60 °C, 3 h, 94 %; c) H_2O_2 (2.0 equiv), THF, 23 °C, 3 h, quantitative; d) PS-SO_3H (10 equiv), MeOH, 50 °C, 12 h, quantitative. Grubbs II = benzylidene [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, PS-SO_3H = polysmer supported sulfonic acid, THF = tetrahydrofuran.



Scheme 7. a) In solution: **51** (1.0 equiv), DIAD (2.0 equiv), Ph_3P (2.0 equiv), toluene, 0 °C, 1 h, 75 %; on solid phase: **51** (2.0 equiv), DIAD (4.0 equiv), Ph_3P (4.0 equiv), toluene, 23 °C, 12 h; b) in solution: H_2O_2 (1.0 equiv), HFIP, 23 °C, 1 h, quantitative; on solid phase: H_2O_2 (4.0 equiv), HFIP/CH_2Cl_2 (1:1), 23 °C, 12 h; c) in solution: KO*t*Bu (1.5 equiv), DMSO, 23 °C, 2 h, then toluene, 120 °C, μwave, 25 min, 98 %; on solid phase: KO*t*Bu (10 equiv), DMSO, 23 °C, 12 h, then toluene, 120 °C, μwave, 25 min, 34 % overall yield based on the loading of thiophenol resin; d) BCl_3 (6.0 equiv), CH_2Cl_2, 0 °C, 15 min, 82 %; e) PS-IBX (3.0 equiv), CH_2Cl_2, 23 °C, 1 h, 86 %; DIAD = diisopropyl azodicarboxylate, DMSO = dimethylsulfoxide, HFIP = hexafluoroisopropanol, IBX = 2-iodobenzoicacid, PS = polystyrene.

had previously reported in the context of radicicol A synthesis[37] that this allylic oxidation could be conveniently carried out with immobilized 2-iodobenzoicacid (IBX).[41] Indeed, this transformation had precedent in the literature with Dess–Martin periodinane (DMP).[42] However, for compounds that did not possess a substituent on the aryl ring *ortho* to the alkene (such as radicicol A), the oxidation of the two different diastereoisomers of the allylic alcohol afforded different products. While the less polar isomer led cleanly to the desired compound (LL-Z1640-2) in 86% yield, the other isomer afforded another mono-oxidation product with an NMR spectrum consistent with the oxidation of the hydroxyl group γ to the alkene. Several other analogues lacking such aryl substituents were also found to afford different oxidation products for the different diastereoisomers of the allylic alcohol. Similar observations were noted by Altmann for the synthesis of L-783277, which is fully saturated at the benzylic position.[43] We then turned our attention to a selective protection of this allylic hydroxyl using a strategy that could lead to both LL-Z1640-2 and L-783277.

As shown in Scheme 8, starting from resin **24**, the toluate position was alkylated with iodide **47** to obtain polymer-bound intermediate **54** following removal of the PMB (2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)) and the TMSE (TBAF). Macrolactonization under Mitsunobu conditions afforded the macrocycle **55**, which was released from the resin under oxidative condition to afford, after benzoate deprotection, macrocycle **56**. Conversely, polymer-bound macrocycle **55** could be released under reductive conditions (R_3SnH, azobisisobutyronitrile (AIBN)) to get macrocycle **59** after benzoate hydrolysis. For the reductive cleavage, the use of a fluorous-tagged tin hydride greatly facilitate product isolation.[44,45] While the benzoate hydrolysis proceeded smoothly in solution phase by using sodium hydroxide without any lactone opening, attempts to perform the same reaction on solid phase failed with a variety of nucleophiles (LiOH, NaOH, NaOMe, NaOBu, NaSMe, hydrazine). A number of alternative protecting groups for the allylic hydroxyl were investigated, such as a 1) PMB, which would require a selective 14-membered versus ten-membered lactonization, and 2) cinnamoyl, which should allow hydrolysis under milder conditions, but none of these resulted in pure final products. Both diastereoisomers of **56** and **59** could now be oxidized to the desired *cis*-enone under slightly more forceful conditions by using DMP in CH_2Cl_2 under reflux. There remained to find appropriate conditions to deprotect the EOM and the acetonide without isomerization of the *cis*-enone. While Lett reported the use of TsOH with moderate success,[46] the outcome of this reaction was too finicky to be used in the context of a library. Other acids such as TFA or HFIP were not suitable either; however, aqueous HF in acetonitrile[47] was found to give very clean deprotection without any isomerization and had the virtue that the crude mixture could be directly lyophilized at the end of the reaction. The *para*-EOM group was found to be the most resistant to acidic cleavage and it was found best



Scheme 8. a) **47** (3.0 equiv), LDA (6.0 equiv), THF/HMPA (10:1), −78 °C, 20 min; b) DDQ (2.4 equiv), CH_2Cl_2/H_2O (2:1), 23 °C, 4 h; c) TBAF (10 equiv), THF, 23 °C, 6 h; d) DIAD (3.0 equiv), Ph_3P (3.0 equiv), toluene, 23 °C, 12 h; e) H_2O_2 (4.0 equiv), CH_2Cl_2/HFIP (1:1), 23 °C, 12 h; toluene, 80 °C, 12 h, 62% over 6 steps; f) 1% NaOH/MeOH, 23 °C, 12 h, 76–80%; g) DMP (3.0 equiv), CH_2Cl_2, 65 °C, 6 h, 85–87%; h) 40% HF in CH_3CN (1:10), 23 °C, 7 h, 50%; i) CH_2N_2 (5.0–10 equiv), Et_2O, 23 °C, 6 h, 63–74%; j) F-OctSnH (5.0 equiv), AIBN (cat), toluene, 150 °C, μwave, 10 min, 52% over 5 steps; k) DMDO (5.0 equiv), CH_3CN, 0 °C, 1 h, 25%; AIBN = azobisisobutyronitrile, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DIAD = diisopropyl azodicarboxylate, DMDO = dimethyldioxirane, DMP = Dess Martin periodinane, F-Oct_3SnH = tris(1H,1H,2H,2H-perfluorooctyl)tin hydride, HFIP = hexafluoroisopropanol, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran.

not to drive the reaction to completion, but rather stop it after 7 h which typically afforded 50% of the desired product **58** and **61** along with 50% of the corresponding mono-EOM analogue (not shown). The natural products LL-Z1640-2 and L-783277 could be obtained by straightforward diazomethane treatment of compounds **58** and **61**, respectively[48] (>90% conversion based on LC/MS, 63-74% isolated yield after HPLC purification). It should be noted that the final product isolated by HPLC were typically contaminated with small amounts (>5%) of a side product that is tentatively ascribed to the *trans*-enone isomer. It had been reported by Lett that LL-Z1640-2 could be regio- and ste-

reoselectively converted to hypothemycin by using *m*CPBA.[46] Attracted by the fact that DMDO should provide the same selectivity while not requiring a work-up, we attempted the selective epoxidation of LL-Z1640-2 with DMDO, which afforded hypothemycin in 25% isolated yield at 50% conversion.[48] While the reaction appeared very clean when the crude reaction mixture was monitored by LC-MS and NMR spectroscopy, attempts to drive it to completion resulted in decomposition. Furthermore, it was found that the epoxide was quite sensitive to acid and partial degradation of the final product was observed upon isolation.

In conclusion, we have extended the scope of the sulfide linker to access all the functionalities present in the natural members of the resorcylic acid lactones. The use of the benzylic sulfide was efficient in providing access to both LL-Z1640-2 and L-783277 by alkylation followed by oxidative elimination or reductive cleavage respectively. LL-Z1640-2 was converted to hypothemycin with excellent regio and stereoselectivity by using DMDO. The benzylic sulfoxide afforded extremely efficient macrocyclization; however, this strategy was only compatible with the synthesis of macrocycles bearing an alkene at the benzylic position and thus precluded access to L-783277.

Experimental Section

The physical characterization and experimental procedures for all new compounds are given in the Supporting Information.

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