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Access to Resorcylic Acid Lactones *via* Phosphonate Based Intramolecular Olefination

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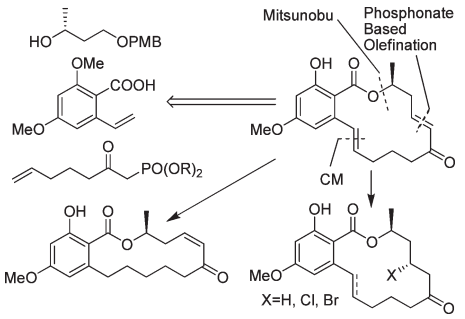
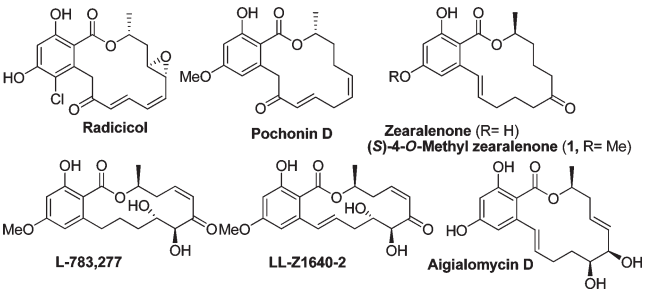


An approach to resorcylic acid lactones is described, exploiting an intramolecular olefination reaction for the generation of the 14-membered macrolactone. The synthetic route gave zearalenone precursors, and the preparations of other RAL analogues, *trans*- and *cis*-resorcylides are included, the latter being prepared by photoisomerization of the *trans*-isomer. β-Haloketone derivatives were also prepared in a highly stereoselective manner by conjugate addition of chloride or bromide to the *E*-enone using boron trichloride and boron tribromide, respectively.

The resorcylic acid lactones (RALs, Chart 1) are endowed with a breadth of biological activity. Compounds within this class span from being transcription factor modulators (zearalenone[1] and zearalenol[2]) to HSP90 inhibitors (radicicol[3] and pochonin D[4]) and reversible (aigialomycin D[5]) as well as irreversible kinase inhibitors (hypothemycin,[6] LL-Z1640-2,[7] and L-783,277[8]).[9] It can thus be argued that the RAL framework is privileged[10] and that analogues of these natural products should be of interest for screening in bioassays. Besides their important biological properties, the RALs are of interest from the synthetic point of view.[11]

CHART 1. Selected RALs



Zearalenone, isolated in 1962 from the fungus *Gibberella zeae*,[12] was the first member of the RAL family to attract the attention of both chemists and biologists due to its potent agonism of the estrogen receptor. Zearalenone was shown to adopt a conformation that mimics the steroid and competes with estradiol binding to the estrogen receptor. As a result of its interesting biological properties, several groups have developed syntheses of this natural product,[13] and it has served as a testing ground for macrocyclization methodologies such as the Corey−Nicolaou macrolactonization,[14] Masamune's thioester-lactonization,[15] ring-closing metathesis (RCM),[16] and more recently late stage aromatization−macrocyclization.[17]

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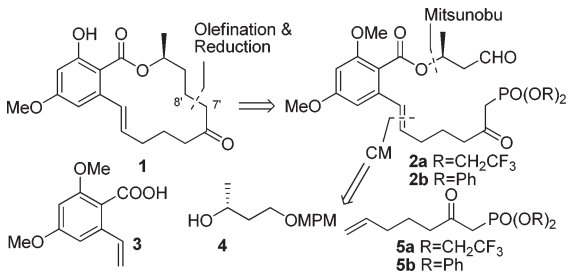
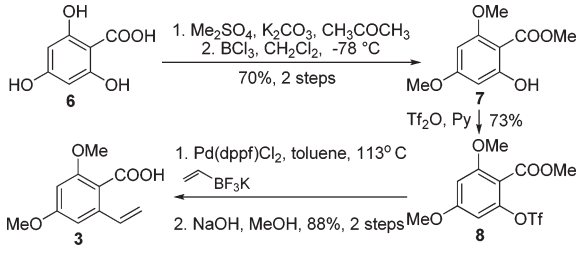
SCHEME 1. Retrosynthetic Analysis of 1



SCHEME 2. Synthesis of 3

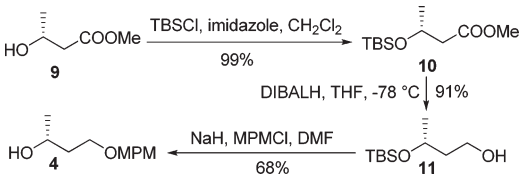


Herein we report an approach to the RAL core scaffold, which exploits cross metathesis followed by modified Horner−Wadsworth−Emmons (HWE) olefination. This was motivated by a desire to generate new analogues of the RAL family[18] for biological evaluation. The syntheses of 4-*O*-methyl zearalenone, *trans*- and *cis*-enone, and *β*-haloketone containing analogues of LL-Z1640-2 and L-783,277 are described herein.

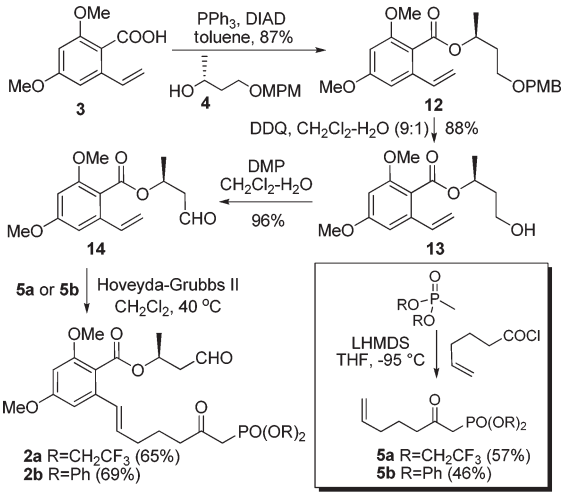
(*S*)-4-*O*-Methyl zearalenone **1** was approached initially. As shown in Scheme 1, the initial disconnection of the C7′−C8′ bond in the upper side chain led to the proposal that key precursor **2** would give **1** after intramolecular olefination followed by chemoselective reduction of the resulting enone and demethylation. The fully functionalized phosphonate **2** was envisaged to be obtained from fragments **3**−**5** *via* Mitsunobu esterification[19] and olefin cross metathesis (CM).[20] While the order of coupling of **3**−**5** is conceptually possible in all permutations, we were interested in investigating the Ando and Still−Gennari variations of the HWE reaction for macrocylization and whether either or both would lead to the *cis*-enone.

The synthesis of the aromatic fragment **3** is shown in Scheme 2. Permethylation of 2,4,6-trihydroxybenzoic acid **6** using dimethyl sulfate was followed by a boron trichloride induced demethylation of the *o*-methyl ether[21] to give **7**; subsequent reaction of **7** with triflic anhydride provided the aryl triflate **8** (51% yield over three steps). Hence, Suzuki−Miyaura-type coupling of **8** with potassium vinyl trifluoroborate catalyzed by $Pd(dppf)Cl_2$ utilizing Molander's procedure[22] and subsequent ester hydrolysis provided the styrene **3** in good yield. Intermediate **4** was conveniently obtained from methyl (*R*)-3-hydroxybutyrate **9** in three steps

SCHEME 3. Synthesis of 4



SCHEME 4. Synthesis of 2a and 2b



(Scheme 3). Conversion of **9** to the TBS ether **10**[23] followed by reduction of the ester afforded primary alcohol **11**.[24] Treatment of **11** with NaH and 4-methoxybenzyl chloride (MPMCl) in anhydrous DMF led in one pot to the protection of the primary alcohol and simultaneous removal of the TBS group to give alcohol **4**[25] in 68% yield.

Next the preparation of **14** was investigated (Scheme 4). The Mitsunobu reaction of benzoic acid **3** with the ether **4**, promoted by triphenylphosphine in the presence of DIAD, gave **12**; subsequent oxidative removal of the 4-methoxybenzyl group from **12** using DDQ provided alcohol **13** (76% over two steps). Oxidation to aldehyde **14** was then attempted. While a number of widely used oxidizing conditions (Swern conditions, pyridinium chlorochromate) were unsuccessful, providing almost exclusively unreacted **13** together with decomposition products, or were low yielding (DCC−H_3PO_4−DMSO, 22%), the treatment of **13** with Dess−Martin periodinane (DMP) in wet CH_2Cl_2[26] smoothly afforded **14** in excellent yield (96%). In order to access the envisaged key intermediates **2a** and **2b**, the CM reactions of the aldehyde **14** with *β*-ketophosphonates **5a** and **5b** were then considered (Scheme 4). Phosphonates **5a** and **5b**, which could respectively be considered Still−Gennari[27] and Ando[28] reagents, were

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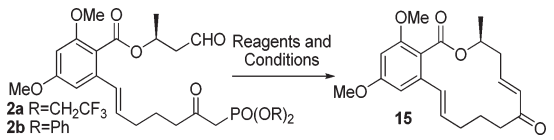
TABLE 1. Intramolecular Olefination



entry	2a/2b	conditions	T (°C)	yield **15** (%)
1	**2a**	KHMDS, 18-crown-6, THF	−83	53
2	**2a**	NaH, THF	0	77
3	**2b**	NaH, THF	0	62
4	**2b**	DBU, NaI, THF	−78	50
5	**2b**	K_2CO_3, 18-crown-6, toluene	70	54

selected with a view to investigating whether the intramolecular olefination reaction would lead to the *cis*-enone product, as is generally the case for intermolecular reactions with these types of reagents. This was necessary to clarify given that the *cis*-enone is found in a number of important RALs such as LL-Z1640-2 and L-783,277. The investigation of the reaction of bis(2,2,2-trifluoroethyl) methylphosphonate and diphenyl methylphosphonate with LDA in THF at −78 °C provided **5a** and **5b** in poor yield (16% and 14%, respectively). An improvement was obtained by carrying out the reaction at −95 °C and by replacing LDA with LHMDS as base; these revised conditions led to the generation of **5a** (57%) and **5b** (46%) in more respectable yields. Cross metathesis of aldehyde **14** with **5a** and **5b** using the Hoveyda−Grubbs' generation II catalyst provided **2a** (65%) and **2b** (69%), with the only *E*-alkene products being obtained in each case.

Intermediate **2a** was found to be unstable to chromatography; efforts to purify **2a** using silica gel, which had been pretreated with 1% triethylamine or using florisil led to the spontaneous conversion to the *E*-enone **15** in 20% and 35% yield, respectively, over two steps. Chromatography using nontreated silica gel afforded a sample of **2a** contaminated with small amount (5−10%) of enone *E*-**15**. The intramolecular olefination was subsequently investigated (Table 1) under a range of conditions. When reacting **2a** with NaH in THF at 0 °C (entry 2), the *E*-isomer **15** was obtained in 77% isolated yield. The phosphonate **2b** gave *E*-**15** in lower yield (62%, entry 3) under the same conditions. The conversion of **15** to **1** was next accomplished (Scheme 5). Thus, chemoselective hydride-mediated conjugate reduction of **15** using the copper(I) hydride cluster $[(Ph_3P)CuH]_6$[29] followed by cleavage of the *o*-methyl ether from **16** readily gave (*S*)-4-*O*-methyl zearalenone (**1**, 72% over two steps). The full de-*O*-methylation of **16** to give zearalenone was described previously.[30]

Although attempts to use the Still−Gennari or Ando phosphonates to promote *Z*-selective intramolecular olefination were unsuccessful, the strategy was efficient for generating *trans*-resorcylides (i.e., **15**), allowing the direct access to the aigialomycin A[31] framework, for example. A challenge was to extend the route to the preparation of *cis*-enone containing resorcylides, which have recently emerged as lead compounds for kinase inhibition.[32] The photoinduced isomerization of the *trans*-enone to the thermodynamically less stable *cis*-isomer was thus investigated. When exposed to light, **15** gave an intractable mixture of products. Hypothesizing that the introduction of intramolecular H-bonding between the macrolactone carbonyl and the phenol hydroxyl group might facilitate the photoisomerization to the *cis*-isomer by acting as stereocontrolling element,[33] we attempted the photoisomerization with the phenol **17**, which was prepared from **15** using the boron trichloride induced cleavage of the *o*-methyl ether. Upon exposure to light (350 nm) **17** was readily isomerized, affording a 3:2 mixture of both the *cis*-enones **18** and **19** (50% conversion, Scheme 5). Efforts to achieve the selective photoisomerization of the enone double bond by using different UV wavelengths (300 nm, 250 nm) were unsuccessful and gave complex mixtures of products and/or degradation of the starting material. Although the two isomers **18** and **19** were not, in our hands, separable by chromatography, the success of the *trans*−*cis* photoconversion represented an important finding as together with the HWE type olefination reaction it potentially allows the preparation of members of both the *trans*- and *cis*-RAL subfamilies. It is also noteworthy that the photoisomerization of the styryl alkene could be of interest, as the *cis*-geometry at this position occurs in aigialomycin E.[34] Interestingly, the *O*-demethylation of **15** afforded, besides the phenol **17**, a small amount (5%) of the 1,4-addition adduct[33,4] **20** as a single diastereoisomer, the configuration at C8′ being established by X-ray crystallography. The β-haloketone **20** has been speculated to be a zearalenone metabolite.[35] Evaluation of compounds as kinase inhibitors where the *cis*-enone functionality is replaced with a β-haloketone would be of interest. Like the *cis*-enone, the β-haloketone could potentially react with a cysteine thiol group that is conserved in some kinases.[6b] Thus, in order to generate samples for biological evaluation, the halides **20** and **21** were obtained after treatment of **17** with boron trichloride and boron tribromide, respectively. These reactions were both highly stereoselective, leading to a single diastereoisomer. Steric factors in the transition state are the major reason for the observed selectivity; the conformation of the macrolide leaves one face of the enone open to, presumably, Lewis acid facilitated nucleophilic attack of the halide. Attempts to carry out a one-pot *O*-demethylation and 1,4-halide addition from **15** to give **20** and **21** were less productive than the two-step process.

Finally, the reduced compounds **22**−**25** (Scheme 6) were prepared, where the styryl double bond was converted to an alkane. While this modification may seem modest, the structural change can alter the macrocycle conformation and consequently the selectivity of RALs.[32a] Thus, catalytic

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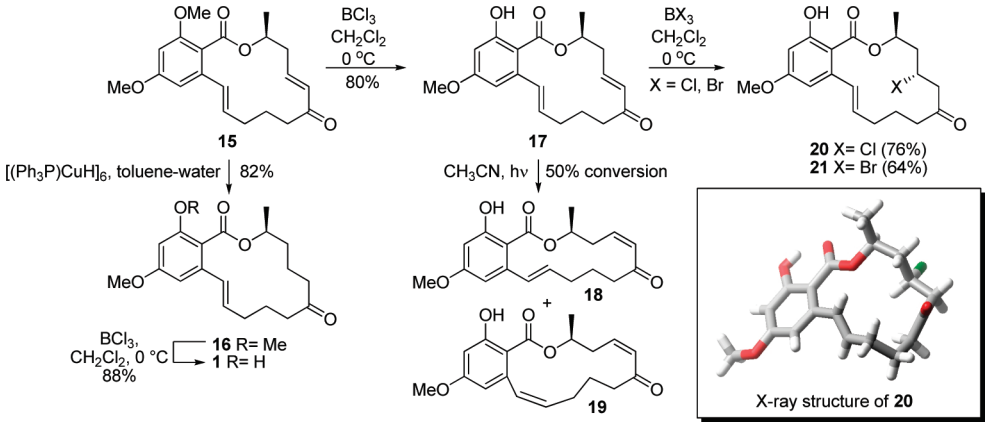
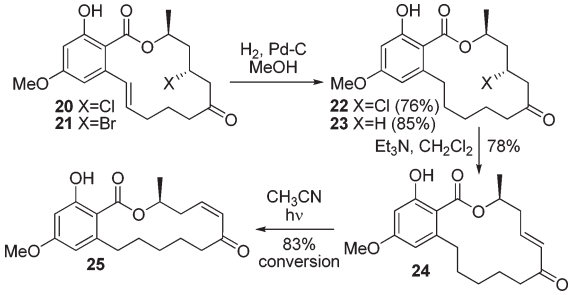
SCHEME 5. Synthesis of Various RALs from 15



SCHEME 6. Synthesis of 22−25



hydrogenation of **20** led to **22** in good yield (76%). The bromide **21** was over-reduced under the same conditions and gave **23** (85%) as the only product. Under basic conditions (Et_3N, CH_2Cl_2) the chloride **22** readily transformed to *trans*-enone **24**, which was then converted to the *cis*-enone **25** photochemically (97% yield, 83% conversion). The efficiency of the latter reaction demonstrated the potential of the photoisomerization in preparing *cis*-RALs after masking or removing the alkene adjacent to the aromatic ring.

The synthesis of a series of simple RAL analogues *via* an efficient intramolecular phosphonate olefination for the generation of the 14-membered lactone ring has been described. Although the olefination gave the *E*-enone product, routes to a *Z*-enone were established by photoisomerization of the initially formed *E*-isomer. Also 1,4-halide addition to the *E*-enone was achieved in a highly stereoselective manner to give *β*-haloketone derivatives. The biological properties of these RALs as kinase inhibitors are currently under investigation and will be reported shortly.

Experimental Section

(7*S*,9*E*,15*E*)-2,4-Dimethoxy-7-methyl-7,8,13,14-tetrahydro-12*H*-6-oxa-benzocyclotetradecene-5,11-dionelenone 15. Sodium hydride (60% oil dispersion, 6.5 mg, 0.16 mmol) was added to a stirred solution of **2a** (50 mg, 0.081 mmol) in dry THF (5 mL) that had been precooled to 0 °C. The resulting mixture was stirred at 0 °C for 2 h, and then H_2O and EtOAc were added. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic portions were dried (Na_2SO_4) and filtered, and the solvent was removed under diminished pressure. Chromatography of the residue (silica gel, CH_2Cl_2−acetone, 100:0 to 95:5) gave **15** (21.5 mg, 77%) as a pale yellow oil. Under similar conditions reported above, treatment of **2b** (20.0 mg, 0.034 mmol) with an excess of NaH (0.047 mmol) afforded, after common workup and purification procedures, **15** (5.6 mg, 62%) as a pale yellow oil; $[\alpha]_D^{20}$ +17.0 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 1.44 (d, *J* 6.5 Hz, 3H, CH_3), 1.68−1.79 (m, 1H), 2.09−2.16 (m, 2H), 2.22 (ddd, *J* 3.5 Hz, *J* 5.5 Hz, *J* 15.0 Hz, 1H), 2.26−2.35 (m, 1H), 2.40−2.55 (m, 2H), 2.77−2.86 (m, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 5.18−5.27 (m, 1H), 6.04−6.13 (m, 1H), 6.09 (d, *J* 16.0 Hz, 1H), 6.28 (d, *J* 15.0 Hz, 1H), 6.36 (d, *J* 2.0 Hz, 1H), 6.62 (d, *J* 2.0 Hz, 1H), 6.85 (dt, *J* 7.5 Hz, 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 20.7 (CH_3), 23.4 (CH_2), 31.5 (CH_2), 35.0 (CH_2), 38.8 (CH_2), 55.4 (CH_3), 56.0 (CH_3), 70.7 (CH), 97.8 (CH), 101.1 (CH), 116.3 (C), 128.6 (CH), 132.6 (CH), 135.0 (CH), 136.6 (C), 142.8 (CH), 157.6 (C), 161.3 (C), 167.5 (C), 192.3 (C). HRMS (ESI): found 367.1433 $[M + Na]^+$, $C_{20}H_{24}O_5Na$ requires 367.1521.

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Supporting Information Available: General and experimental procedures, ^{1}H and ^{13}C NMR spectra, and X-ray structure of **20** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.