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A short diastereoselective synthesis of the (±)-rishirilide B core structure ☆

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Abstract—A series of diastereoselective reactions are reported to form the core of (±)-rishirilide B. The key reactions include: (1) a regioselective tautomerization and etherification of an asymmetric cyclohexa-1,3-dione, (2) an alkoxide directed 1,2-addition of an organometallic reagent and carbamate cleavage and protonation sets two stereocenters, and (3) a novel RuO_4 cleavage of an α-hydroxy vinyl ether provides the α-hydroxy ester.

(+)-Rishirilide B (+)-(**1**) was isolated in 1984 from the Actinomycetes *Streptomyces*, a common soil bacterium, which has yielded most of the antibiotics used in clinical medicine today.[1] This particular natural product was observed to inhibit *S*-glutathione transferase and α2 macroglobulin.[2] From a synthetic standpoint the molecule presents several unique challenges: (1) construction of the naphthol ring system in its regiochemical relationship with the adjoining cyclohexanone ring, (2) creation of three contiguous stereocenters, which include two tertiary alcohols disposed in an *anti* arrangement in the cyclohexanone ring, and (3) development of an enantioselective process leading to the (+)-natural product. Despite considerable efforts by Hauser and Xu, and Allen and Danishefsky,[3] the natural product (+)-**1** has not been synthesized. In a previous letter we described our construction of the naphthol ring system using cyclohexadienone chemistry.[4] A comprehensive review of this and related building blocks has recently appeared.[5] Herein we report a solution to the second challenge, installation of the three contiguous stereocenters and requisite functionality (Fig. 1).

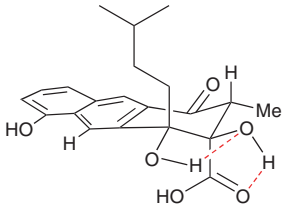

Figure 1. (+)-Rishirilide B (**1**).

An examination of (+)-**1** and its conformers by molecular modeling reveals some unique stereochemical relationships. In its most stable form, the methyl residue adjacent to the ketone resides in an equatorial position. This epimer is most likely thermodynamically preferred because of the axial isopentyl residue. An axial isopentyl residue may seem unfavorable; however, it experiences only one A-1,3 interaction, which is energetically offset by two *anti* tertiary alcohols in equatorial positions further stabilized by hydrogen bonding. If the isopentyl residue were to reside in the equatorial position, then allylic strain would occur with an aromatic C–H moiety. We theorized that these interdependent stereochemical relationships stabilize the conformation and prevent β-elimination of the hydroxyl residue that is α to the carboxylic acid. Furthermore, we speculated that the stereocenter containing the isopentyl residue could direct the creation of those remaining .

To test this notion, we hydrolyzed the cyclohexadienone vinylogous esters **2a** and **2b**, which had been previously prepared in nine and eight pots, respectively.[4] The bromine derivatives **2a** appear upon exposure (0.03 M 4:1/THF–H_2O) to 4 equiv of a 0.12 M LiOH solution for

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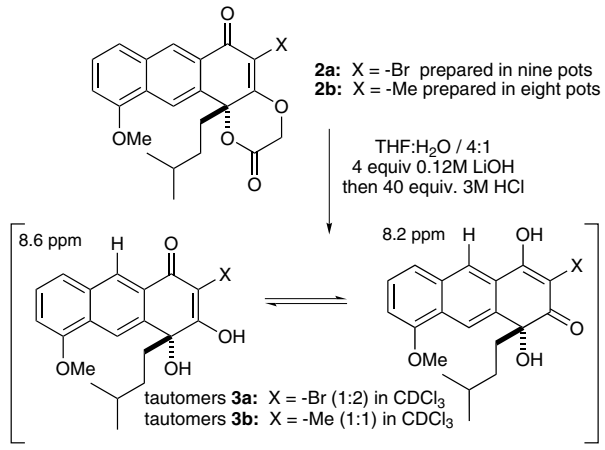


Scheme 1. Hydrolysis leads to tautomers.

12 h, followed by treatment of the resulting lithium carboxylate with 40 equiv of 3 M HCl for 30 min. For the methyl analogs **2b** warming to 60 °C is required for saponification. Inspection of the crude product by ^{1}H NMR reveals the desired tautomeric mixtures **3a** and **3b** form (Scheme 1).[6]

A particular tautomer can have a profound influence on the biological activity of a molecule. For example, the potency of tetracycline is attributed to a single tautomeric form.[7] Deciphering the structure of tautomeric mixtures can usually be accomplished by ^{17}O NMR.[8] However, rationalizing the equilibrium and reactivity of tautomers is often challenging. For example, in epoxysorbicillinol one tautomer predominates.[9] Presumably, the type-2 structure is favored by hydrogen bonding (Fig. 2, example i). However, most cases are not so pronounced. For example, Pattenden finds that 1,3-cyclopentadiones are distributed in an equally populated mixture (Fig. 2, examples ii and iii).[10] Acylation of the 2-methyl-1,3-cyclopentadione (example ii) with Ac_2O/NaOAc affords the corresponding acyl type-2 derivative as the sole product. The analogous methyl type-2 derivative is prepared as a single product by treatment with $(MeO)_2SO_2$ and K_2CO_3. Interestingly, exposure of the *des*-2-methyl derivative (example iii) to similar conditions affords 1:1 mixtures of the respective acylated and methylated tautomers. Akhrem finds addition of acyl chloride and pyridine to the 1:1 tautomeric mixture of 4-hydroxy-1,3-cyclohexadiones affords a 1:1 mixture of the corresponding diacyl derivatives.[11] However, treatment of the tautomeric 4-hydroxy-1,3-cyclohexadiones with 1 M HCl and methanol affords a type-2 vinylogous ester as the sole product.[12] On the other hand, Carnduff and Leppard reports that treatment of the dihydroxy-isopropyl-naphthalenone (example v) with diazomethane affords a 1:1 mixture of the corresponding vinylogous esters.[13] In addition, Porta and co-workers disclosed that methylation of the 4,4-dimethylcyclohexa-1,3-dione (example vi) with catalytic $TiCl_4$ and MeOH followed by the addition of TEA leads to a 4:1 mixture favoring the corresponding type-1 vinylogous ester product.[14] Clearly, the ratio of products formed by etherification or acylation of an oxygen atom

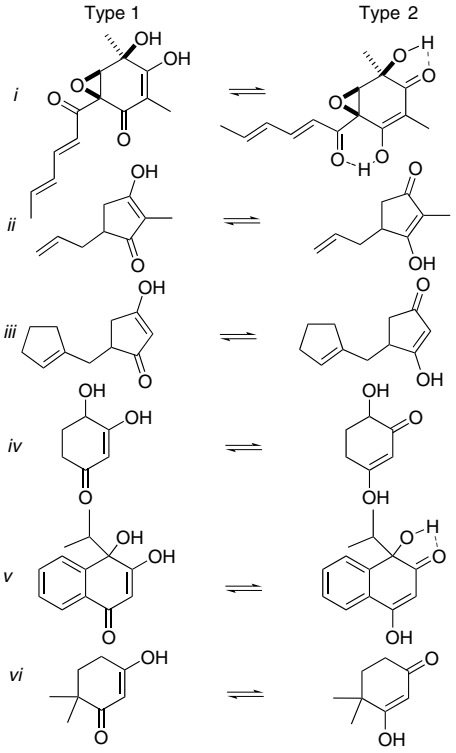


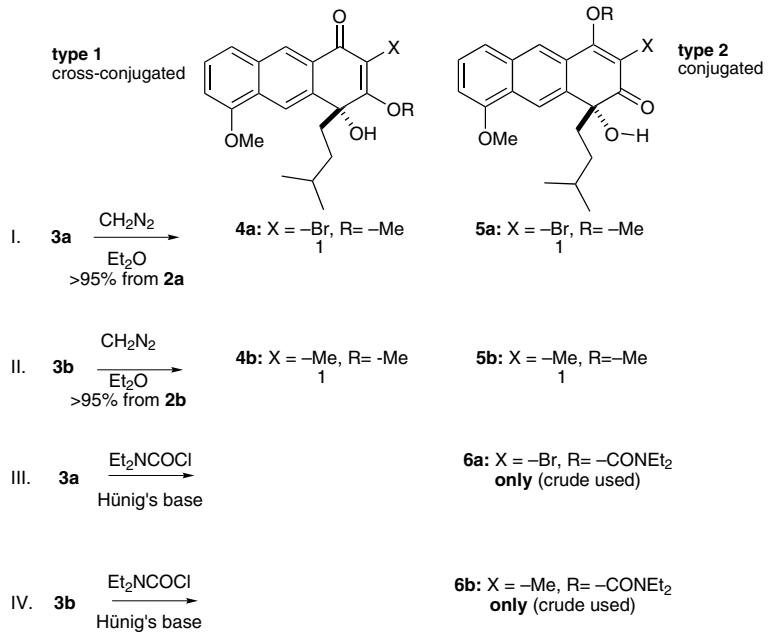
Figure 2. Substituents effects on the ratio of tautomer products.

in a 1,3-dienone can be hard to predict, if the dione is asymmetric.

We were therefore very concerned that the tautomeric mixtures **3a** and **3b**, which are derived from lactones **2a** and **2b**, respectively, might lead to mixtures of the corresponding vinylogous esters.[15] However, we anticipated that type-2 products would predominate due to steric interactions, hydrogen bonding and conjugation.

Much to our chagrin, treatment of the crude tautomeric mixture **3a** with excess CH_2N_2 in Et_2O affords a 1:1 mixture of the separable vinylogous esters **4a** and **5a** (Scheme 2, entry I) with a combined yield of greater than 95% from **2a**. Similarly, treatment of the crude tautomeric mixture **3b** with excess CH_2N_2 in Et_2O affords a separable 1:1 mixture of adducts **4b**:**5b** in >95% yield from **2b** (Scheme 2, entry II). However, treatment of either **3a** or **3b** (0.5 M CH_2Cl_2) with *N*,*N*-diethyl carbamyl chloride (1.2 equiv) and Hünigs base (3.0 equiv) affords the type-2 vinylogous esters **6a** and **6b**, without any of the corresponding type-1 adduct. These carbamates **6a** and **6b** are surprisingly unstable toward chromatography and are used in crude form for the subsequent reactions in Scheme 3.

With the desirable vinylogous esters in hand we began investigating their reactivity with organometallic reagents. Addition of at least 2 equiv of an organometallic reagent to an α-hydroxy cyclohexanone should procure the corresponding *anti* diol. In principle deprotonation occurs first and the resulting metal alkoxide directs by chelation the subsequent addition to the vicinal ketone and thereby affords the *anti* diol. This transformation



Scheme 2. Construction of a specific tautomer.

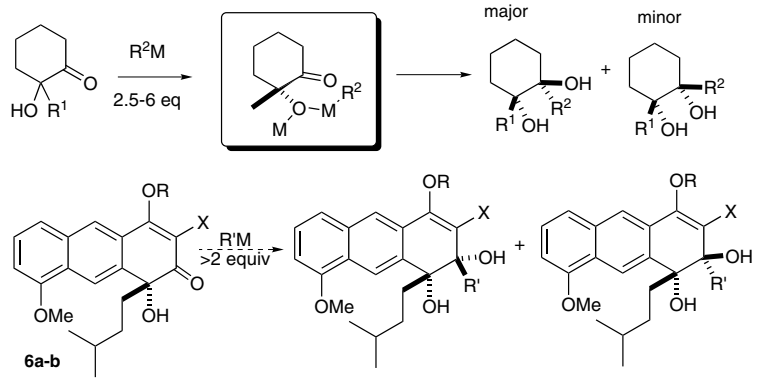


Figure 3. Addition of excess organometallic reagent to 2-hydroxy-cyclohexanones favors formation of the *anti*-diol. Selectivity usually follows the trend of Li < Mg < Ce.

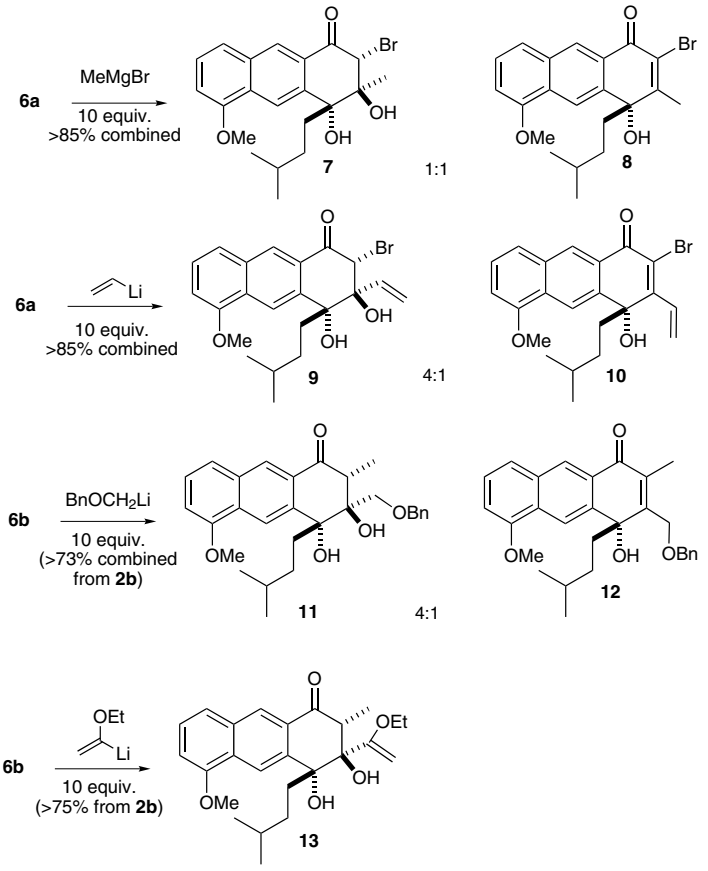
was observed sometime ago with organolithium reagents[16] and more recently with cerium and magnesium reagents (Fig. 3).[17] We intended to implement this strategy with vinylogous esters **6a**–**b**.

A recent report suggested that enol carbamates are cleaved upon prolonged contact with organometallic nucleophiles resulting in the corresponding enolate.[18] Therefore, in principle our anticipated reaction might afford all of the desired functionality upon enolate protonation in a single pot.

Addition of MeMgBr (10 equiv) to **6a** (0.1 M Et_2O, −78 °C), affords a 1:1 mixture of products (Scheme 3). After separation by chromatography, one of these products was identified as the *anti* diol **7**, which proves unreactive toward $NaIO_4$. The other product is the enone **8**. Similar treatment of **6a** with vinyl lithium affords a 4:1 ratio of diol **9** and the enone **10**.

Next, we focused on the methyl derivative **6b**. We were gratified to find that treatment of **6b** (0.3 M THF) with $BnOCH_2Li$ (10 equiv, 0.9 M THF) affords the ketone **11** and the enone **12** in a 4:1 ratio. Better still, addition of lithiated ethyl vinyl ether (10 equiv, 0.6 M THF) to **6b** (0.5 M THF) affords **13** as the sole product in a 75% isolated yield from **2b**. It appears that larger nucleophiles afford a greater preponderance of the corresponding *anti* product. It is interesting and perhaps fortuitous that excess of the organometallic reagent cleaves the carbamate before work-up and results in the corresponding enolate that thermodynamically equilibrates to give only the desired isomer **13**.

We speculate that the enone products **8**, **10**, and **12** arise from initial formation of the undesired *syn* diastereomer, which readily undergoes β-elimination to afford their respective enones. As shown in Figure 4, the *syn* diastereomer is aligned for elimination with the



Scheme 3. Additions to vinylogous esters **6**.

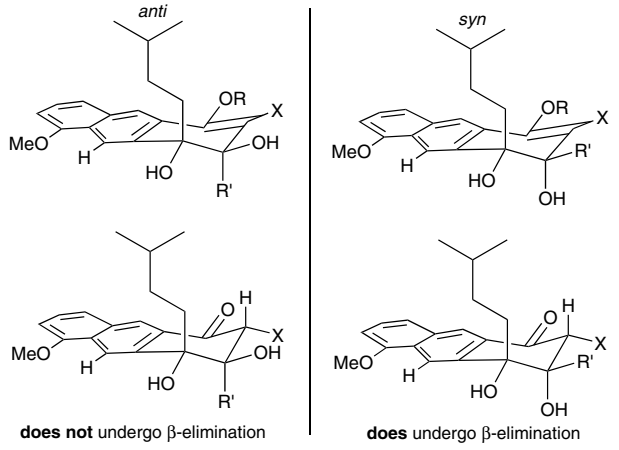
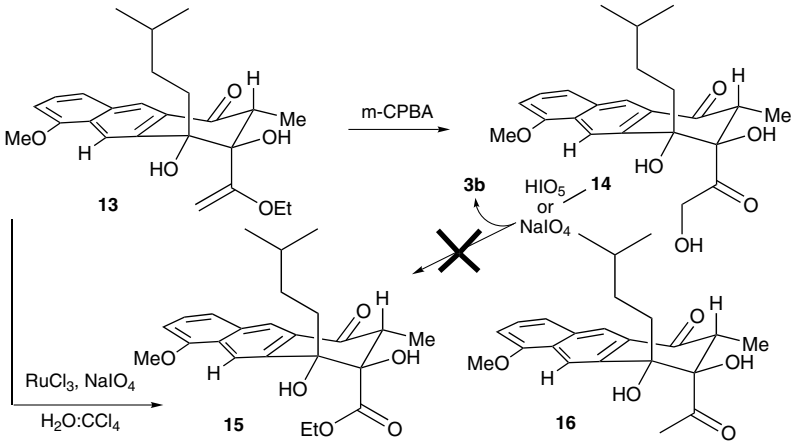


Figure 4. Stability of *anti* and *syn* adducts.

neighboring π-orbital, while the *anti* diastereomer is not.

With **13** in hand, we sought methods for its conversion to the corresponding ester or acid analogs of (±)-rishirilide B (**1**). Unfortunately, ozonolysis of **13** led to decomposition (Scheme 4), presumably because of the reactivity of the naphthalene ring toward ozone. Treatment of **13** with OsO_4 and $NaIO_4$, returns a tautomeric mixture of **3b**. It appears that the bis-α-hydroxy ketone **14** likely cleaves at the undesirable site between the tertiary alcohol and carbonyl because of steric interactions associated with the approach towards the ketone and primary alcohol. The α-hydroxy ketone **14** can be produced cleanly by treatment of **13** with *m*-CPBA. Yet despite references to the contrary, treatment with of the bis-α-hydroxy ketone **14** with a variety of reagents ($NaIO_4$, HIO_5, etc.) returns the tautomeric mixture **3b**. Gratifyingly, the enol ether **13** (0.4 M 2:1/CCl_4–H_2O) undergoes reaction with catalytic RuO_4, which is generated by the combination of $RuCl_3$ (0.2 equiv) with $NaIO_4$ (1 equiv), and affords the ethyl ester **15** along with the enol hydrolysis product **16** in 1:1 ratio and a combined yield of 60%. The ethyl ester **15** compared quite favorably with the corresponding methyl ester, for which a crystal structure has been reported.[3c]

The sensitivity of the rishirilide B core to basic conditions, which can result in retro-aldol ring opening and stereochemical corruption, are well documented.[3c] Therefore, compound **15** cannot be easily converted to rishirilide B (**1**). Nevertheless, we anticipate an enantioselective synthesis of the fully elaborated natural enantiomer will appear shortly using our recently disclosed method for the dearomatization of resorcinols[19] in combination with our solution for construction of the naphthol ring system,[4] and the strategy reported herein where the tertiary alcohol serves as the stereogenic center for those remaining. Therefore, our attentions have turned to the enantioselective synthesis of **17** (X = O), which we expect can undergo deprotection under mild conditions. Furthermore, we believe that the



Scheme 4.

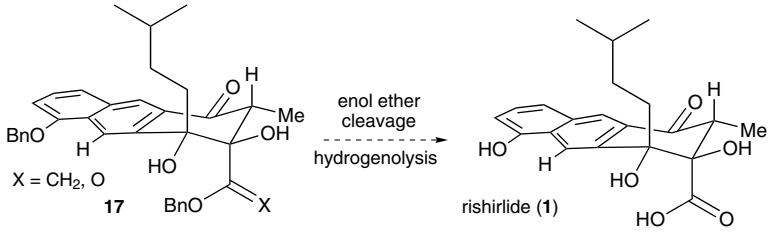


Figure 5. Our anticipated endgame for (+)-rishirilide B (**1**).

penultimate step, RuO_4 cleavage of the enol ether **17** ($X = CH_2$), can be buffered to prevent the formation of the corresponding methyl ketone (Fig. 5).

Supplementary material

Key spectroscopic data for **3a**,**b**, **4a**,**b**, **5a**,**b**, crude **6a** and **6b** along with **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, and **16** are available for download.

Acknowledgements

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