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Toward the total synthesis of elisapterosin B: A $Hg(OTf)_2$-promoted diastereoselective intramolecular Friedel-Crafts alkylation reaction

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Abstract

As part of an approach to the synthesis of the antitubercular agent elisapterosin B, we prepared two different chiral, non-racemic olefinic substrates and examined their diastereoselective ring closure using mercury salts. The effort yielded potential precurors to elisapterosin B in good yield with good to excellent diastereocontrol.

Keywords

benzothiazine; elisapterosin B; Friedel-Crafts; mercuric acetate; tuberculosis

1. Introduction

Tuberculosis is a major worldwide health problem, with as many as one third of the planet's population infected with the causative organism. Approximately 10% of those infected proceed to active disease and between one and two million people die annually as a result. Current chemotherapies against TB are often effective, but require months of treatment, during which time compliance with dosing regimens can be compromised. This and other factors have given rise to the emergence of multidrug resistant (MDR) and extremely (extensively) drug resistant (XDR) strains of tuberculosis.[1] These require new, more aggressive therapies to effect cures. There is thus a need for new chemotherapeutic agents that are more potent and efficacious that those currently in clinical use, both to combat resistant strains of TB and to shorten the time necessary for treatment of all forms of TB, so that treatment can be effected in a conveniently timely fashion, mitigating problems of noncompliance with long-term chemotherapies.

There is therefore much current interest in exploring new leads for the treatment of TB. One approach involves the discovery of natural products that have antitubercular activity.[2] For example, elisapterosin B (**1**), was isolated from the gorgonian coral *Pseudopterogorgia elisabethae* and found to have antitubercular activity, inhibiting the growth of *M.*

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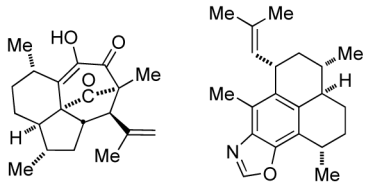
Supplementary data Supplementary data (experimental procedures, charaterization data; ^1H and ^{13}C spectra for new compounds) associated with this letter can be found in the online versions at doi:XXXXXXXX.

tuberculosis H37Rv to the extent of 79% at 1.5 μg/mL.[3] This is but one of a family of related terpenes that also showed various degrees of activity against tuberculosis. Another example is the amphilectane diterpene, pseudopteroxazole.[4]

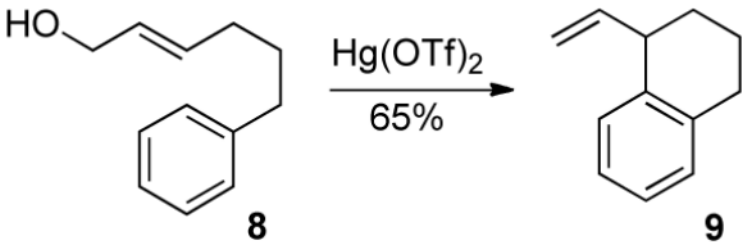


1, elisapterosin B **2**, pseudopteroxazole

Our interest in this area was stimulated both by the serious nature of the medical problem and the fact that we had developed benzothiazine chemistry that we thought applicable to the synthetic challenges of compounds like **1** and **2**. In fact, we reported that our completely stereoselective approach to benzothiazines[5] was a powerful approach to the synthesis of pseudopteroxazole.[6] Further, we used the chemistry to synthesize related molecules like curcumene, curcuphenol and erogorgiaene in enantiomerically pure form;[7,8] and used it in an approach to seco-pseudopteroxazole.[9]

Our approach to elisapterosin B is presently centered on a formal total synthesis that intersects the Rychnovsky route[10,11] to **1** at **3**, which can be converted to **1** via a Lewis acid-mediated (5+2)-cycloaddition (Scheme 1). It is anticipated that **3** can be obtained from **4** and that the stereoselective formation of **4** can be accomplished by an intramolecular Friedel-Crafts alkylation (IFCA) of **5**. Finally, **5** would be available using our benzothiazine synthesis, leading retrosynthetically to **6** and **7** (Scheme 1).

The intramolecular cyclization, the subject of this paper, was anticipated to be successful based on a report by the Nishizawa group, who reported a mercury-catalyzed arylene cyclization (Eq. 1).[12] Allylic alcohol **8** was cyclized to **9** in good yield. However, the critical factor for us was the diastereocontrol available in such a process.



(1)

2. Preparation of benzothiazine 6

The synthesis of benzothiazine began with the known aldehyde **7**.[13] A Horner-Wadsworth-Emmons (HWE) reaction afforded the *ortho*-bromocinnamate **10** in quantitative yield. A Buchwald-Hartwig coupling reaction[14] between **10** and enantiomerically pure (+)-sulfoximine (*S*)-**11** gave an *N*-arylated sulfoximine intermediate, which was converted with complete diastereocontrol into benzothiazine **6** via intramolecular Michael addition[8] by using LiHMDS as base.[5]

3. Preparation of 5a and 5b

In considering a study of the cyclization process and its diastereoselectivity, we chose to synthesize both **5a** and its desmethyl analogue **5b**. Thus, benzothiazine **6** was reduced with LAH and desulfurized with Na/Hg to give aniline **12** in excellent yield. Oxidation of **12** with CAN afforded quinone **13** in 76% yield,[15] which was reduced and methylated to give alcohol **14** in one pot. Compound **14** was oxidized to the aldehyde, which was homologated to **15**. A HWE reaction using Roush conditions[16] and reduction with DIBAL afforded **5a** and **5b** in good yield.

4. The mercury-catalyzed cyclization of 5a

In an effort to optimize the preparation of **4**, particularly in the context of stereocontrol, conditions were sought for the mercury-catalyzed cyclization of **5a** that would be optimal. The results of the study are shown in Table 1. Using catalytic amounts of $Hg(OTf)_2$, the reaction was performed at different temperatures in toluene. Beginning the process at a relatively high temperature was better than beginning at ambient temperature followed by warming (entries 1-4). However, when the initial temperature as increased to 110 °C, both the conversion and diastereoselectivity decreased (entry 5). Under these reaction conditions, the reaction was not clean. Side reactions such as double bond migration may have occurred due to presence of triflic acid produced in the reaction. In order to suppress these side reactions, 2,6-*tert*-butylpyridine was added; however, no reaction was observed even at 110 °C (entry 6). Further, solvent effects were studied (entries 7-10). The reaction did not proceed in acetonitrile. Interestingly, when dichloromethane was the solvent, the diastereoselectivity was high (entry 8); and with 1,2-dichloroethane was the solvent, the diastereoselectivity was even higher, up to 15:1 (entry 9). However, both reactions gave low yields due to unwanted side reactions. When $Hg(SO_3C_4F_9)_2$ was the catalyst, the reaction was very poor (entry 10).

The structural assignment of the products was carried out using proton and carbon NMR. The stereochemical assignment was based on the fact that the alkene methylene protons of the major *trans* isomer were upfield from those of the minor isomer, which was assigned as *cis*.[17] A similar phenomenon was observed for the isomers of cyclization products derived from **5b**, and the stereochemistry of the major product was established by X-ray analysis in that case. Furthermore, a report by Schmalz on the cyclization of a compound related to **5a** (and which did not work with **5a**) indicated that same basic pattern in chemical shifts, the methylene protons of the *trans* cyclization products resonated upfield from those of the corresponding *cis* isomer.[18]

5. The mercury-catalyzed cyclization of 5b

The mercury-catalyzed IFCA reaction of the allylic alcohol **5b** was also investigated. The results of this reaction are tabulated in Table 2. Using benzene as solvent and $Hg(SO_3C_4F_9)_2$ as catalyst, at room temperature, the cyclized product **16** was obtained in 50% isolated yield with good selectivity (*dr* = *trans*:*cis* > 10:1, entries 1 and 2, Table 2), but the reaction was slow. At higher temperatures, the yield improved but the selectivity dropped somewhat and remained relatively constant over a temperature range of 70-110 °C. This suggests kinetic control in the cyclization process, as one would expect an increase in the amount of *trans*-**16** at higher temperatures if the reaction were reversible.[19] Overall, the best reaction conditions appeared to be heating at 70 °C in benzene or toluene for 15 min (Table 2, entries 3, 6).

In order to verify the structure of **16**, an attempt was made to produce a crystalline derivative. Hydroboration of alkene **16** with BH_3·THF, followed by oxidation gave **17** in 71% isolated yield. Reaction of **17** with TsCl furnished **18** in 84% isolated yield. Treatment

of **18** with thiophenol and potassium carbonate in DMSO, followed by oxidation of intermediate sulfide with *m*-CPBA, furnished the sulfone **19** in 63% yield over two steps (Scheme 4). The major isomer of **19** was separable by recrystallization from MeOH/CH_2Cl_2. The X-ray crystal structure[20] confirmed the stereochemistry of **16**. It should be noted that the terminal vinyl proton trans to the internal vinyl proton resonated at 4.62 ppm for *trans*-**16** but appeared at 4.89 ppm in *cis*-**16**. This helped in assigning the stereochemistry of the isomers of **4**, as mentioned above.

The basis for the *trans* selectivity in these cyclization presumbably arises from a chairlike six-membered transition state in which the substituents are disposed in a pseudoequatorial orientation. How substitution patterns on the aromatic ring and the putative allylic cation intermediate affect this selectivity must be the subject of future studies.

6. Conclusion

In summary, using benzothiazine chemistry and $Hg(OTf)_2$-catalyzed diastereoselective IFCA, we have synthesized the potential precursors (**4** and **16**) to elisapterosin B. We are now targeting the synthesis of diene **3** to finish this total synthesis. The results of these studies will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. 4.79 and 3.94 ppm for *trans*-**4** and 4.81 and 4.43 ppm for *cis*-**4**.
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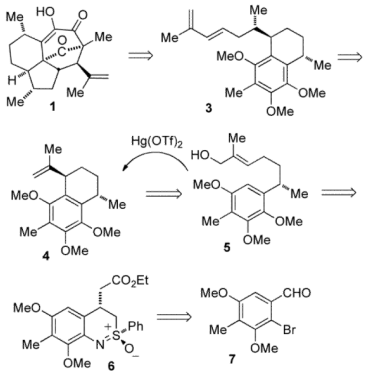
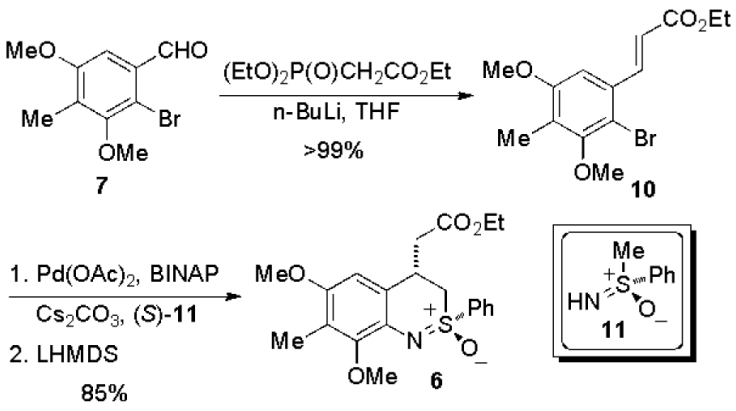
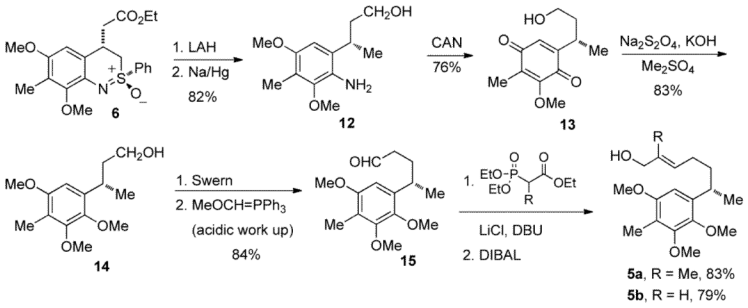
20. Crystallographic data (excluding structure factors) for **19** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 734229. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; deposit@ccdc.ac.uk].



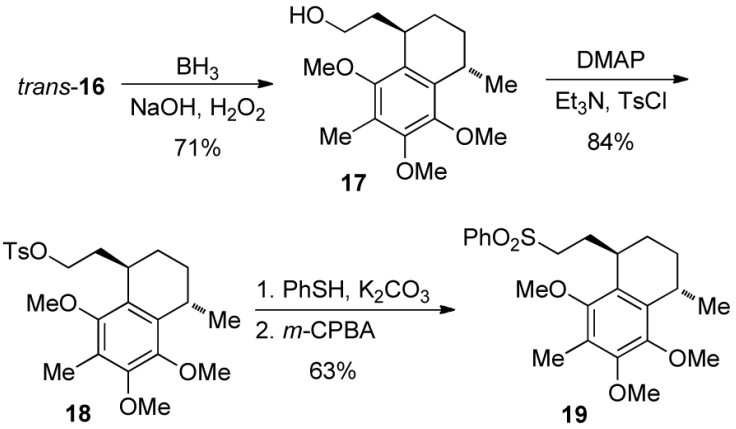
Scheme 1.
Retrosynthesis for elisapterosin B.



Scheme 2.
Synthesis of benzothiazine **6**.



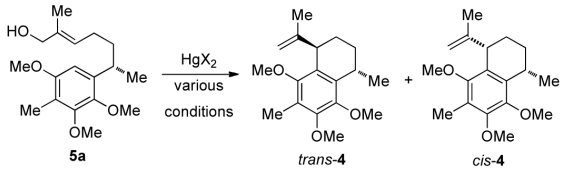
Scheme 3.
Synthesis of alcohols **5a** and **5b**.



Scheme 4.
Synthesis of a crystalline derivative of *trans*-**16**.

Table 1

Mercury-catalyzed IFCA reaction of **5a**



Entry	HgX_2, (equiv)	Conditions	Yield %,[a] (trans:cis)[b]
1	$Hg(OTf)_2$, (0.005)	PhMe, rt, 1.5 h; 48 °C, 25 h	40%,[d] 12.5:1
2	$Hg(OTf)_2$, (0.005)	PhMe, rt, 20 min; 60 °C, 25 h	54%,[d] 8:1,
3	$Hg(OTf)_2$, (0.005)	PhMe, 45 °C, 4 h	54%, 9:1
4	$Hg(OTf)_2$, (0.005)	PhMe, 55 °C, 4 h	50%, 9:1
5	$Hg(OTf)_2$, (0.005)	PhMe, 110 °C, 10 min	34%, <9:1
6	$Hg(OTf)_2$,(0.01)[c]	PhMe, 60 °C, 30 min; 110 °C, 12 h[c]	0
7	$Hg(OTf)_2$, (0.005)	MeCN, rt, 20 min; 70-80 °C, 19 h	0
8	$Hg(OTf)_2$, (0.005)	CH_2Cl_2, rt, 35 min; 90 °C, 5 h	13%,[d] 12.5:1
9	$Hg(OTf)_2$, (0.005)	$ClCH_2CH_2Cl$, rt, 35 min; 90 °C, 5 h	27%,[d] 15:1
10	$Hg(SO_3C4F_9)_2$, (0.005)	PhMe, rt, 24 h; 80 °C, 15 min	*e*

[a] Yields are for isolated products unless otherwise stated.

[b] The diastereomeric ratio was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

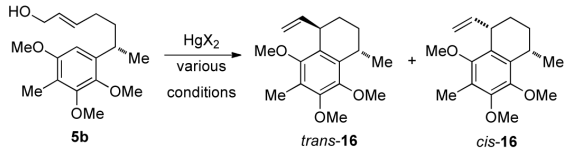
[c] 2,6-di-*tert*-butylpyridine was added.

[d] Crude yield.

[e] A complex mixture was formed.

Table 2

IFCA reaction of allylic alcohol **5b**



Entry	HgX_2, (equiv)	Conditions	Yield % (dr = *trans:cis*)
1	0.02 equiv $Hg(SO_3C_4F_9)_2$	benzene, rt, 2d	trace
2	0.02 equiv $Hg(SO_3C_4F_9)_2$	benzene, rt, 4d	50%, *dr* > 10:1
3	0.02 equiv $Hg(OTf)_2$	benzene, rt, 1h, 70 °C, 30 min	73%, *dr* = 6.3:1
4	0.02 equiv $Hg(OTf)_2$	benzene, 70 °C, 15 min	73%, *dr* = 6.3:1
5	0.005 equiv $Hg(OTf)_2$	benzene, rt, 35 min, 80 °C, 1.5 h	73%, *dr* = 5.9:1
6	0.02 equiv $Hg(OTf)_2$	PhMe, 70 °C, 15 min	72%, *dr* = 6.3:1
7	0.005 equiv $Hg(OTf)_2$	PhMe, 110 °C, 5 min	73%, *dr* = 5.6:1
8	0.005 equiv $Hg(OTf)_2$	PhMe, 110 °C, 20 min	58%, *dr* = 5.6:1

[a] Yields are for isolated products.

[b] The diastereomeric ratio was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture