Synthesis of Cyclic Ethers via Lewis Acid Mediated Oxepane Formation

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INTRODUCTION:

The gambieric acids, which were isolated from the culture medium of *Gambierdiscus toxicus* by Yasumoto and co-workers, are the most potent antifungal compounds known to mankind.¹ Their antifungal activity against *Aspergillus niger* were over two thousand times greater than that of amphotericin B, a widely used antifungal agent.² Furthermore, gambieric acid A did not demonstrate any observable toxicity towards mice at a dose of 1 mg/ Kg. Structurally, gambieric acids are polycyclic ethers³ consisting of nine *trans*-fused ether rings, ranging from six to nine membered, and an isolated tetrahydrofuran. Their complex molecular architecture, biological properties and low toxicity provide the incentive for the synthetic endeavors outlined herein.

Figure 1. Gambieric acids.

This focus of this project was on the development of a reaction sequence for the construction of the EF ring system of Gambieric acids. We envisioned the formation of the oxepane E ring by a lewis-acid mediated opening of a donor-acceptor substituted cyclopropane as depicted in Scheme 1.

Scheme 1. Retrosynthetic analysis of 2.

The synthetic utility of the cyclopropane ring-expansion methodology in the construction of small rings has been demonstrated. In this context, Yadav has shown that donor acceptor substituted cyclopropanes can be used to synthesize tetrahydropyrans and five and six membered carbocycles.⁴

Mechanistically, cyclopropanes of type **4** could react either with a nucleophile through the silicon stabilized positive terminus of the dipole or with an electrophile through the negative terminus. The reaction that we have contemplated falls under the later domain, in which the electrophile is attacked by the negative terminus of the dipole. Treatment of **4** with Lewis acid should furnish an oxocarbenium ion, which can then be attacked by the negative end of the dipole leading to the formation of the oxepane ring E. A terminal double bond should also be generated in the reaction which will allow the formation of the nine membered ring *via* ring-closing metathesis.⁵

Scheme 2. Mode of reactivity of the cyclopropane 4.

The electron withdrawing group on the cyclopropane ring is believed to be crucial for this reaction since it helps to stabilize the developing negative charge on the adjacent carbon (Scheme 2). However, the presence of the ether oxygen decreases this effect. Hence, it is necessary to determine a suitable electron withdrawing group which offsets the effect of the ether oxygen and promotes the reaction as shown in Scheme 2.

SYNTHETIC STRATEGY: Scheme 3 illustrates the sequence of steps leading to the synthesis of the required donor-acceptor cyclopropane for the lewis-acid mediated ring expansion.

Scheme 3. Strategy for making the donor-acceptor substituted cyclopropane.

It seemed reasonable that before subjecting the optically active starting material for developing this reaction, a model study would be undertaken with a simpler substrate. This study would utilize cyclohexanol instead of the alcohol 7. The phenyl sulfone group was chosen as the electron withdrawing group for this study because of it's strong electron withdrawing nature and functionalization.

RESULTS AND DISCUSSION: The first step in the synthesis was to prepare (1-bromoallylsulfonyl)benzene **13**. It was contemplated that this sulfone should be accessible *via* an allylic bromination of allyl phenyl sulfone. However, treatment of allyl phenyl sulfone with *N*-bromosuccinimide led to a complex mixture of compounds.

Scheme 4. Failure of NBS to give 13

It was anticipated that a selenium dioxide mediated allylic oxidation would lead to the corresponding alcohol which could subsequently be converted to 13. However, the allyl phenyl sulfone failed to undergo oxidation with selenium dioxide. Other reagents for allylic oxidation, such as PCC, PDC and copper/perester were explored but without success.

Meyers and coworkers have shown that α -halogenated sulfones can be obtained by treatment of the corresponding sulfone with carbon tetrachloride in basic media. However, all the examples cited utilized benzylic sulfones. It was also demonstrated that α,α -dibromo benzylic sulfones could be reductively

debrominated to give α -bromo substituted sulfones. An attempt to extend this methodology to allylic sulfones met with mixed success. Treatment of the allyl phenyl sulfone with carbon tetrachloride led to the corresponding α,α -disubstituted sulfone in 40% yield. However, reductive dechlorination of the dichloro compound **14** proved problematic. The yield of the dichlorination dropped dramatically upon scale-up due to polymerization reactions.

Scheme 5. Formation of (1,1-dichloroally/sulfony/)benzene

Since the desired functionalization of the sulfone was proving problematic, it was envisioned that the corresponding sulfide could be used, which could later be oxidized to the sulfone. A further search of the literature revealed that allyl phenyl sulfide upon treatment with N-chlorosuccinimide leads to the rearranged terminal alkene 15. The displacement of the chloride with a copper alkoxide in an S_N2 fashion would furnish the desired ether functionality. However, all attempts to displace the chloride by the copper alkoxide of cyclohexanol failed. There was no reaction and the chloride was recovered.

Scheme 6. Synthesis of (3-chloroprop-1-enyl)(phenyl)sulfide

It is known that silver salts can be used for etherification of α -halo sulfides and that these reactions proceed *via* a sulfur stabilized carbenium ion. Extending this idea to the chloride **15**, it was likely that on treatment with silver triflate, the allylic carbenium ion A would rearrange to form the more stable carbenium ion B. However, the reaction with silver(I) triflate led to the formation of the primary ether, thus demonstrating that this system does not behave as a π -allyl system.

Scheme 7. Synthesis of allylic ether using silver(I) triflate.

A recent report by Hartwig shows that primary and secondary allylic carbonates undergo an Iridium catalyzed allylic substitution to yield allylic ethers with a terminal double bond.⁹

$$R \longrightarrow OCO_2^{t}Bu + (R^1O)_2CuLi \xrightarrow{[Ir(COD)CI]_2} R \xrightarrow{OR^1} + R \longrightarrow OR^1$$
18 19 20 21

Major Minor

Scheme 8. Iridium catalyzed allylic etherification.

We deicided to test this methodology on the corresponding sulfur substituted primary carbonate 25 which in principle, could be obtained from the chloride 15 in

two steps *via* the corresponding alcohol. The copper catalyzed hydrolysis of the chloride **15** did give the corresponding alcohol, albeit in extremely poor yield. Free radical addition of thiophenol to propargyl alcohol¹⁰ was then used to synthesize the alcohol **24** which was then converted to the carbonate **25** by treatment with di-*tert*-butyl dicarbonate. It was difficult to obtain large quantities of the alcohol **24** in pure form so the less polar impurities were removed by flash chromatography and the remaining mixture was used to prepare **25**. In his report, Hartwig has shown that the secondary ethers were obtained in high yield if the phosphoramidite **31** was used as the ligand. However, since sulfur substituted carbonates were not studied for this type of reaction, it was decided to test triphenyl phosphite as the ligand. The crude NMR showed that both the primary and secondary allylic ethers **26** and **27** were formed in the ratio of 2:1 favouring the primary. Also, the reaction did not proceed to completion after 18 hours.

HO SPh
$$\frac{(BOC)_2O}{DMAP, DCM}$$
 PhS OCO_2^tBu

PhS
$$OCO_2^tBu$$
 + OH Cul , LiHMDS, P(OPPh)₃ OCO_2^tBu + OO SPh + OO 27

Scheme 9. Synthesis of carbonate **25** and the Iridium catalyzed etherification.

The next task was to synthesize the phosphoramidite **30**. Since stereochemical outcome is not a consideration in our system, we decided to make the racemic version of **30**. The literature procedure for making the phosphoramidite involves the reaction of the binaphthol **28** with phosphorous trichloride followed by treatment of the product with the corresponding secondary amine. ¹¹

Scheme 10. Method for preparation of the phosphoramidite 30.

The required secondary amine was prepared from 1-(1'-naphthylethyl amine) and 1-acetonaphthone using a one-pot sequence of imine formation and reduction. 12

Scheme 11. Synthesis of the secondary amine **33**.

Since the above approach was not giving the desired substrate easily, it was deicded to explore an alternate pathway as we worked on the existing scheme. As shown in scheme 11, the oxathioacetal would be utilized to gain access to the required sulfur substituted allylic ether.

Scheme 12. Retrosynthetic analysis for the synthesis of allylic ether **27**.

The cyclohexanone acetal of formaldehyde was prepared in 72% yield. The acetal was then subjected to acetyl chloride and catalytic amount of methanol to afford the chloride **37**. The reaction mixture was neutralized and used in crude form for the next step. ¹³

Scheme 13. Synthesis of (Chloromethyloxy)cyclohexane 36

FUTURE RESEARCH: The synthesis of the required sulfur substituted allylic ether posed substantial difficulties which have to be overcome. The difficulty of

synthesizing a seemingly simple moiety is exemplified by the absence of any examples in the literature. It is believed that the Iridium catalyzed allylic etherification will afford the desired ether which can then be used to examine this strategy. The alternate route using oxathioacetal also looks promising in this regard. The future work will focus on the synthesis of the phosphoramidite ligand and it's application in the Iridium catalyzed etherfication and the new route to the allylic ether 27 proceeding *via* the oxathioacetal will also be explored.

CONCLUSION: Various methods for the synthesis of the allylic ether **27** were explored *en route* to the substrate required for the key ring opening reaction. After many unsuccessful attempts, the required functionality was obtained by the Iridium catalyzed etherification. Although the desired compound was formed as the minor product, it suggests that modulation of the reaction conditions such as change of ligand can give the desired compound selectively. It was also found that the carbenium ion formed by the chloride **15** does not behave like a π -allyl system and hence affords the allylic ether **26** *via* a direct substitution. These early results coupled with the detours in the synthetic scheme provide some understanding about the behavior of such systems which can be applied to plan the use of such motifs in a synthetic study.

EXPERIMENTAL:

Starting materials obtained from commercial sources were used without purification unless stated otherwise. Methylene chloride, ether, toluene, and tetrahydrofuran were dried via an alumina column solvent system. Triphenyl phosphite was distilled under vacuum before use. Chloroform was dried by distilling over phosphorous pentoxide. Analytical TLC was carried out on Merck 60 A silica gel. ¹H NMR were recorded on a Varian VRX at 400 MHz using CDCl₃ as solvent with the residual solvent peak as the internal standard (¹H NMR: 7.24 ppm). All reactions were carried out in flame dried glassware, under an atmosphere of dry nitrogen or argon unless otherwise indicated. Silver(I) triflate and [Ir(COD)Cl]₂ were stored and transferred in a glove box.

To a stirred solution of allyl phenyl sulfone (12) (0.059 g, 0.326 mmol) in *tert*-butanol (6 mL), cooled to 0 °C, was added carbon tetrachloride (10 mL) and KOH (0.439 g, 7.82 mmol). The reaction mixture was allowed to stir for 14 hours at ambient temperature. Water was added to the reaction and the mixture was extracted with ether. The combined organic phases were washed with brine, dried over anhydrous MgSO₄ and the solvent was removed *in vacuo* to afford a crude yellow oil. Purification by flash chromatography on silica gel (eluting with 5-10% ethyl acetate/hexanes) afforded the dichloro compound 14 (28.9 mg, 40%): IR (neat) 3068 (w), 2924 (w), 1610 (s), 2854 (s), 1583 (w), 1448 (m) cm⁻¹;

 1 H NMR (400 MHz, CDCl₃) δ 6.35 (dd, J = 10.8 Hz, J = 16.8 Hz, 1H) 5.87 (d, J = 16.4 Hz, 1H), 5.72 (d, J = 10.4 Hz, 1H).

(3-chloroprop-1-enyl)(phenyl)sulfide 15: Cl SPh

To a solution of allyl phenyl sulfide (0.751 g, 5.0 mmol) in CCl_4 , was added N-chlorosuccinimide (0.668 g, 5.0 mmol) and the resulting mixture was stirred at 5 °C on a cryogenic cooler for *ca.* 24 hours. Solvent was evaporated and the resulting oil contained essentially the monochloroproduct **15** (877.5 mg, 95%). Attempts to chromatograph **15** on silica gel led to its decomposition into unidentifiable compounds: IR (neat) 3059 (w), 2952 (w), 1610 (s), 1583 (s), 1479 (s), 1439 (s) cm⁻¹; ¹H NMR (400 MH_z, CDCl₃) δ 7.39-7.26 (m, 5H), 6.52 (d, J = 14.8 Hz, 1H), 5.81 (dt, J = 14.8 Hz, J = 7.6 Hz, 1H), 4.09 (d, J = 7.6 Hz, 2H).

Etherification of 15 with cyclohexanol using AgOTf:

A suspension of molecular sieves 4A (1.0 g) in CH₂Cl₂ (8mL) was cooled to -60 °C. To this mixture was added cyclohexanol (217.0 mg, 2.16 mmol). After 5 min. at -60 °C, AgOTf (556.32 mg, 2.16 mmol) and 2,6 di-tertbutyl pyridine (444.6 mg, 2.16 mmol) were added in one portion. The yellow suspension was stirred for *ca*. 5 minutes at the same temperature before the addition of the sulfide (100 mg, 0.54 mmol) in CH₂Cl₂. The reaction mixture was stirred for one hour at -60 to -30 °C and then allowed to stir for 12 hours at ambient temperature. The reaction mixture was then filtered through a pad of silica gel and washed with EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography

(eluting with 3% ethyl acetate/hexanes) to give the compound **17**. ¹H NMR (400 MH_z, CDCl₃) δ 7.36-7.21 (m, 5H), 6.44 (d, J = 15.2 Hz, 1H), 5.933-5.896 (m, 1H), 4.04 (d, J = 6.0 Hz, 2H), 3.32-3.24 (m, 1H), 1.90-1.88 (m, 4H), 1.73-1.72 (m, 4H), 1.63-1.68 (m, 2H).

3-(Phenylthio)prop-2-en-1-ol: HO____SPh

Thiophenol (4.4 mL, 40 mmol), Propargyl acohol (2.328 mL, 40 mmol) and AIBN (1.96 g, 12 mmol) were taken in dry benzene (30 mL) and refluxed at 80 °C for 4 hours. The solvent was removed *in vacuo* and the residue was purified using flash chromatography (eluting with 15% ethylacetate/hexanes) to give the alcohol **24** (5.32 g, 80%); IR (neat) 3353 (s), 3059 (m), 2976 (s), 2925 (s), 1739 (s), 1582 (m), 1477 (s), 1440 (s) cm⁻¹; ¹H NMR (400 MH_z, CDCl₃) δ 7.41-7.27 (m, 5H), 6.49 (dq, J = 15.2 Hz, J = 1.2 Hz, J = 1.2

Tert-butyl 3-(phenylthio)allyl carbonate 25: PhS OCO₂tBu

The alcohol **20** (1.662 g, 10 mmol) was taken in CH₂Cl₂ (10 mL) and di-tert-butyl di-carbonate (3.272 g, 15 mmol) was added follwed by DMAP (2.44g, 20 mmol). The reaction mixture was allowed to stir for *ca.* 12 hours. Saturated NaHCO₃ solution (10 mL) was added and the reaction was stirred for *ca.* 30 minutes. The reaction mixture was extracted with CH₂Cl₂ and the combined organic phases were washed with brine and dried over anhydrous MgSO₄. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (eluting with 3% ethylacetate/hexanes). The di-tert-butyl dicarbonate could not be

separated from the product by column chromatography and hence it was removed by using Kugelhohr distillation under vacuum to give the pure carbonate **25** (2.36 g, 89%): IR (neat) 3060 (m), 2980 (s), 2935 (s), 1738 (s), 1615 (m), 1583 (m), 1479 (s), 1440 (s) cm⁻¹; ¹H NMR (400 MH_z, CDCl₃) δ 7.37-7.26 (m, 5H), 6.53 (d, J = 15.2 Hz, 1H), 5.84-5.77 (m, 1H), 4.55 (d, J = 6.8 Hz, 2H), 1.46 (s, 9H).

Allylic etherification of 21 using [lr(COD)Cl]₂:

[lr(COD)CI]₂ was taken in THF (0.8 mL) and stirred at room temperature until a homogeneous solution was formed. In a separate flask, lithium bis(trimethylsilyl)amide (263 μL, 0.263 mmol, 1.0M solution in THF) was added dropwise to a suspension of copper(I) iodide (53.6 mg, 0.282 mmol, pyrolyzed before use) and cyclohexanol (28.2 mg, 0.282 mmol) in anhydrous THF (0.8 mL) at room temperature, and the anion allowed to form over ca. 5 minutes resulting in a green homogeneous solution. The catalyst was transferred to the alkoxide via a Teflon cannula and the resulting solution was cooled to 0°C before the addition of the carbonate(50 mg, 0.188 mmol). The reaction was allowed to proceed for 12 hours after which it was filtered through a pad of silica gel. The solvent was removed *in vacuo* and the crude mixture was analyzed by 1 H NMR.

Cyclohexanol (20.0 g, 200 mmol) was placed in a round bottom flask and anhydrous CaCl₂ (3.0 g, 40 mmol) and concentrated hydrochloric acid (140 μ L) were added subsequently. The reaction mixture was placed in an ice bath and Formalin (8.2 mL, 100 mmol ,37% aqueous solution) was added dropwise. After complete addition of Formalin, the reaction mixture was vigorously refluxed for 15 minutes and was then allowed to stir at ambient temperature for 8 hours. The reaction mixture was diluted with water and extracted with ether. The combined organic phases were washed with water, brine and dried over anhydrous MgSO₄. The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column (eluting with 5% ethyl acetate/hexanes) to afford a colourless oil 37 (15.4 g, 72%): IR (neat) 2931 (s), 2856 (s), 1450 (m), 1041 (s) cm⁻¹; 1H NMR (400 MH_z, CDCl₃) δ 4.79 (s, 2H), 3.59-3.56 (m, 2H), 1.94-1.89 (m, 4H), 1.75-1.72 (m, 4 Hz), 1.6-1.53 (m, 2H),1.32-1.90 (m, 10H).

Compound 37 (15.5 g, 73 mmol) and anhydrous methanol (200 µL) were stirred at room temperature for five minutes. Freshly distilled acetyl chloride(5.2 mL, 73 mmol) was then added dropwise with a syringe. The reaction mixture was allowed to stir at room temperature for *ca.* 36 hours after which a saturated sodium bicarbonate solution was added. The reaction mixture was partitioned between water and ether, the combined organic phases were washed with brine,

dried (MgSO₄). The solvent was removed *in vacuo* and the crude material was used in the next step.

Bis-1-(1'-naphthyl)ethylamine 33:

A mixture of acetonaphthone (0.681 mg, 4.0 mmol), 1-(1-naphthyl)ethylamine (685 mg, 4.0 mmol) and titanium (IV) isopropoxide(3.58 mL, 12 mmol) was stirred at ambient temperature for three hours. The reaction mixture was then subjected to hydrogenation with 10% palladium on charcoal under vigorous stirring for 12 hours. The reaction mixture was diluted with EtOAc and filtered through celite. EtOAc was removed in vacuo and the paste obtained was dissolved in ether. A solution of HCl in ether (3 mL, 6 mmol, 2M solution in dietyl ether) was then added and the reaction was stirred for 3 hours. Water was added to the reaction and a clear separation of two phases was observed. The ether layer was extracted with water and the combined aqueous phases were neutralized with 1N NaOH. The resulting mixture was then extracted with CH₂Cl₂. The solvent was evaporated and the amine 34 was obtained as a yellow liquid (715.2 mg, 55%): IR (neat) 3364 (s), 3048 (s), 2965 (s), 2924 (s), 2868 (s), 1596 (s), 1510 (s), 1447 (m) cm⁻¹; ¹H NMR (400 MH_z, CDCl₃) δ 8.13 (d, J = 8.0 Hz, 2H), 7.86 (d. J = 8 Hz, 2H), 7.73 (d. J = 8 Hz, 2H), 7.65 (d. J = 7.2 Hz, 2H), 7.53-7.44 (m, 6H), 4.95 (q, J = 6.8 Hz, 2H), 1.59 (br, s), 1.54 (d, J = 6.8 Hz, 6H).

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