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Asymmetric Synthesis of Corsifuran A by an Enantioselective Oxazaborolidine Reduction†

Harry Adams, Nathan J. Gilmore, Simon Jones,* Mark P. Muldowney,‡ Stephan H. von Reuss,§ and Ramesh Vemula

Department of Chemistry, University of Sheffield, Dainton Building, Brook Hill, Sheffield S6 1XD, U.K.

simon.jones@sheffield.ac.uk

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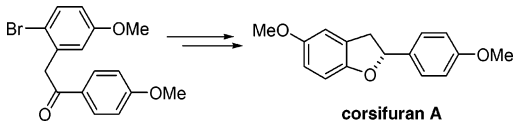
ABSTRACT



corsifuran A

Corsifuran A has been prepared in an enantiomerically pure form for the first time by an asymmetric reduction procedure, allowing confirmation of the absolute stereochemistry of the natural product as (*R*).

Corsifuran A (**1**) is one of a group of three corsifurans, composed of a 4′,5-dioxygenated-2-arylbenzofuran skeleton, recently isolated from the Mediterranean liverwort *Corsinia coriandrina* (Figure 1).[1] The corsifuran skeleton is thought to be constructed biogenetically from a stilbenoid precursor and the naturally occurring material has shown to be of high enantiomeric purity.

Corsifuran A has been prepared twice in racemic form. The first synthesis involved a cycloaddition of 4-methoxystyrene with *p*-quinone to yield corsifuran B, which when methylated gave racemic corsifuran A in an overall yield of around 50%.[1] The second route involved an anodic oxidation of a phenol and styrene, which provided the target in 57% yield.[2]

At the outset of this work the absolute configuration of corsifuran A had not been identified. Our strategy for installing the lone O-stereocenter of corsifuran A would entail us applying our recently reported "one-pot" oxazaborolidine methodology to ketol **3** to generate **2**.[3]

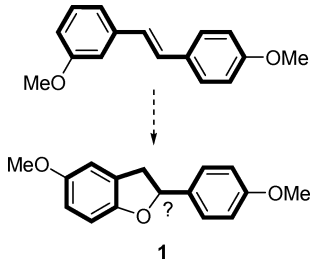


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Figure 1. Biogenetic pathway for corsifuran A (stilbenoid unit drawn in bold).

Our approach to the dihydrofuran ring would involve a metal-catalyzed cycloetherification being applied to enantiomerically pure alcohol **2** (Scheme 2). A Friedel−Crafts reaction would provide the ketone **3**, and carboxylic acid **4** and anisole **5** would serve as its possible precursor.

2-Bromo-5-methoxyphenylacetic acid **4** was obtained from carboxylic acid **6** in essentially quantitative yield (Scheme 2).[4] Adaptation of an existing literature procedure[5] allowed

† Dedicated to the memory of the late Dr. David R. Kelly, School of Chemistry, Cardiff University, Cardiff, U.K.

‡ Shasun Pharma Solutions Ltd., Dudley, Northumberland NE23 7QG, U.K.

§ Institute Für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-29146 Hamburg, Germany.

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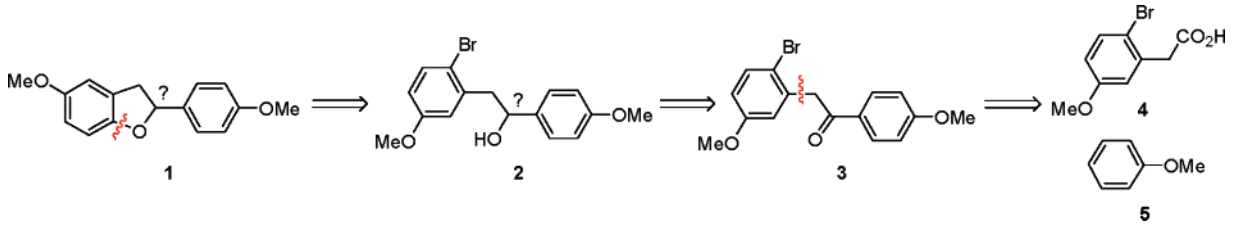
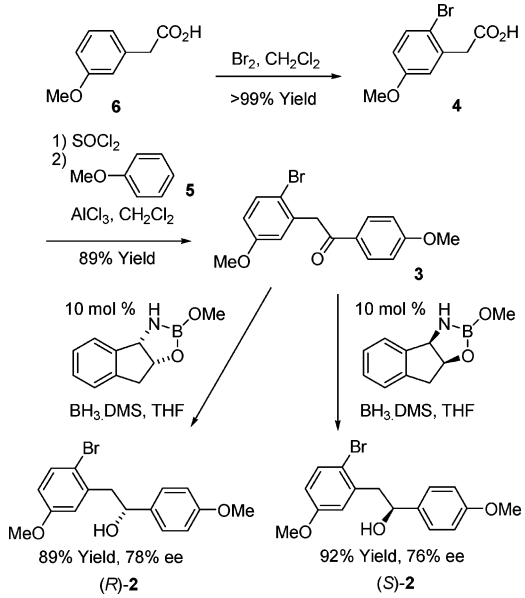
Scheme 1. Retrosynthesis of Corsifuran A



acid **4** to be coupled with anisole. The key ketone **3** was isolated in 89% yield after chromatography. Asymmetric reduction of this ketone **3** with either the *B*-OMe oxazaborolidine derived from (1*R*,2*S*)- or (1*S*,2*R*)-*cis*-1-amino-indan-2-ol gave the *S* and *R* enantiomers of the alcohol **2** in 76% and 78% ee, respectively. Recrystallization to >99% enantiomeric purity allowed confirmation of the absolute configuration through comparison of the Flack parameter obtained by single-crystal X-ray crystallography.

Scheme 2. Preparation of Alcohol **2**

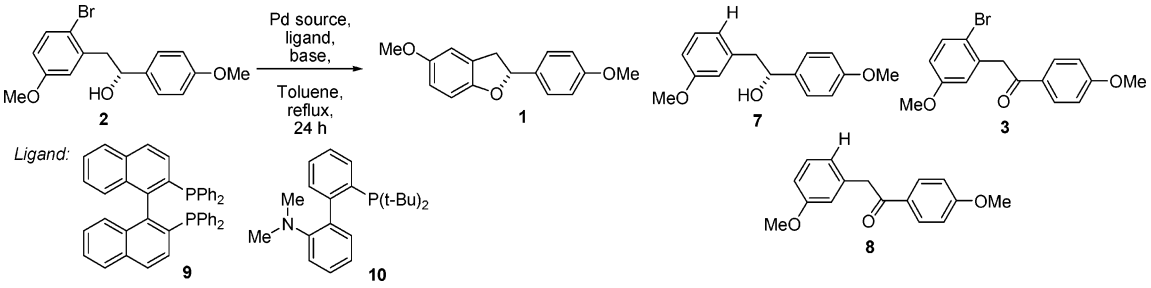


With the key alcohol **2** in hand, cycloetherification was attempted with various palladium catalysts in conjunction with popular ligands and bases (Scheme 3, Table 1). Previous work has shown that the choice of ligand is extremely important in accelerating the rate of the desired reductive elimination pathway and hence obtaining high yields of product.[6] 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene (BINAP) **9** was chosen as a benchmark ligand for comparison purposes, and 2-di-*tert*-butylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl **10**, which has been shown to be a useful phosphine for Pd-catalyzed etherification, was also employed.

The desired corsifuran A **1** was only produced in two reactions, neither of which gave satisfactory results. Pd(OAc)$_2$, BINAP, and *t*-BuONa (entry 1) gave poor yields and did provide the target compound in high ee. By way of contrast, a simple change of the Pd source gave a complete conversion to product (entry 4). However, extensive racemization had occurred. Cs_2CO_3 led to no reaction (entries 2 and 5), and in certain circumstances (entries 1, 2, 3, and 6) varying quantities of unreacted starting material **2**, debrominated starting material **7**, and ketones **3** and **8** were also obtained in each case, the identities of which were confirmed by independent syntheses. However, even with the drop of enantioselectivity, we were able to conclude that the absolute configuration of naturally occurring corisfuran A **1** was indeed (*R*) by comparison of the chiral phase GC with that of the authentic natural product and by comparison of the optical rotation {[α]$_D$ −11.5 (*c* 1, $CHCl_3$), lit.[7] −11.1 (*c* 0.1 $CDCl_3$), ee 92%}.

Corsifuran A obtained from natural sources has a high enantiomeric purity and has been shown to be configurationally stable in air. Storage in dichloromethane in the presence

Scheme 3. Preparation of Corsifuran A by Pd-Catalyzed Intramolecular Etherification of Alcohol (*R*)-**2**[a]



[a] Reactions performed as described in Table 1.

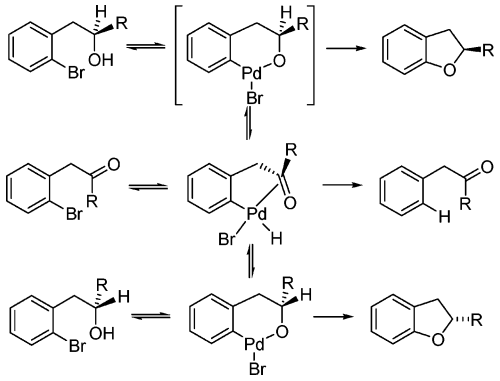
Table 1. Optimization of Pd-Catalyzed Intramolecular Etherification[a]

				conversion (%)[b] [ee (%)][c]				
entry	Pd source (3 mol %)	ligand (3.5 mol %)	base (1.5 equiv)	**1**[d]	**2**	**7**	**3**	**8**
1	$Pd(OAc)_2$	9	NaOt-Bu	5 [100]	0	5 [40]	3	87
2	$Pd(OAc)_2$	9	Cs_2CO_3	0	97 [100]	0	0	3
3	$Pd(OAc)_2$	9	KOt-Bu	0	0	0	0	100
4	$Pd_2(dba)_3$	10	NaOt-Bu	100 [45]	0	0	0	0
5	$Pd_2(dba)_3$	10	Cs_2CO_3	0	100 [100]	0	0	0
6	$Pd_2(dba)_3$	10	KOt-Bu	0	0	0	5	95

[a] Reactions performed in toluene at reflux for 24 h under a nitrogen atmosphere. [b] Based on comparison of ratios of integrals of appropriate signals in the ^{1}H NMR spectrum of the crude reaction mixture. [c] Values for ee determined by chiral phase GC analysis (see Supporting Information for further details). [d] Refers to isolated product.

of an acidic ion-exchange resin (Amberlyst 15) for 1 h does, however, cause complete racemization.[7] Therefore, given the reaction conditions, any loss in enantioselectivity most probably occurs by the reversible formation of a palladium hydride species formed by β-hydride elimination from the palladium(II) aryl oxide intermediate. (Scheme 4). A similar

Scheme 4. Racemization by β-Hydride Elimination

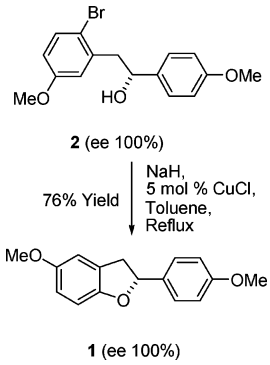


process has been reported in a Pd-catalyzed amination process.[6b] This was supported by analysis of the ee of dehalogenated alcohol **7** (entry 1, Table 1), which revealed a significant reduction in enantioselectivity, alcohol **7** being recovered in 40% ee.

As an alternative approach to circumvent the racemization process, a copper-catalyzed intramolecular etherification was considered. Such reactions have been reported in the literature, with high yields being obtained for the copper(I) chloride catalyzed etherification of aryl halides, with only minor quantities of byproducts being formed.[8]

Additionally, Buchwald et al. have reported a related intermolecular copper-catalyzed etherification with enantiomerically pure 1-phenylethanol that proceeded with retention of configuration.[9] Thus, this system was applied to the preparation of corsifuran A in order to evaluate the intramolecular variant and obtain a high yield of enantiopure compound. When heated at reflux for 24 h corsifuran A **1** was obtained in 76% yield as essentially one enantiomer, confirming that this method preserves the stereochemical integrity (Scheme 5).

Scheme 5. Corsifuran A by Copper-Catalyzed Intramolecular Etherification



Etherification reactions of this type are thought to proceed via a catalytic cycle in which the copper coordinates initially to the alkoxide before oxidative addition to the Ar−X bond. Reductive elimination then yields the desired coupled product.

In summary, we have achieved a synthesis of enantiomerically enriched corsifuran A **1** by two routes: one in low yield/high ee (5%, 100% ee, Pd route), the other in high yield and high ee (76%, 100% ee, Cu route). We have thereby established the absolute configuration of the natural product. We have also demonstrated that copper-catalyzed

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intramolecular etherifications lead to significantly higher yields and no racemization compared to their palladium counterparts.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds and X-ray data of compounds (*R*)- and (*S*)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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