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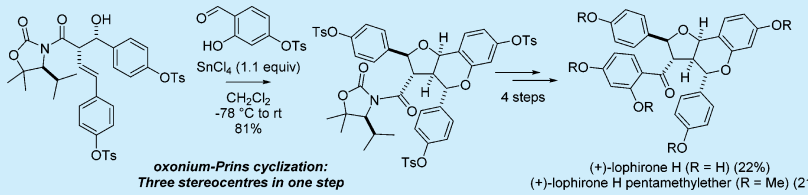
Total Synthesis of (+)-Lophirone H and Its Pentamethyl Ether Utilizing an Oxonium−Prins Cyclization

Hossay Abas,[†] Sean M. Linsdall,[†] Mathias Mamboury, Henry S. Rzepa, and Alan C. Spivey*

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, U.K.

Supporting Information



ABSTRACT: The first total synthesis of (+)-lophirone H (**1**) and its pentamethyl ether **29**, featuring an oxonium−Prins cyclization/benzylic cation trapping reaction, is described.

Lophirone H is a pentaphenolic flavonoid[1] natural product that was first isolated by Bodo and Martin et al. in 1990 from the stem bark of *Lophira lanceolate* ("African Oak", genus *Ochnaceae*)[2] collected in Cameroon.[3] It was subsequently isolated by Ranga Rao et al. from the root bark of *Ochna squarrosa* ("Yerra Juvvi", genus *Ochnaceae*).[4] The *Ochnaceae* genus generally comprises small flowering trees, the extracts of which are widely used as components of traditional medicines in the African savannah.[5] Although the specific biological activity of lophirone H has not been reported, some of its biogenetically related coisolates (i.e., lophirones A,[6] B−C,[7] D−E,[8] F−G,[3] I−J,[9] K,[10] and L−M[11]) exhibit a range of interesting activities. These include anticancer (i.e., PKC and EBV inhibition),[12] antioxidant,[13] anti-inflammatory,[4,14,15] analgesic,[4] and antibacterial/microbial[16] activity. The lophirones appear to derive from dimerization of the triphenolic natural chalcone, isoliquiritigenin (**3**),[17] which itself displays a wide range of biological activity.[18] Lophirone H is unique in having a *cis*-fused 4*H*-furo[3,2-*c*]benzopyran core (Figure 1).

The 4*H*-furo[3,2-*c*]benzopyran ring system[19−21] is also found in other bioactive natural products, notably cordigol,[22] which differs from lophirone H only by the presence of an additional phenolic hydroxyl group (Figure 1). The pterocarpans,[21,23,24] which are a large family of bioactive isoflavonoids, contain a related motif in which the tetrahydrofuran ring is replaced by a dihydrobenzofuran unit. Synthetic approaches to these and other natural tetra- and dihydrofurans have been reviewed.[25,26]

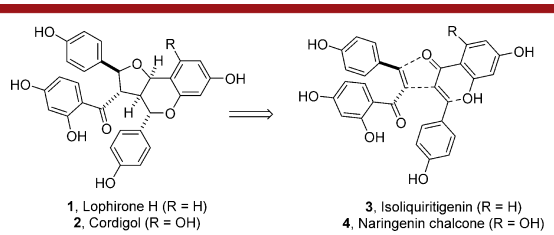


Figure 1. Putative biogenesis of lophirone H (**1**) via homodimerization of isoliquiritigenin (**3**) (and cordigol (**2**) via heterodimerization of isoliquiritigenin (**3**) and naringenin chalcone (**4**)).

Herein, we demonstrate the utility of a highly stereoselective $SnCl_4$-mediated oxonium−Prins cyclization as a key step in the preparation of (+)-lophirone H and its pentamethyl ether.

Mechanistic Considerations. In 2010, we published a diastereoselective synthesis of *cis*-fused 4*H*-furo[3,2-*c*]-benzopyran (**7**) by the Lewis acid promoted cyclocondensation of styryl homoallylic alcohol **5** with salicylaldehyde (**6**). We envisioned this reaction proceeding via a stepwise, oxonium−Prins/cation-trapping pathway involving 5-*endo*-*trig* cyclization via an envelope transition state with trapping of the resulting benzylic cation by the phenolic hydroxyl group from the most accessible face (Figure 2).[27]

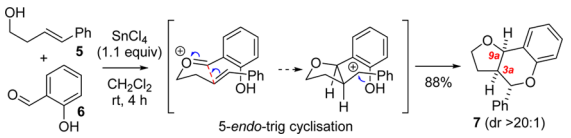


Figure 2. Our $SnCl_4$-mediated synthesis of the *cis*-fused core of lophirone H via a proposed oxonium−Prins pathway.[27]

Recently, Zhao et al. reported a related method for the synthesis of *trans*-fused 4*H*-furo[3,2-*c*]benzopyrans (e.g., **9**) by the Brønsted acid promoted cyclocondensation of homoprenyl alcohols **8** with salicaldehyde **6**.[28] They proposed a mechanism via a concerted *o*-quinonemethide formation/$[\pi_{2s} + \pi_{4s}]$-hetero-Diels−Alder (HDA) pathway (Figure 3).

Intrigued by the stereochemical divergence of these transformations, we have investigated each of them computationally and conclude that both reactions proceed via the oxonium−Prins

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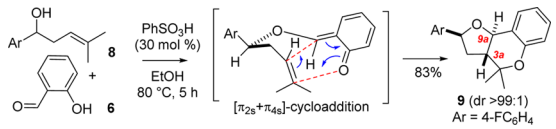


Figure 3. Zhao et al.'s acid mediated synthesis of *trans*-fused 4*H*-furo[3,2-*c*]benzopyrans via a proposed HDA pathway.[28]

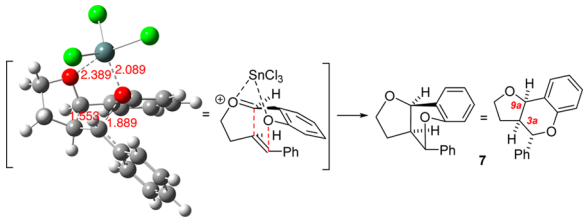


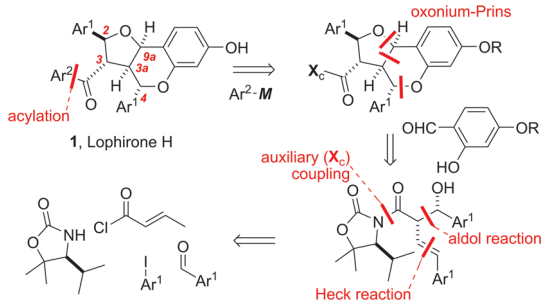
Figure 4. Computed geometry of the rate-limiting transition state for $SnCl_4$-mediated cyclization to form *cis*-fused 4*H*-furo[3,2-*c*]benzopyran **7** (bond lengths in Å).[29]

cyclocondensation pathway.[29] The $SnCl_4$-mediated cyclization selectively delivers the *cis*-3a,9a-stereochemistry required for lophirone H as the result of two oxygen atoms and the tin atom participating in the crucial 5-*endo*-*trig* cyclization transition state (Figure 4).

In the absence of these crucial interactions, the analogous proton-mediated transition state leading to the *trans* stereochemistry (Figure 3) is computed[29] as being 2.7 kcal/mol lower in free energy than the alternative *cis* stereoisomer (B3LYP +D3BJ/Def2-TZVPP/SCRF = CH_2Cl_2 model), consistent with the observations of Zhao et al.[28]

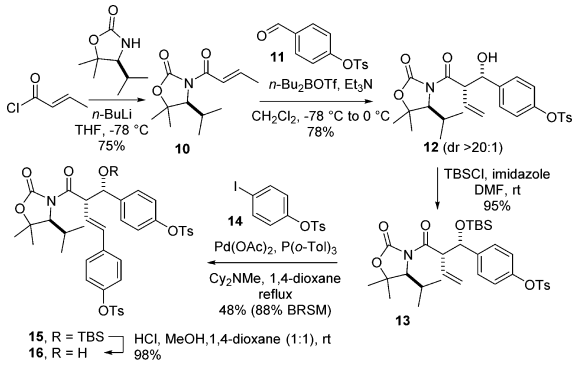
Retrosynthetic Analysis. The 4*H*-furo[3,2-*c*]benzopyran core of lophirone H contains five contiguous stereocenters. Our initial retrosynthetic design invoked the use of an Evans-type asymmetric aldol reaction to control the absolute stereochemistry of the C2 and C3 stereocenters. A Heck reaction of the aldol adduct would then set up the styrenyl motif of the homoallylic alcohol **16** for the $SnCl_4$-mediated oxonium−Prins reaction, which would control the formation of the remaining C3a, C4 and C9a stereocenters. Finally, either a Friedel−Crafts acylation (not shown) or an aryl metal-mediated acylation reaction would introduce the benzoyl unit at C3 (Scheme 1).

Scheme 1. Initial Retrosynthetic Analysis of Lophirone H



The Davies SuperQuat chiral auxiliary[30] was selected over the standard Evans auxiliary[31] for control of the asymmetric aldol reaction as this auxiliary is known to impart enhanced levels of stereoinduction and offer milder deprotection conditions.[32,33] Our choice of *p*-toluenesulfonyl (Ts) protection for the phenolic hydroxyl groups followed from the observations of Willis et al.

Scheme 2. Synthesis of Homoallylic Alcohol 16



during their synthesis of the 2,8-dioxabicyclo[4.4.0]decane skeleton of blepharocalyxin D.[34,35]

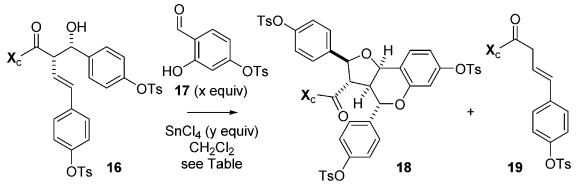
Synthesis. Enantiomerically pure enone **10** was prepared from reaction of crotonyl chloride with the Davies (*S*)-configured[35] SuperQuat chiral auxiliary in 75% yield (Scheme 2).[36]

Enone **10** was then subjected to an asymmetric aldol reaction using dibutylboron triflate to give terminal alkene **12** as a single (2*S*,3*S*) diastereoisomer in 78% yield.[37] All attempts to remove the chiral auxiliary at this stage or to perform a Heck coupling on this compound proved unsuccessful due to its tendency to undergo a facile retro-aldol reaction. Consequently, the hydroxyl group was protected as *tert*-butyldimethylsilyl (TBS) ether **13** (95%) prior to performing the Heck reaction to give styrene **15**. This reaction gave yields >80% on a small scale (<30 mg) using an aryl bromide partner, but we were unable to scale this up. On a preparative scale we employed a protocol[38] using aryl iodide **14** which furnished styrene **15** in 48% yield along with 46% unreacted starting material **13** which could be readily recycled. Acidic conditions were required for removal of the TBS group from product **15** to give alcohol **16** (98%); use of TBAF resulted in retro-aldol reaction.

We investigated various conditions to achieve an efficient oxonium−Prins reaction between alcohol **16** and aldehyde **17** (e.g., Table 1).

Using the conditions we had previously optimized,[27] the desired 4*H*-furo[3,2-*c*]benzopyran **18** was obtained in 23% yield together with 60% of alkene **19**, which results from retro-aldol reaction of alcohol **16** (Table 1, entry 1). Stability studies showed that while benzopyran **18** was stable to the reaction conditions,

Table 1. Optimization of the Oxonium−Prins Cyclization (16 → 18)



entry	*x*	*y*	conditions	yield (%) of **18** and **19**
1	1.0	1.1	rt (24 h)[a]	23, 60
2	1.4	1.2	−78 °C (4 h) → rt (24 h)[b]	67, trace
3	1.4	1.2	−78 °C (16 h) → 0 °C (9 h) → rt (10 h)[b]	81, 0

[a]No premixing; all reagents added together. [b]$SnCl_4$ and aldehyde **17** premixed for 20−30 min prior to addition of alcohol **16** at −78 °C.

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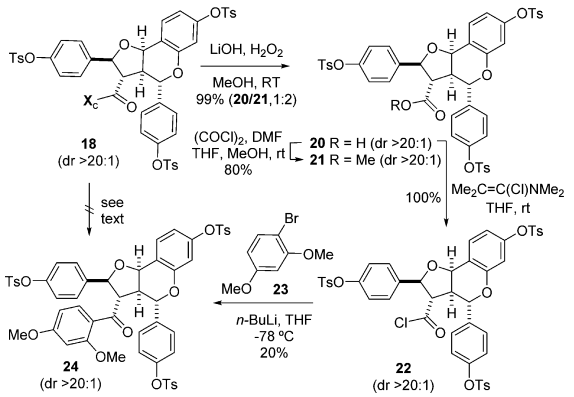
alcohol **16** decomposed readily when exposed to $SnCl_4$ at room temperature (rt). Consequently, an excess of aldehyde **17** (1.4 equiv) relative to $SnCl_4$ (1.2 equiv) was premixed at −78 °C followed by addition of alcohol **16** to minimize its exposure to $SnCl_4$. No reaction was seen at −78 °C after 4 h; however, after allowing the reaction to stir at rt for 24 h, a 67% yield of benzopyran **18** and only a trace amount of alkene **19** were isolated (Table 1, entry 2). After further optimization, it was found that allowing the reaction mixture to warm slowly to 0 °C and then stirring at rt overnight improved the yield of benzopyran **18** to 81% with no trace of alkene **19** (Table 1, entry 3).

The relative stereochemistry of oxonium−Prins product **18** was determined by analysis of its NMR spectra (see Supporting Information).

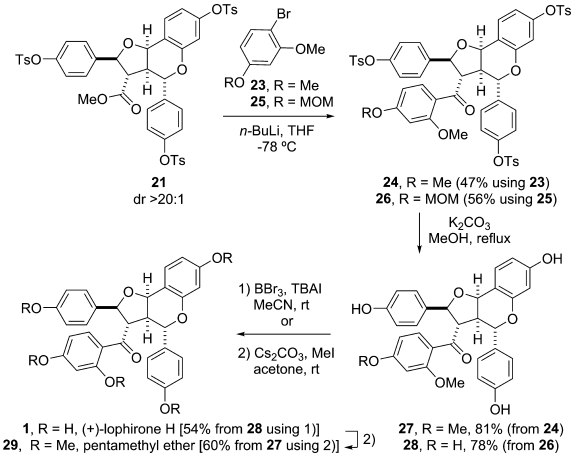
With all of the stereocenters now established, the remaining challenge was to exchange the auxiliary in compound **18** for the required resorcinol-derived ketone without epimerization at C3. Attempts to achieve this by direct reaction of compound **18** with various arylmetal species resulted in no reaction, so hydrolysis of the auxiliary was performed by stirring as a 0.01 M solution in methanol with basic aqueous hydrogen peroxide.[37,39] This yielded a ca. 1:2 mixture of the expected carboxylic acid **20** and the methyl ester **21** in a near-quantitative yield (Scheme 3).

Scheme 3. Removal of the Chiral Auxiliary and Attempted Ketone Formation



Functionalization of acid **20** was attempted before investing efforts at suppressing the ester formation. In parallel, it was found that acid **20** could be esterified in 80% yield using oxalyl chloride and methanol, thereby allowing a total yield of 93% of methyl ester **21** from oxazolidinone **18**. Acid **20** could be quantitatively converted to the corresponding acid chloride **22** using Ghosez's reagent.[40] Attempted Friedel−Crafts acylation reactions of both acid **20** and acid chloride **22** with resorcinol, 1,3-dimethoxybenzene, and 1,3-ditosyloxybenzene catalyzed by a range of Lewis acids resulted in complex inseparable mixtures of products, as did attempted Pd-catalyzed coupling between (2,4-dimethoxyphenyl)boronic acid and acid chloride **22**.[41] A range of aryl metal reagents generated from 1-bromo or 1-iodo-2,4-ditosyloxybenzene also failed to provide any ketone from acid chloride **22**. By contrast, the aryllithium species generated from 1-bromo-2,4-dimethoxybenzene **23** reacted with acid chloride **22** to provide ketone **24** in 20% yield along with numerous side products which were difficult to separate. Use of methyl ester **21** in place of the acid chloride **22** resulted in a cleaner reaction and the formation of ketone **24** in 47% yield; no *tert*-alcohol was isolated (Scheme 4).

Scheme 4. Synthesis of (+)-Lophirone H (1) and Its Pentamethyl Ether (29)



Treatment of ketone **24** with K_2CO_3 in refluxing methanol gave triphenol **27** (81% yield), which upon reaction with Cs_2CO_3 and MeI in acetone gave lophirone H pentamethyl ether **29** in 60% yield. The spectroscopic data (^1H and ^{13}C NMR, MS, IR) for this derivative matched exactly those reported by Bodo and Martin et al.[3] for the corresponding derivative of the isolated natural product. Their natural derivative had an optical rotation value $[\alpha]_D^{22}$ −47 (c = 0.4, acetone), and they did not determine its absolute configuration. Our (2*S*,3*S*,3a*S*,4*S*,9b*R*)-pentamethyl ether **29** had an optical rotation value $[\alpha]_D^{20}$ +65 (c = 0.3, acetone), indicating that natural lophirone H is the antipode of that prepared.

Next, we turned our attention to preparing lophirone H itself, which has not been characterized in the literature: neither Bodo and Martin et al.[3] nor Rao et al.[4] report its data. As we were unable to deprotect the *p*-methyl ether in aryl ketone **27** we installed a MOM ether at this position. Thus, acylation of methyl ester **21** with the MOM-protected aryl bromide **25** gave ketone **26** (56%), which upon removal of the Ts groups using K_2CO_3 in refluxing methanol, followed by a rapid acidic workup to remove the MOM group, gave tetraphenol **28** in 78% yield. Treatment of this unstable compound with BBr_3/TBAI in acetonitrile for 15 min gave (+)-lophirone H in 54% yield. More than the previous polyphenolic compounds, lophirone H proved to be exceedingly unstable and decomposition occurred while recording its ^{13}C NMR spectrum. Its complete conversion to the pentamethyl ether **29** upon treatment with Cs_2CO_3 in acetone-d_6, however, confirmed its identity.

To conclude, (−)-lophirone H (*ent*-**1**) is a highly labile pentaphenolic flavonoid natural product which has previously been characterized only as its more stable pentamethyl ether (−)-**29**. We have developed the first total synthesis of (+)-lophirone H in 9 steps and 11.5% overall yield from crotonate **10**. Our spectroscopic characterization of this material and its transformation into its pentamethyl ether (+)-**29** establishes the absolute configuration of the natural product for the first time: (−)-(2*R*,3*R*,3a*R*,4*R*,9b*S*)-lophirone H (i.e., the antipode of that depicted in Figure 1). The synthesis features an oxonium−Prins cyclization/benzylic cation-trapping reaction which sets up three of the five contiguous stereocenters of the *cis*-fused 4*H*-furo[3,2-*c*]benzopyran core. DFT calculations have illuminated the intimate role of $SnCl_4$ in mediating this highly diastereoselective ring-forming reaction, which we are currently

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exploring for the preparation of other tetrahydrofuran-containing natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00642.

Full experimental details, copies of NMR spectra for all new compounds, and links to the DFT calculations and NMR MNova files (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.c.spivey@imperial.ac.uk.

ORCID

Alan C. Spivey: 0000-0001-5114-490X

Author Contributions

†H.A. and S.M.L. contributed equally.

Notes

The authors declare no competing financial interest.

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(36) At the outset, the choice of enantiomer was arbitrary since the absolute configuration of natural (−)-lophirone H was unknown.

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