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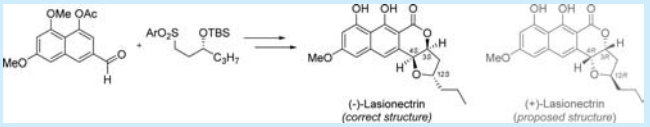
Total Synthesis and Structural Confirmation of the Antimalarial Naphthopyrone Lasionectrin

Vincent L. Poral, Daniel P. Furkert,* and Margaret A. Brimble*

School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland 1010, New Zealand

Supporting Information

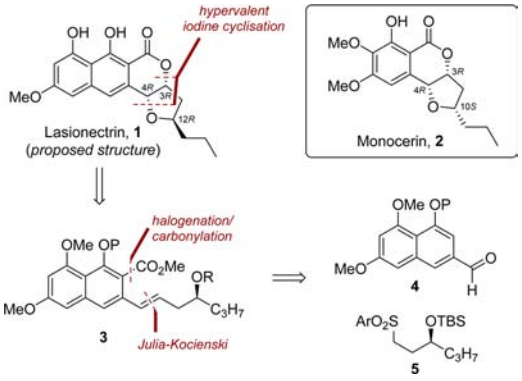
ABSTRACT: The total synthesis of lasionectrin, a naphthopyrone metabolite of an *Acremonium*-like fungus collected in Equatorial Guinea, is reported. Divergent access to four stereoisomers confirmed the natural product to be the enantiomer of the originally proposed structure. Highlights of the synthesis include ring opening of a chiral oxetane using a thiol, a highly *E*-selective Julia–Kocienski olefination, and a modified Sharpless/Upjohn dihydroxylation. Palladium-catalyzed carbonylative lactonization was used to assemble the fused naphthopyrone ring system.



Lasionectrin (**1**) is a tetracyclic naphthopyrone natural product that was isolated in 2012 from fermentation of the fungus *Lasionectria* (F-176,994).[1] The *Acremonium*-like fungus was colleced from leaf litter in Equatorial Guinea as part of a screening program for fungal metabolites inspired by genomic sequencing of species from the order Hypocreales. Lasionectrin was isolated by fractionation of extracts exhibiting in vitro activity against *Plasmodium falciparum* Pf3D7. The development of novel malaria therapeutics is a pressing global issue, with resistance established against the most readily available drug, chloroquine, and emerging against frontline treatments such as artemesinin. Lasionectrin can be considered a benzannulated congener of the monocerin (**2**) family of benzopyrones, which are active against multidrug-resistant *P. falciparum* K1.[2] The all-*R* 3,4-*cis*-4,12-*trans* stereochemistry was proposed for **1** on the basis of the 3*R*,4*R* configuration of **2** and ^{1}H NMR NOESY correlations.[1] No synthetic work toward lasionectrin has been reported to date.

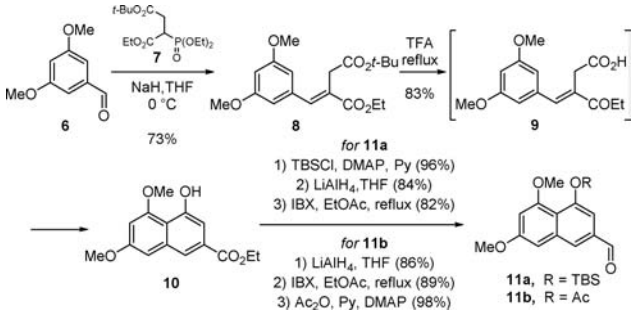
Our initial strategy for the synthesis of **1** (Scheme 1) hinged on the formation of the bicyclic core from ester **3** using hypervalent iodine reagents, inspired by recent work toward the monocerin ring system.[3] Ester **3** would be available from regioselective halogenation and palladium-catalyzed carbonylation of the naphthalene core, which could be accessed by Julia–Kocienski olefination of suitably substituted aldehyde **4** and sulfone **5**.

Scheme 1. Initial Retrosynthetic Analysis of Lasionectrin (1)



The synthesis of the naphthaldehyde fragment (Scheme 2) began from Horner–Wadsworth–Emmons coupling of commercially available 3,5-dimethoxybenzaldehyde (**6**) with diester phosphonate **7**[4] to afford cinnamic ester **8** in 73% yield.[5] Exposure of **8** to trifluoroacetic acid in dichloromethane delivered the expected carboxylic acid **9** by deprotection of the *tert*-butyl ester, along with a minor byproduct identified as the fully cyclized naphthalene **10**.[6] The reaction was readily optimized to favor this cyclization product, directly providing the desired naphthol **10** in 83% yield, a small improvement over previously reported two-step sequences for the synthesis of similar compounds.[7] Ester **10** was then converted to two potential Julia–Kocienski coupling partners, TBS-protected naphthaldehyde **11a** and the corresponding acetate **11b**, using standard transformations.

Scheme 2. Synthesis of Naphthaldehydes 11a and 11b



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The preparation of the requisite sulfone **5** (Scheme 3) commenced with ring expansion of enantiopure (*S*)-2-propyloxirane (**12**)[8] to obtain oxetane **13** using trimethylsulfoxonium iodide in the presence of *tert*-butoxide.[9] Ring opening was then effected with phenyltetrazole thiol **14** in the presence of lithium bromide to give chiral alcohol **15** (>98% *ee*, HPLC). Silyl protection and subsequent oxidation of the sulfide then afforded the desired sulfone **5** in excellent yield over the two steps. Attempts to effect Julia–Kocienski coupling of naphthaldehyde **11a** and sulfone *rac*-**5**[10] using standard conditions (KHMDS or LHMDS as the base, DME or THF as the solvent) proved largely unsuccessful (Table 1, entries 1 and 2). Lithium bromide or chloride was found to be essential to obtain useful yields of the olefin. These conditions additionally conferred high selectivity for the desired *E* isomer (Table 1, entries 3 and 4).

Scheme 3. Synthesis of Sulfone 5 via Enantiopure Oxetane 13

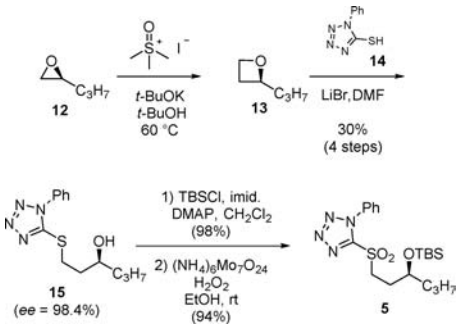
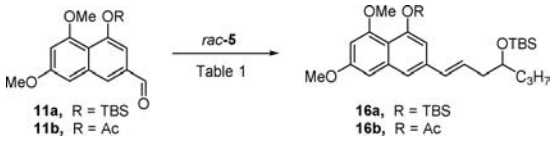


Table 1. Julia–Kocienski Coupling of Fragments 11 and 5



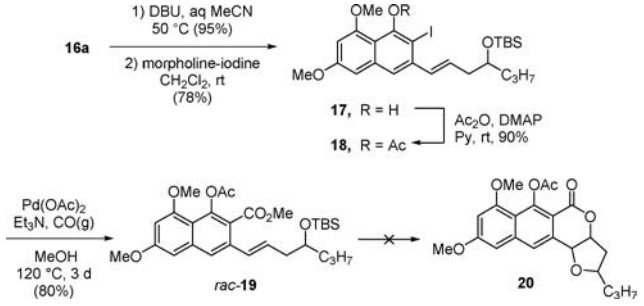
entry	11	conditions	additive	yield (%)	*E*:*Z*
1[a]	**11a**	KHMDS, DME	–	0	–
2	**11a**	LHMDS, THF	–	13	94:6
3	**11a**	LHMDS, THF	LiBr	71	94:6
4	**11a**	LHMDS, DME	LiBr	69	90:10
5	**11a**	KMHDS, THF	LiBr	60	98:2
6	**11a**	**KHMDS, THF**	**LiCl**	**94**	**98:2**
7	**11b**	KHMDS, THF	LiCl	75	98:2
8[b]	**11b**	**KHMDS, THF**	**LiCl**	**98**	**98:2**

[a]Aldehyde **11a** or **11b** was added to the base + sulfone **5** mixture at −78 °C, and the resulting mixture was then warmed to rt overnight. [b]Precooled base + sulfone **5** mixture was added to aldehyde **11a** or **11b** and LiCl at −20 °C, and the resulting mixture was then warmed to 0 °C after 2 h.

Optimization of the base and solvent finally delivered the desired TBS-protected product in 94% yield with excellent *E* selectivity (Table 1, entry 6). Later in our investigation it was found that an acetate group on the naphthol delivered greater synthetic efficiency, so the olefination was also performed on naphthaldehyde **11b**, affording a 75% yield of the corresponding acetate-protected product **16b** (Table 1, entry 7). Pleasingly, reversing the order of addition and altering the reaction temperature from −78 to −20 °C improved the yield to nearly quantitative with excellent *E* selectivity (Table 1, entry 8).

In order to elaborate olefin **16a** into a suitable substrate for the proposed hypervalent iodine cyclization, the phenolic TBS ether was selectively deprotected using DBU in aqueous acetonitrile (Scheme 4).[11] Attempts to halogenate the resultant naphthol **17** using pyridinium tribromide resulted in only undesired *para*- or dihalogenation. Pleasingly, the use of morpholine–iodine complex[12] selectively afforded the desired *ortho* product **17** in high yield. Because of the instability of iodide **17**, it was immediately protected as the acetate **18**. Attempts to effect carbonylation of the iodide to give ester **19** were unsuccessful using a variety of methods,[13] with protodehalogenation predominantly occurring. Eventually, carbonylation was successfully achieved in a sealed tube at 120 °C under a carbon monoxide atmosphere in the presence of palladium acetate and triethylamine.[14]

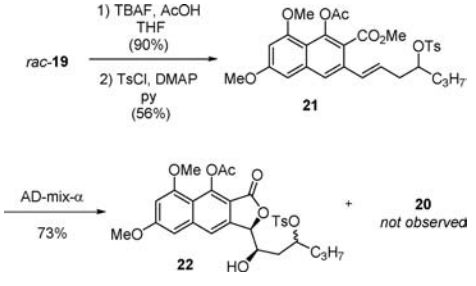
Scheme 4. Unsuccessful Hypervalent Iodine Cyclization



With the desired ester *rac*-**19** in hand, the key hypervalent iodine cyclization was investigated. Unfortunately, despite the precedent for the monocerin system, all attempts to form fused naphthopyran lactone **20** using iodobenzene diacetate (PIDA) or iodobenzene bistrifluoroacetate (PIFA) under a wide variety of conditions resulted only in decomposition. Although disappointing, this result served to highlight the electronic differences between the benzopyran ring system of monocerin and the naphthopyran system of lasionectrin, which are likely responsible for the contrasting reactivities observed.

Because of this setback, an alternative synthetic approach was required in order to install the fused naphthopyrone ring system. Returning to ester **19**, a dihydroxylation–lactonization–S_N2 substitution sequence was briefly investigated (Scheme 5). The secondary silyl ether was first removed using TBAF buffered with acetic acid, and the resulting free alcohol was converted to the corresponding tosylate **21**.

Scheme 5. Kinetic Preference for Five-Membered Lactone Formation[a]



[a]Bold bonds indicate *cis* relative stereochemistry only.

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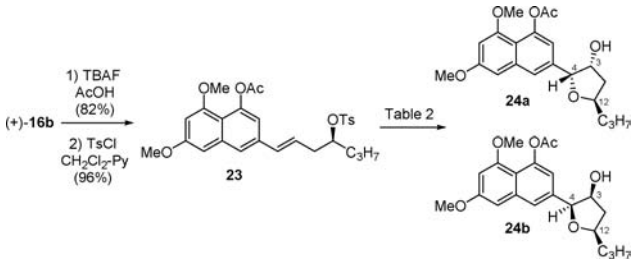
However, Sharpless asymmetric dihydroxylation of the olefin delivered only lactone **22**, indicating that the expected kinetic preference for five-membered lactonization clearly ruled out the possibility of initial tetrahydropyranone formation followed by intramolecular S_N2 substitution of the tosylate by the benzylic alcohol.

This result indicated that the tetrahydrofuran ring would need to be installed before introduction of the six-membered lactone. Accordingly, our strategy was readjusted to form the tetrahydrofuran ring via a dihydroxylation−intramolecular S_N2 sequence, which would then be followed by palladium-catalyzed carbonylation/lactonization. Our revised route (see Scheme 6) began from acetate **16b**, which was directly accessed in the Julia−Kocienski coupling (see Table 1). Removal of the TBS group revealed the secondary alcohol, which was converted to the tosylate using a mixture of pyridine and dichloromethane. This solvent mixture was important, as the use of neat pyridine resulted in substantial formation of the corresponding chloride, presumably via nucleophilic substitution of the initially formed tosylate.

With alkene **23** in hand, the dihydroxylation−S_N2 cyclization sequence was investigated. Sharpless conditions proved unsuccessful, giving either no conversion or decomposition of the starting material (Table 2, entries 1 and 2). The use of

Table 2. Dihydroxylation of Tosylate 23



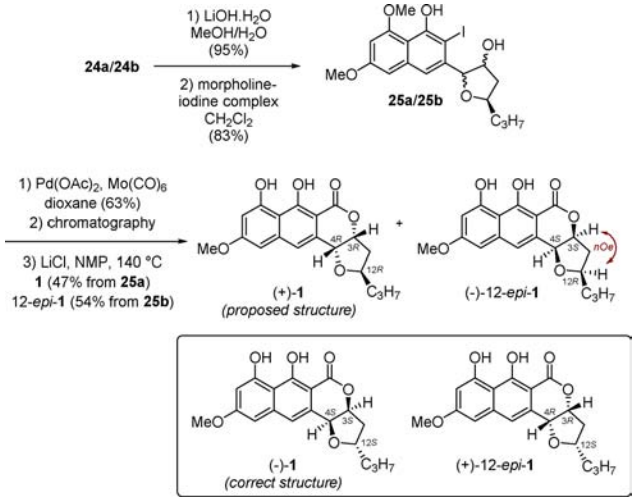
entry	conditions	temp	yield (%)	24a:24b
1	Sharpless[a]	0 to rt	0	–[c]
2	Sharpless[a]	55 °C	0	–[d]
3	Upjohn[b]	rt	97	1:1
4	**Upjohn[b] with $(DHQ)_2PHAL$**	**rt**	**68**	**4:1**
5	**Upjohn[b] with $(DHQD)_2PHAL$**	**0 °C**	**68**	**1:4**

[a]Sharpless: AD-mix-α, $MeSO_2NH_2$ (1 equiv), *t*-BuOH/H_2O (1:1). [b]Upjohn: OsO_4 (5 mol %), NMO (2.1 equiv), acetone/H_2O (1:1), ligand (10 mol %). [c]No reaction. [d]Decomposed.

Upjohn conditions effected a complete turnaround, affording an inseparable mixture of the cyclized tetrahydrofurans **24a** and **24b**, where intramolecular displacement of the tosyl group occurred spontaneously following dihydroxylation, in nearly quantitative yield (Table 2, entry 3). Useful selectivity (**24a**:**24b** = 4:1) was achieved by the inclusion of the chiral Sharpless ligand $(DHQ)_2PHAL$ in the Upjohn dihydroxylation conditions (Table 2, entry 4), and the selectivity could be readily reversed (**24a**:**24b** = 1:4) using the pseudoenantiomeric ligand $(DHQD)_2PHAL$.

Removal of the acetate and *ortho* iodination of the free phenol using the morpholine−iodine complex conditions (Scheme 6) gave a mixture of the iodides **25a** and **25b** in excellent yield. Initial attempts to form the fused pyranofuran by carbonylation of the iodide followed by intramolecular cyclization using the previously successful conditions resulted predominantly in protodehalogenation. After some experimentation, the carbonylation was successfully achieved in the presence of palladium diacetate using molybdenum hexacarbonyl as the in situ source of carbon monoxide.[15] Concomitant lactonization led to the formation of a mixture of the fully cyclized naphthopyran 4,12-*trans* and 4,12-*cis* diastereoisomers in 63% yield, which were chromatographically separable at this point. Several reagents for selective demethylation *peri* to the free phenol were unsuccessful (BBr_3,[16] BCl_3,[17] EtSH[18]), but heating the individual methyl ethers at 160 °C in NMP in the presence of lithium chloride[19] successfully afforded both the natural product target lasionectrin (**1**) as a coloress solid and the 4,12-*cis* diastereoisomer (12-*epi*-**1**).

Scheme 6. Successful Lasionectrin Endgame via Carbonylative Lactonization



Comparison of the ^1H and ^{13}C NMR spectra of synthetic and natural **1** showed excellent agreement in all respects. In particular, the three methine protons at the ring junctions, namely, H3 (5.24 ppm), H4 (4.93 ppm), and H12 (4.33 ppm), resonated at identical chemical shifts in the two spectra. In contrast, differing shifts were observed for the corresponding protons in the synthetic 4,12-*cis* diastereoisomer 12-*epi*-**1**: H3 (5.10 ppm), H4 (4.66 ppm), and H12 (4.17 ppm). A NOESY correlation between methines H3 and H12 in 12-*epi*-**1** that is absent in **1** served to confirm the original assignment of the relative stereochemistry at C3, C4, and C12. The measured specific rotation of +148 (*c* 0.17, MeOH), however, was in disagreement with the value reported at the time of isolation [−43.8 (*c* 0.17, MeOH)]. To unambiguously confirm the structure of the natural product, (−)-**1**, *rac*-**1**, (+)-12-*epi*-**1**, and *rac*-12-*epi*-**1** (box in Scheme 6) were additionally prepared beginning from (2*R*)-**12** and *rac*-**12**, respectively. Chiral HPLC (Chiralpak AD-H, ^{i}PrOH/hexane) established that synthetic (+)-**1** (*ee* = 97%) and (−)-**1** (*ee* = 98%) were essentially enantiopure and exhibited specific rotations of +148 (*c* 0.17, MeOH) and −138 (*c* 0.16, MeOH), respectively. Similar purities and specific rotations were also established for the 4,12-*cis* diastereomers (−)-12-*epi*-**1** [*ee* = 97%; −192 (*c* 0.13, $CHCl_3$)] and (+)-12-*epi*-**1** [*ee* = 99%; +197 (*c* 0.13, $CHCl_3$)]. Taken together, these data indicate that the relative stereochemistry of C12 with respect to C3 and C4 is the key determinant of the specific rotation in these systems and that lasionectrin (−)-**1** is the antipode of the structure initially reported by Reyes et al.

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In summary, the first total synthesis of the natural product lasionectrin (**1**) has been achieved. The stereochemistry at C12 was installed by ring opening of an enantiopure oxetane, and the two key structural components were united using a highly *E*-selective Julia−Kocienski olefination. After hypervalent iodine cyclization proved unsuccessful, assembly of the target structure was achieved through a modified Sharpless/Upjohn dihydroxylation followed by an S_N2 cyclization/carbonylative lactonization sequence. The synthesis provided convenient access to the lasionectrin diastereomers (+)-12-*epi*-**1** and (−)-12-*epi*-**1** for stereochemical elucidation and will enable subsequent comparative investigation of their biological activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03202.

Experimental procedures (PDF)

Spectra and chiral HPLC traces for **1**, 12-*epi*-**1**, and **26** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*d.furkert@auckland.ac.nz

*m.brimble@auckland.ac.nz

Notes

The authors declare no competing financial interest.

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