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Synthesis and Absolute Stereochemistry of Thysanone[1]

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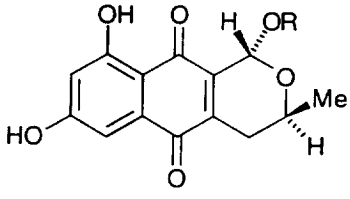
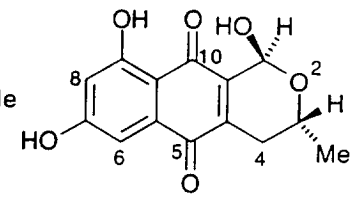
Abstract: The structure and absolute stereochemistry of thysanone 3 , a fungal benzoisochromanquinone with potent human rhinovirus 3C-protease inhibitory activity, is established by the total synthesis of its antipode 1 from (S)-propylene oxide.

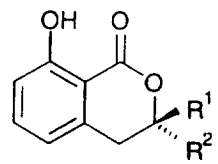
Thysanone, $[\alpha]_D$ +29 (*c*, 1.62 in MeOH), is a yellow crystalline benzoisochromanquinone that was isolated from solid state fermentations of the fungus *Thysanophora penicilloides* by workers at Merck Sharp and Dohme during the screening of microbial extracts for lead compounds aimed at the eventual control or cure of the common cold.[2] Thysanone shows potent activity (IC_{50} of 13 μg/ml) against HRV 3C-protease, one of a the family of picornaviruses that are responsible, *inter alia*, for human diseases such as polio and hepatitis A.[3] The structure **1** for thysanone was proposed by Singh *et al.* from spectroscopic data, and the relative stereochemistry between the C-1 and C-3 stereogenic centres (but *not* their absolute configuration) was determined from a single crystal X-ray analysis of the methyl acetal **2**.[2] The acetal **2** was itself prepared from thysanone by treatment with methanol in the presence of concentrated sulfuric acid. To date, there has been no report in the literature of the total synthesis of thysanone and, hitherto, its absolute configuration has remained unknown. We report here the synthesis of (1*R*,3*S*)-thysanone **1** beginning from (*S*)-propylene oxide, which establishes the stereochemistry of the natural product as (1*S*,3*R*) as shown in formula **3**.



1 R = H
2 R = Me



3



4 R^1 = Me, R^2 = H
5 R^1 = H, R^2 = Me

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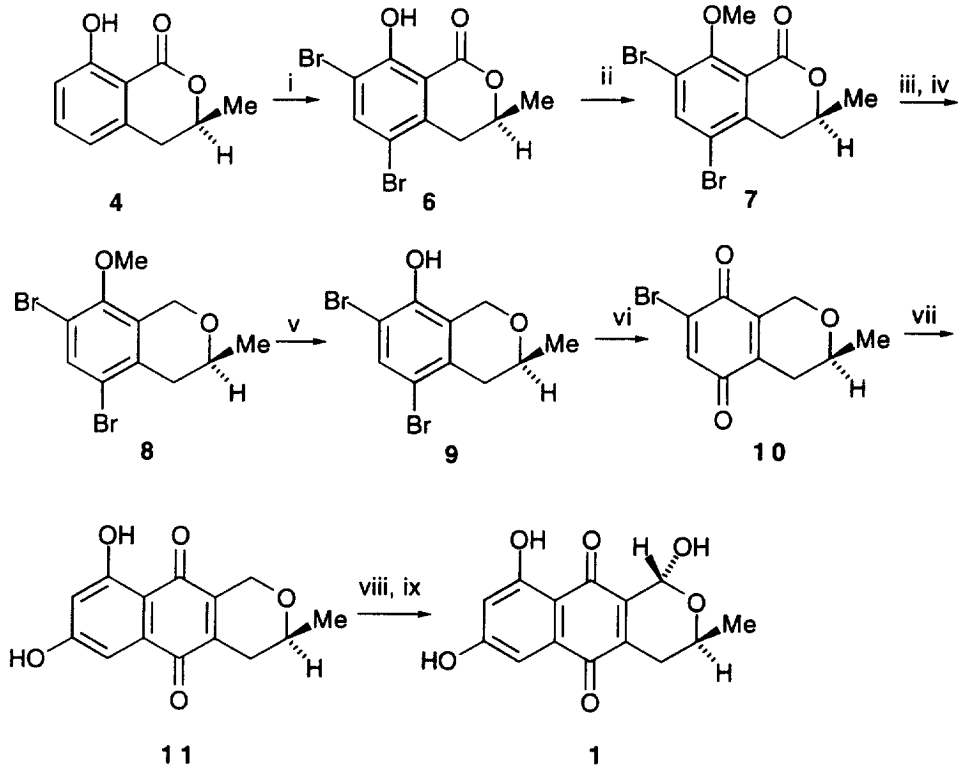
We recently reported the synthesis of both enantiomers, **4** and **5**, of the natural product mellein beginning from the corresponding stereoisomers of propylene oxide.[4] For the synthesis of (1*R*,3*S*)-thysanone **1** (Scheme 1) descibed here, (*S*)-mellein **4** serves as the starting point. Thus, (*S*)-mellein **4**, $[\alpha]_D$ +101 (*c*, 0.67), was first brominated with two equivalents of *N*-bromosuccinimide in the dark and the resulting dibromophenol **6**, $[\alpha]_D$ +80.4 (*c*, 1.01), was methylated by using dimethyl sulfate and potassium carbonate in acetone at reflux. The benzoisocoumarin **7**, $[\alpha]_D$ +147 (*c*, 1.17), was reduced first to the corresponding lactol with DIBAL-H and then to the benzopyran **8**, $[\alpha]_D$ +85.8 (*c*, 1.00), with sodium borohydride in the presence of trifluoroacetic acid. Cleavage of the ether group in the pyran **8** by using benzylselenide anion and subsequent oxidation of the resulting bromophenol **9**, $[\alpha]_D$ +101 (*c*, 1.00), with ceric ammonium nitrate afforded the unique chiral bromopyranobenzoquinone **10**, $[\alpha]_D$ +195 (*c*, 0.64). Diels-Alder cycloaddition of the quinone **10** and



Scheme 1. *Reagents:* i, NBS (2 equiv.), DMF, r.t., dark, 16 h, 91% yield; ii, Me_2SO_4, K_2CO_3, acetone, reflux, 1 h, 98% yield; iii, DIBAL-H, toluene -70°C; iv, $NaBH_4$, TFA, THF, 30°C, 1h, 90% yield over 2 steps; v, $(PhCH_2Se)_2$, $NaBH_4$, DMF, reflux, 1 h, 86% yield; vi, CAN, MeCN, H_2O, r.t., 0.5 h, 82% yield; vii, 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene, toluene, reflux, 3 h, 73% yield; viii, Br_2 (1 equiv.), CCl_4, hv, 0.5 h; ix, THF, H_2O, r.t., 1 h, 85% yield over 2 steps.

1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene in toluene at reflux during 3 h gave the novel naphthoquinone **11**, $[\alpha]_D$ +160 (*c*, 0.28), in 73% yield. Benzylic bromination of **11** by using molecular bromine followed by *in situ* treatment of the intermediate bromide with aqueous tetrahydrofuran gave (1*R*,3*S*)-thysanone **1**, m.p. 197-198°C (dec.) [lit.[2] 205-206°C (dec.)], $[\alpha]_D$ -29.7 (*c*, 0.002, MeOH), in 35% yield over 7 steps from (*S*)-mellein **4**. The ^1H and ^{13}C NMR data for the synthetic sample of (1*R*,3*S*)-thysanone **1**[5] are collected alongside the data published for the natural product[2] in Table 1; when these are compared it becomes clear that both natural and synthetic molecules possess the same substitution pattern and *trans* relative configuration in the lactol ring. The absolute configuration of the synthetic compound **1** must be (1*R*,3*S*) by

Table 1. ^1H and ^{13}C NMR data [chemical shift (δ), multiplicity and coupling constant (*J*/Hz)] for natural[2] and synthetic thysanone (400 MHz for ^1H; 100 MHz for ^{13}C; d_6-acetone).

	Thysanone from *T. penicilloides*[2]		Synthetic thysanone **1**	
Position	δ_H	δ_C	δ_H	δ_C
1	5.84, s	86.5	5.90, s	86.6
3	4.21, m	62.0	4.30, m	62.1
4 (H_{ax})	2.05, dd, 19.4, 11.0	29.9	2.10, dd, 19.4, 11.3	30.0
4 (H_{eq})	2.62, dd, 19.4, 3.5		2.65, dd, 19.4, 3.5	
4a	-	144.0	-	144.1
5	-	184.2	-	184.4
5a	-	134.6	-	134.7
6	6.97, d, 2.3	108.7	7.02, d, 2.4	108.8
7	-	165.2	-	165.5
8	6.53, d, 2.3	108.4	6.57, d, 2.4	108.4
9	-	165.1	-	165.2
9a	-	109.5	-	109.5
10	-	187.3	-	187.4
10a	-	142.0	-	142.2
3-Me	1.25, d, 6.3	21.4	1.28, d, 6.2	21.3
9-OH	12.19, s	-	12.23, s	-

virtue of its derivation from (*S*)-propylene oxide and subsequent chemistry (Scheme 1) that does not involve any configurational changes. Comparison of the chiroptical data obtained for the synthetic material (cited above) with the data published for the natural product[6] establishes that the two substances are enantiomers. Consequently, the absolute configuration of thysanone as it occurs in *Thysanophora penicilloides* must be (1*S*,3*R*) as shown in structure **3**.

This is the first report of the total synthesis of thysanone. That the method leads to optically pure material allows, for the first time, the determination of the absolute configuration of the natural product. The method described here is applicable in principle to the synthesis of analogues of the natural product with the potential for modified biological profiles.

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References and Footnotes

1. Part 53 in the series 'Pigments of Fungi'. For Part 52 see *Aust. J. Chem.*, 1999, in press.
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3. J. M. Gwaltney Jr., in "Viral Infection of Man: Epidermicology and Control" 2nd Edtn, 1982, E. A. Evans (Ed.), Plenum Publishing Co., New York, pp. 491-517.
4. C. Dimitriadis, M. Gill and M. F. Harte, *Tetrahedron: Asymmetry*, 1997, **8**, 2153.
5. ^{1}H and ^{13}C NMR data for **1** were recorded on a JEOL JNM GX-400 spectrometer. Assignments in the spectra of the synthetic compound were confirmed by the results of HMQC and HMBC experiments.
6. Natural thysanone is reported to show $[\alpha]_D$ +29 (*c*, 1.65 in MeOH).[2] We have been unable to obtain consistent readings at concentrations of this magnitude due, presumably, to insufficient transmission through the yellow solution. Nevertheless, the fluctuating readings were always negative. At higher dilution (*c* 0.002) the fluctuations decreased significantly and an average $[\alpha]_D$ value of -29.7 was recorded. Unfortunately, no figure is quoted in the literature for the specific rotation of the methyl acetal **2**. In our hands, treatment of the synthetic quinone **1** with acidic methanol gave the acetal **2** as yellow needles from methanol, m.p. 202-205°C, $[\alpha]_D$ -93.6 (*c*, 0.002 in MeOH). The optical rotation of the acetal **2** is also very sensitive to concentration changes. The ^{1}H NMR spectrum of the acetal **2** obtained by us agrees well with the published data for the naturally derived methyl acetal.[2]