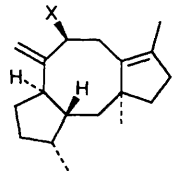
Total Synthesis of Optically Active Sordaricin Methyl Ester and its Δ^2-Derivative†

Nobuo Kato,*[a] Shigenori Kusakabe,[b] Xue Wu,[a] Masashi Kamitamari[b] and Hitoshi Takeshita*[a]

[a] *Institute of Advanced Material Study, 86, Kyushu University, Kasuga-koen, Kasuga, Fukuoka 816, Japan*
[b] *Graduate School of Engineering Sciences, 39, Kyushu University, Kasuga-koen, Kasuga, Fukuoka 816, Japan*

Optically active sordaricin methyl ester and its Δ^2-derivative have been synthesised *via* intramolecular Diels–Alder reaction of appropriate precursors derived from dimeric condensates of iridoid synthons for the first time.

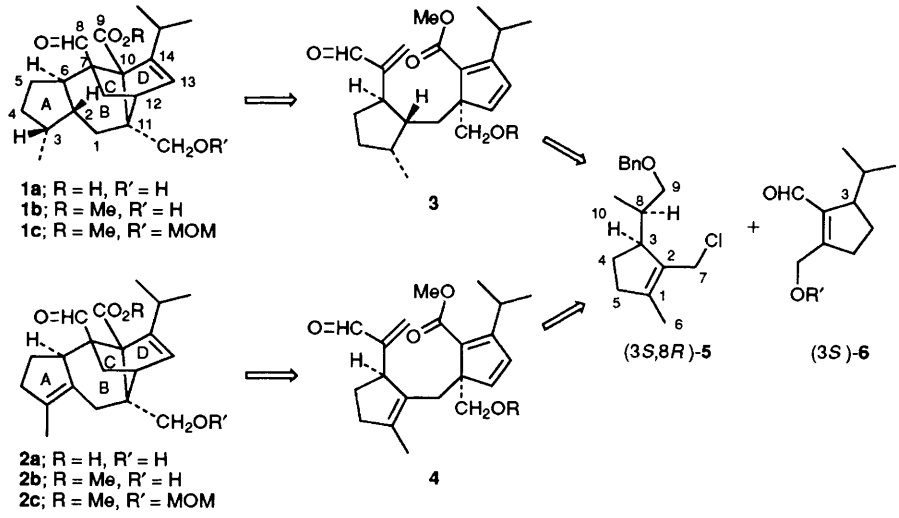
Sordaricin **1** is the aglycon of sordarin, an antibiotic isolated from *Sordaria araneosa*,[1] and its carbon skeleton has been verified as being biosynthesised *via* intramolecular Diels–Alder reaction of two electron-deficient diene and dienophile moieties, generated from congeners, cycloaraneosene **A** and



A; X = H
B; X = OH

Fig. 1

† This work was presented at the 36th Symposium of Terpenes, Essential Oils, and Aromatic Compounds, November, 1992, (Nishinomiya, Hyogo), Abstract Paper, pp. 90–92.



Scheme 1

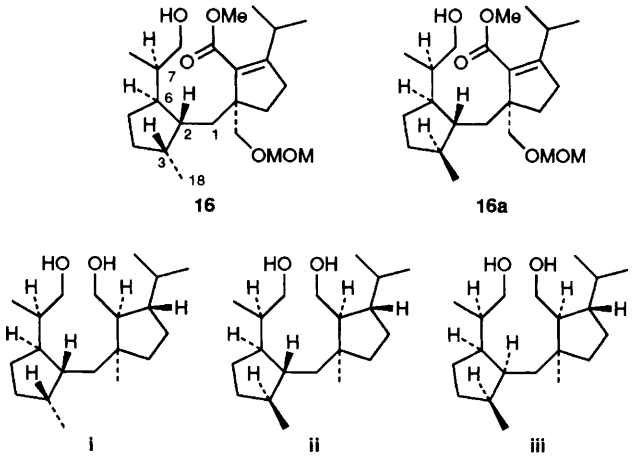


Fig. 2

'hydroxycycloaraneosene' **B**;[2] the total synthesis of **B**,[3] as well as **A**,[4] led to revision of the structure of **B** from that originally proposed.

Construction of the tetracyclic framework of **1** has already been reported by two groups *via* the intramolecular Diels–Alder reaction with simpler derivatives.[5,6]

Based on a retrosynthesis outlined in Scheme 1, we have now completed the first total synthesis of sordaricin methyl ester **1b** and its Δ^2-dehydro derivative **2c** *via* an intramolecular Diels–Alder reaction of B-secocycloaraneosane derivatives **3** and **4**, whose first step of preparation was the condensation of two optically active iridoid synthons **5** and **6**.

At first, the stereochemically more simple compound, **2b**, was selected as the target molecule. The starting iridoids, the optically active (3*S*,8*R*)-9-benzyloxy-7-chloroirid-1-ene **5**[7] and (3*S*)-6-methoxy-1-iriden-7-al **6**‡ were condensed with $CrCl_2$[8] in dimethylformamide (DMF) to obtain a condensate **7** in 83% yield. Instead of the thermally stable trimethylsilyl (TMS) group used in our previous papers, the methyl ether **8** was selected as the protective group for the secondary alcohols for a convenient transformation to the methoxycarbonyl group.

The Cope rearrangement occurred smoothly at 200 °C *via* a 'boat-transition state'[7] to yield a methoxyethene **9**, which was then subjected to singlet-oxygen oxidation;[9] AcCl-promoted rearrangement of the resultant methoxylated allylhydroperoxy group gave the α,β-unsaturated ester group **10**. The benzyloxy group of **10** was hydrogenolysed with $Pd(OH)_2$[10] to give alcohol **11** and reprotected with the *tert*-butyldimethylsilyl (TBDMS) group to give **12**. Then, **12** was converted into a dehydro derivative **13** having a cyclopentadiene group by means of MoO_5-mediated oxidation[11] and successive dehydration. The silyl ether of **13** was then oxidized to give aldehyde **14** *via* deprotection of silyl ether and Swern's oxidation. Its enolate, generated by treatment with $Li(TMS)_2N$,[12] was trapped with TMSCl to form a silyloxyethene **15**. The $Pd(OAc)_2$-oxidation[7,13] of **15** yielded the desired α,β-unsaturated aldehyde **4**. Spontaneous Diels–Alder reaction of **4** by standing at room temperature for 24 h afforded a tetracyclic compound, **2c**, m.p. 99.5–101 °C, in 66% yield. With this successful Diels–Alder reaction of a model system, we turned our attention to the synthesis of **1**.

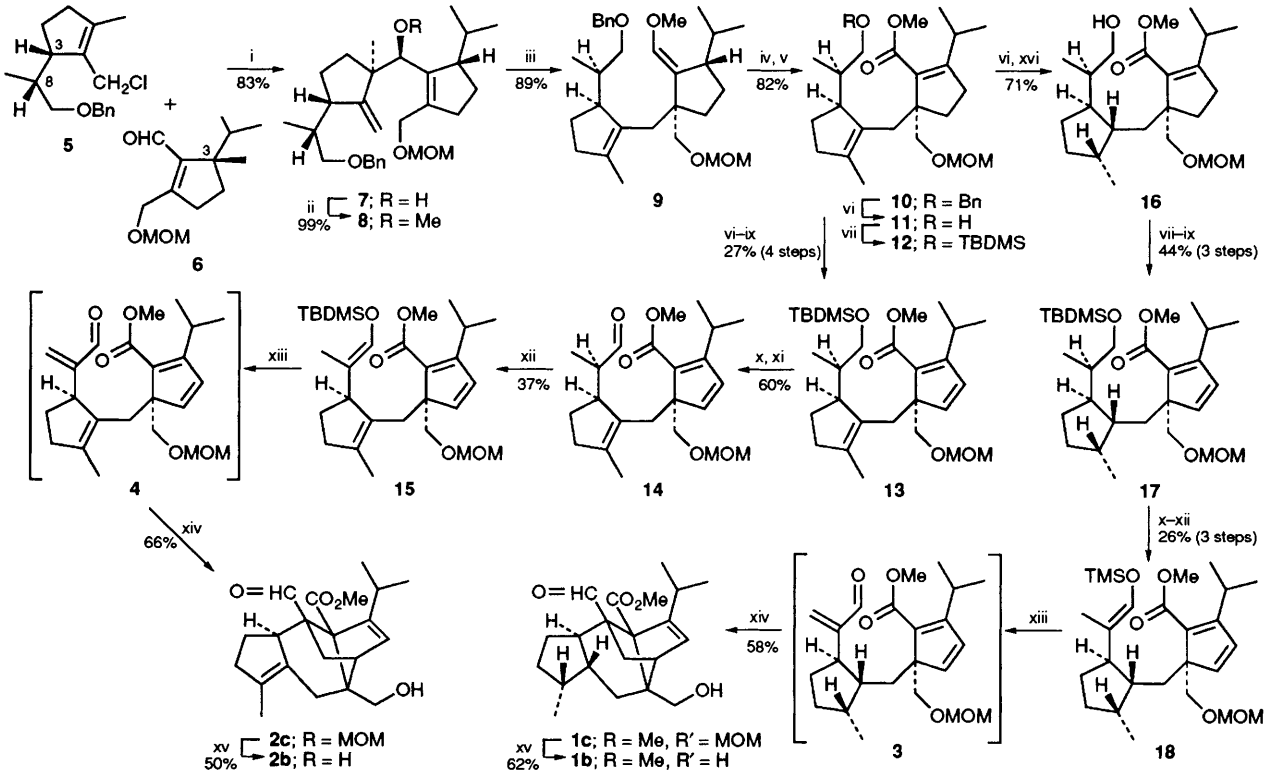
For the synthesis of **1**, the tetrasubstituted double bond in the D-ring needs to be reduced after the Cope rearrangement step. However, the previously successful method, an intramolecular proton-transferred metal reduction,[4,14] was not applicable owing to the presence of an α,β-unsaturated ester group in **11**. Thus, hydrogenation of **11** was investigated intensively. Among several catalysts examined, iridium black catalyst[15] gave the dihydro derivative **16** with a good stereoselectivity.§

The stereostructure of **16**¶ was confirmed by ^{13}C NMR comparisons with reference compounds, **i** [^{13}C NMR ($CDCl_3$) δ 37.4 (C-7), 32.5 (C-1), 41.7 (C-2), 47.0 (C-6), 36.8 (C-3) and 15.5 (C-16)], **ii** [^{13}C NMR ($CDCl_3$) δ 40.1 (C-7), 43.0 (C-1), 45.9 (C-2), 52.4 (C-6), 41.0 (C-3) and 21.4 (C-16)] and **iii** [^{13}C NMR ($CDCl_3$) δ 35.0 (C-7), 26.5 (C-1), 40.2 (C-2), 50.9 (C-6), 39.1 (C-3) and 16.9 (C-16)], prepared during our total

‡ **6** was prepared from (3*S*)-1-iriden-7-al.[6] details of this derivation will be reported in a full paper.

§ With other catalysts, *e.g.* $Pd(OH)_2/C$ and PtO_2, '*trans*'-reduction to give **16a** occurred to a considerable extent.

¶ The numbering on the carbon framework is based on the biogenetical isoprene rule. Therefore, it is different from that defined in the original paper reporting **1**.[1,2]



Scheme 2 *Reagents and conditions*: i, $CrCl_3$–lithium aluminium hydride, DMF; ii, NaH, MeI; iii, xylene, 200 °C; iv, $^1O_2$; v, AcCl–pyridine (py); vi, H_2–$Pd(OH)_2$; vii, imidazole, TBDMSCl; viii, $(TMS)_2NLi$; MoO_5·py complex, hexamethylphosphoramide; ix, $SOCl_2$, py–Ac_2O; x, Bu_4NF; xi, $(COCl_2)_2$–dimethyl sulfoxide, Et_3N; xii, $(TMS)_2NLi$, TMSCl; xiii, $Pd(OAc)_2$; xiv, benzene, 40 °C; xv, AcOH–H_2O; xvi, H_2–Ir–Bu^{t}OH, 4 bar

synthesis of **A**.[4] Namely, ^{13}C NMR ($CDCl_3$) δ 36.8 (C-7), 32.9 (C-1), 41.2 (C-2), 47.0 (C-6), 36.5 (C-3) and 15.7 (C-16) of **16** are in good accordance with those of **i**. An undesired epimer **16a**§ [^{13}C NMR ($CDCl_3$) δ 38.7 (C-7), 42.8 (C-1), 45.6 (C-2), 52.6 (C-6), 40.6 (C-3) and 21.4 (C-16)] was identified to have the same stereochemistry as **ii**.[4]

By means of transformations parallel to those described above, **16** afforded an α,β-unsaturated aldehyde **3** *via* a cyclopentadiene **17** and a silyloxyethene **18**. The final step, the biomimetic Diels–Alder reaction of **3** to **1c** [^1H NMR ($CDCl_3$) δ 0.77 (3H, d, *J* 7.0 Hz), 0.87 (3H, d, *J* 6.5 Hz), 1.03 (3H, d, *J* 6.5 Hz), 2.24 (1H, br sept, *J* 7.0 Hz), 2.79 (1H, t, *J* 4.0 Hz), 3.33 (3H, s), 3.52 (1H, d, *J* 9.0 Hz), 3.77 (1H, d, *J* 9.0 Hz), 3.76 (3H, s), 4.54 (1H, d, *J* 6.5 Hz), 4.55 (1H, d, *J* 6.5 Hz), 6.07 (1H, dd, *J* 4.0, 1.5 Hz) and 9.73 (1H, s); ^{13}C NMR ($CDCl_3$ δ 17.4, 21.0, 22.2, 26.4, 27.6, 29.0, 29.4, 31.0, 32.0, 41.4, 41.5, 46.2, 51.8, 55.0, 58.9, 65.4, 72.1, 72.9, 96.7, 130.6, 148.1, 172.7 and 204.3], occurred with a somewhat slower rate than in the case of **4** to **2c** but was completed by heating in benzene at 40 °C for 3 days, in 58% yield (based on **18**). The hydrolysis of **1c** with aqueous AcOH gave **1b** [colourless crystals, m.p. 110–111 °C (lit.[1] m.p. 103 °C)]. Key signals observed in its ^1H NMR (500 MHz, $CDCl_3$) spectrum confirmed the identity with the sample derived from natural product, *i.e.* δ 0.79 (3H, d, *J* 7.0 Hz), 0.89 (3H, d, *J* 6.5 Hz), 1.094 (3H, d, *J* 6.5 Hz), 2.26 (1H, br sept, *J* 7.0 Hz), 2.57 (1H, t, *J* 4.0 Hz), 3.53 (1H, d, *J* 11.5 Hz), 3.81 (3H, s), 3.91 (1H, d, *J* 11.5 Hz), 6.09 (1H, dd, *J* 4.0, 1.5 Hz) and 9.66 (1H, s). Since the biogenesis of **1a** from **B** is established,[2] and the optically active **B** has been synthesised,[3] the present work starting from common precursors constitutes the synthesis of **1b** with the correct absolute stereochemistry.

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