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The First Total Synthesis of Sideroxylonal B

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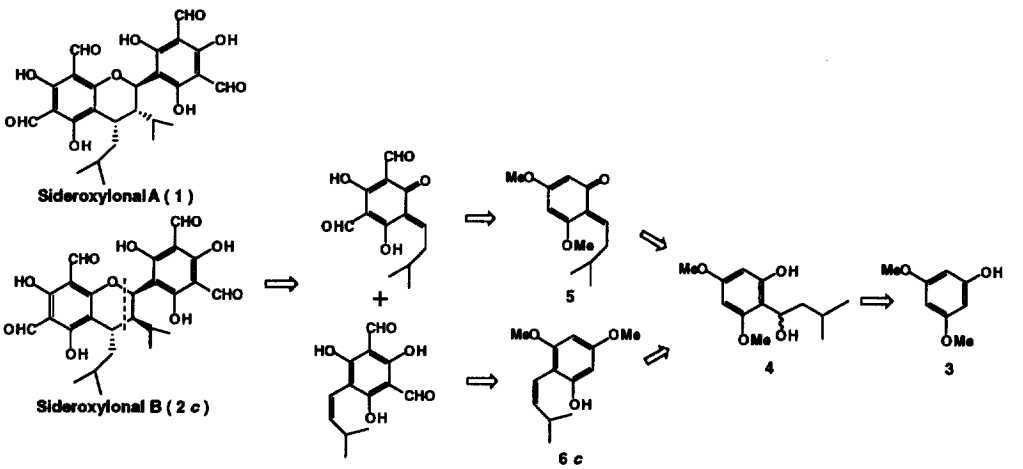
Abstract: Sideroxylonal B (**2c**) has been synthesized through biomimetic cycloaddition of the *o*-quinone methide and the isopentenyl intermediates (**5** and **6t**), both of which were simultaneously derived from isopentenyl phloroglucinol precursor **4**.

Sideroxylonal A and B (**1** and **2c**) are racemic flavanoid components isolated from extracts of *Eucalyptus sideroxylon*, which show biological activities against Gram-positive bacteria, HeLa S-3 cells and aldose reductase.[1] These structures were established by spectroscopic analysis to have a fully functionalized 2-phenyl-1-benzopyran skeleton as a common core.[1] Biogenetically, these compounds apparently are formed from isopentenyl phloroglucinol precursors by a hetero-Diels-Alder coupling process.[2]

Herein, we report the implementation of a novel biomimetic strategy for the first total synthesis of sideroxylonal B (**2c**). The critical element in the design of the synthetic plan was inspired by the proposed biosynthetic sequence as shown in retrosynthetic sequence to assemble the 2-phenyl-1-benzopyran skeleton from the isopentenyl phloroglucinol precursor **4** through cycloaddition of the *o*-quinone methide and the isopentenyl intermediates (**5** and **6c**).



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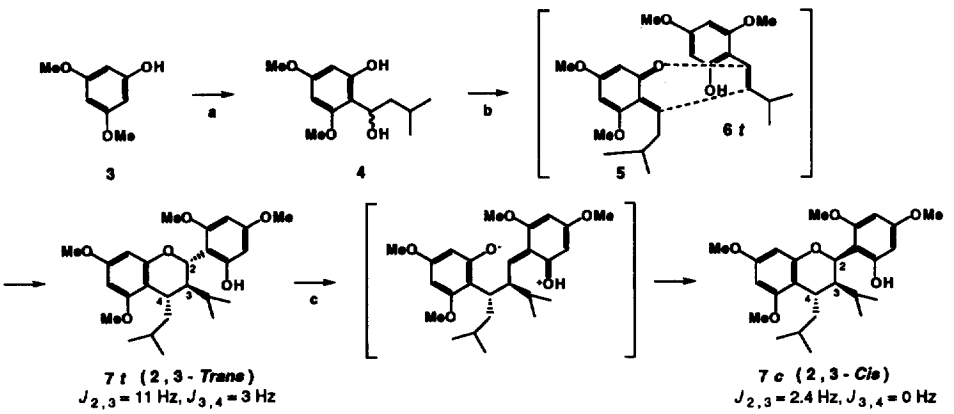
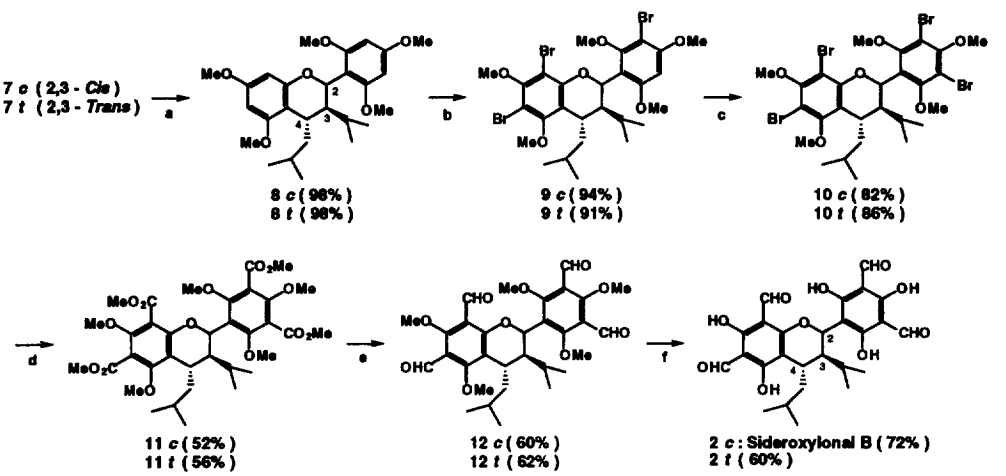


Scheme 1

The key intermediate **4** was prepared from 3,5-dimethoxyphenol (**3**). Reaction of **3** with isovaleric acid in the presence of BF_3·Et_2O gave the ketone (84%, mp 45°C), which was reduced to the alcohol **4**[3] (82%,oil). The hetero-Diels-Alder reaction was assayed under various conditions using Lewis acids, bases, and so on. The best result was obtained by treatment of **4** with EtMgBr[4] to give simultaneously the *o*-quinone methide **5** and the isopentenyl derivative **6t** *in situ*, a mixture of which was submitted to the cycloaddition in question. The *trans* isomer **6t** could be observed in the reaction medium and was isolated (6%, mp 81°C). On refluxing for 30 min., the 2,3-*trans* isomer **7t** was obtained as a major adduct in 39% yield (theoretically 78%, mp 42°C). The isomer **7t** was reasonably expected to be produced through reaction of the *trans* isomer **6t** with **5** in the transition state (Scheme 1). On the other hand, longer refluxing time (29 hrs.) afforded the 2,3-*cis* isomer **7c** as a major product in 37% yield [theoretically 74%, mp 138°C, TLC(hexane : EtOAc = 4 : 1): **7c**: R_f 0.55; **7t**: R_f 0.43)]. This result indicated that the 2,3-*trans* isomer **7t** was thermodynamically changed to the 2,3-*cis* isomer **7c** through pyran ring-opening and -closing process[5] as shown in Scheme 1. It is not likely that the 2,3-*cis* isomer **7c** is reconstructed *via* another transition state including **5** and the *cis* isomer **6c**, the latter of which has more steric hindrance than the *trans* isomer **6t**. The configurations of **7c** and **7t** were supported by the NMR studies[6] and further transition to sideroxylonal B (**2c**) and its 2,3-*trans* isomer **2t**.

First of all, we attempted conversion of the 2,3-*cis* isomer **7c**, which has the same configuration as that of sideroxylonal B (**2c**), to the natural product **2c** (*c*-series in Scheme 2). *O*-Methylation of **7c** to give the fully protected compound **8c** (98%, mp 139°C), followed by bromination with benzyltrimethylammonium tribromide under basic conditions,[7] produced the tribromide **9c** (94%, mp 172°C). According to Hundt and Roux,[8] the benzopyran ring seemed to be preferentially dibrominated. Further bromination of **9c** was conducted by using the same reagent under acidic conditions[9] to give the tetrabromide **10c** (82%, mp 165°C), although direct bromination of **8c** to **10c** was very difficult. Lithiation of **10c** with *t*-BuLi followed by treatment with methyl chloroformate afforded the methyl ester **11c** (52%, mp 76°C). The ester **11c** was submitted to hydride reduction with DIBAL to give the tetraol, which was oxidized with PDC to provide the aldehyde **12c** (60%, mp 178°C). Direct reduction of **11c** to **12c** was attempted under a variety of conditions but in vain. De-*O*-

methylation was effectively achieved with $BBr_3 \cdot SMe_2$ to give sideroxyronal B [**2c**: 72%, mp 213°C (MeOH)]. The synthetic product **2c** was identical with the natural product in all respects.[10]



Conditions : (a) MeI , $Ba(OH)_2 \cdot 8H_2O$, BaO / DMF, rt (b) $BnN^+Me_3Br_3^-$, $NaHCO_3$ / CH_2Cl_2 , MeOH , rt
(c) $BnN^+Me_3Br_3^-$, $ZnCl_2$ / AcOH , 70°C (d) t-BuLi / THF , -78°C , then $ClCO_2Me$
(e) 1) DIBAL / PhMe , -78°C 2) PDC / CH_2Cl_2 (f) $BBr_3 \cdot SMe_2$ / $ClCH_2CH_2Cl$, 70°C

Scheme 2

Next, the 2,3-*trans* adduct **7t** was converted through **8t** (mp 111°C) and **9t** (mp 171°C) to the tetrabromide **10t** (mp 122°C) by using similar conditions as described above (*t*-series in Scheme 2). Treatment of the lithiated **10t** with methyl chloroformate to give the methyl ester **11t** (56%, mp 56°C), successively followed by hydride reduction and PDC oxidation gave the aldehyde **12t** (62%, mp 150°C). De-*O*-methylation of **12t** with $BBr_3 \cdot Me_2S$ gave the 2,3-*trans* isomer of the natural product [**2t**: 60%, mp 178°C (MeOH)].

The biological evaluation of **2t** and other related analogs is an exciting prospect.

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2. Singh, I. P.; Hayakawa, R.; Etoh, H.; Takasaki, M.; Konoshima, T. *Biosci. Biotech. Biochem.*, **61**, 921-923 (1997).
3. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. Significant ^{1}H-NMR spectral data (in $CDCl_3$, 270 and 500MHz, δ; TMS = 0) are the following.
2c: 0.74(3H, d, *J*=7.1Hz), 0.96(3H, d, *J*=6.7Hz), 0.98(3H, d, *J*=6.7Hz), 1.09(3H, d, *J*=6.4Hz), 1.53 (1H, ddd, *J*=13.5, 10.4, 2.1Hz), 1.65 (1H, ddd, *J*=13.5, 10.4, 2.1Hz), 1.75(1H, m), 1.97 (1H, m),

2.02(1H, dd, *J*=2.4, 2.4, 0Hz), 2.98(1H, dd, *J*=10.4, 2.1, 0Hz), 5.92(1H, d, *J*=2.4Hz), 8.59(1H, s), 10.02(1H, s), 10.17(1H, s), 10.21(1H, s), 10.24(1H, s), 13.38(1H, s), 13.53(1H, s), 13.57(1H, s), 13.59(1H, s), $J_{2,3}$=2.4Hz, $J_{3,4}$=0Hz. **7c**: 0.66(3H, d, *J*=7.1Hz), 0.83(3H, d, *J*=7.1Hz), 0.97(3H, d, *J*=6.7Hz), 1.07(3H, d, *J*=6.4Hz), 1.73(1H, m), 1.84(1H, dd, *J*=2.4, 2.4, 0Hz), 1.94(1H, m), 2.86(1H, dd, *J*=9.2, 3.7, 0Hz), 3.75(6H, s), 3.79(3H, s), 3.81(3H, s), 5.72(1H, d, *J*=2.4Hz), 6.05(1H, d, *J*=2.5Hz), 6.06(1H, d, *J*=2.5Hz), 6.12(1H, d, *J*=2.0Hz), 6.13(1H, d, *J*=2.0Hz), 8.39(1H, s), $J_{2,3}$=2.4Hz, $J_{3,4}$=0Hz. **8c**: 1.56(1H, dd, *J*=2.8, 2.8, 0Hz), 2.84(1H, dd, *J*=6.7, 5.8, 0Hz), 3.73(3H, s), 3.79(6H, s), 3.80(3H, s), 3.82(3H, s), 5.75(1H, d, *J*=2.8Hz), $J_{2,3}$=2.8Hz, $J_{3,4}$=0Hz. **9c**: 1.59(1H, dd, *J*=2.5, 2.5, 0Hz), 2.94(1H, dd, *J*=7.6, 5.2, 0Hz), 5.73(1H, d, *J*=2.5Hz), 6.38(1H, s), $J_{2,3}$=2.5Hz, $J_{3,4}$=0Hz. **10c**: 1.58(1H, dd, *J*=2.8, 2.8, 0Hz), 2.84(1H, dd, *J*=12.0, 2.0, 0Hz), 5.61(1H, d, *J*=2.8Hz), $J_{2,3}$=2.8Hz, $J_{3,4}$=0Hz. **11c**: 1.62(1H, dd, *J*=2.8, 2.8, 0Hz), 2.92(1H, dd, *J*=9.0, 2.8, 0Hz), 3.75(3H, s), 3.79(6H, s), 3.80(3H, s), 3.86(3H, s), 3.87(3H, s), 3.93(3H, s), 3.94(6H, s), 5.61(1H, d, *J*=2.8Hz), $J_{2,3}$=2.8Hz, $J_{3,4}$=0Hz. **12c**: 1.71(1H, dd, *J*=2.7, 2.7, 0Hz), 3.06(1H, dd, *J*=5.2, 4.0, 0Hz), 5.83(1H, d, *J*=2.7Hz), 10.31(1H, s), 10.35(2H, s), 10.36(1H, s), $J_{2,3}$=2.7Hz, $J_{3,4}$=0Hz.

2t: 0.85(3H, d, *J*=6.7Hz), 0.90(3H, d, *J*=6.5Hz), 0.97(3H, d, *J*=5.8Hz), 1.00(3H, d, *J*=6.9Hz), 1.33-1.53(3H, m), 1.72(1H, m), 2.29(1H, ddd, *J*=11.0, 2.5, 2.5Hz), 3.25(1H, ddd, *J*=9.0, 6.0, 2.5Hz), 5.19(1H, d, *J*=11.0Hz), 7.92(1H, s), 9.98(1H, s), 10.20(1H, s), 10.21(1H, s), 10.28(1H, s), 13.12(1H, s), 13.28(1H, s), 13.49(1H, s), 13.52(1H, s), $J_{2,3}$=11.0Hz, $J_{3,4}$=2.5Hz. **7t**: 0.78(3H, d, *J*=7Hz), 0.83(3H, d, *J*=7Hz), 0.92(3H, d, *J*=7Hz), 0.93(3H, d, *J*=7Hz), 2.22(1H, ddd, *J*=11, 3, 3Hz), 3.17(1H, dt, *J*=9, 9, 3Hz), 3.69(3H, s), 3.74(3H, s), 3.78(3H, s), 3.79(3H, s), 5.01(1H, d, *J*=11Hz), 6.04(1H, d, *J*=3Hz), 6.17(1H, d, *J*=3Hz), 6.19(2H, s), 7.38(1H, s), $J_{2,3}$=11Hz, $J_{3,4}$=3Hz. **8t**: 2.64(1H, ddd, *J*=12, 3, 3Hz), 3.09(1H, dt, *J*=8, 8, 3Hz), 3.70(3H, s), 3.78(9H, s), 3.84(3H, s), 5.04(1H, d, *J*=12Hz), $J_{2,3}$=12Hz, $J_{3,4}$=3Hz. **9t**: 2.75(1H, ddd, *J*=10, 5, 2Hz), 3.14(1H, dt, *J*=9, 9, 2Hz), 4.91(1H, d, *J*=10Hz), 6.40(1H, s), $J_{2,3}$=10Hz, $J_{3,4}$=2Hz. **10t**: 2.78(1H, ddd, *J*=12, 3, 3Hz), 3.15(1H, ddd, *J*=6, 3, 3Hz), 4.82(1H, d, *J*=12Hz), $J_{2,3}$=12Hz, $J_{3,4}$=3Hz. **11t**: 2.73(1H, ddd, *J*=11, 2, 2Hz), 3.07(1H, dt, *J*=8, 8, 2Hz), 3.75(3H, s), 3.80-3.85(9H, br.s), 3.87(3H, s), 3.90(3H, s), 3.93(3H, s), 3.94(6H, br.s), 4.77(1H, d, *J*=11Hz), $J_{2,3}$=11Hz, $J_{3,4}$=2Hz. **12t**: 2.76(1H, ddd, *J*=11, 2, 2Hz), 3.23(1H, ddd, *J*=8, 6, 2Hz), 5.02(1H, d, *J*=11Hz), 10.29(1H, s), 10.35(1H, s), 10.36(2H, s), $J_{2,3}$=11Hz, $J_{3,4}$=2Hz.

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10. An authentic sample of sideroxylonal B (**2c**) was kindly provided by Prof. Hideo Etoh, Faculty of Agriculture, Shizuoka University.