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The First Synthesis of Optically Pure (+)- and (-)-Isokotanin A and the Assignment of Their Absolute Configuration

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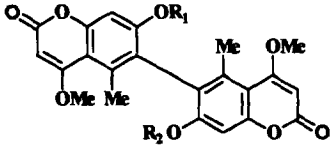
Abstract The first asymmetric synthesis of optically pure (+) and (-)-Isokotanin A is described. The key steps involve the asymmetric Ullmann coupling and selective demethylation. The absolute configuration of the naturally occurring (+)-Isokotanin A is assigned as a*R*. Copyright © 1996 Elsevier Science Ltd

Many fungi produce durable physiological structures called sclerotia as a mechanism for the long-term survival and propagation of the species. Some sclerotia contain secondary metabolites that play a role in protecting them from potential predators. In 1994, J. B. Gloer and his coworkers[1] isolated several structurally similar Bicoumarins from the sclerotia of *Aspergillus alliaceus*, and named them Isokotanin A-C (**1a-c**).

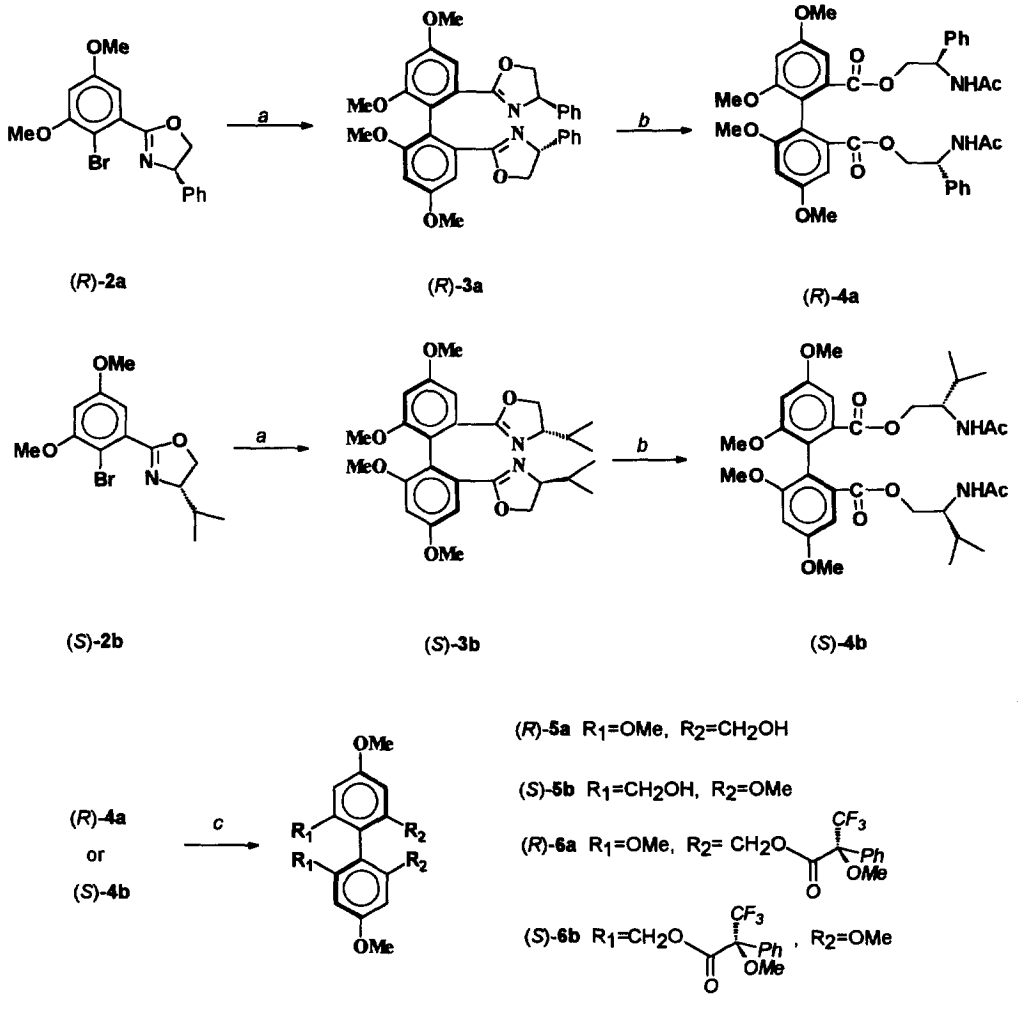


1a Isokotanin A R_1=R_2=Me
1b Isokotanin B R_1=H, R_2=Me
1c Isokotanin C R_1=R_2=H

These compounds possess axial biaryl chirality. Although the first total synthesis of racemic (±)-Isokotanin A was reported by us[2], the absolute configuration of **1a** still remained undetermined. As a continuation of our efforts in this area, we report here the first synthesis of both optically pure (+)- and (-) - Isokotanin A, in which the asymmetric Ullmann coupling of bromo-oxazoline (*R*)-**2a** or (*S*)-**2b** developed by Meyers' group[3] and selective demethylation were employed as the key steps. Subsequently, We assign the absolute configuration of the naturally occurring (+)-Isokotanin A as a*R* by comparison of the specific rotation value of the intermediate (**8a**) with that of the known compound in the literature[4].

As shown in scheme 1, Asymmetric Ullmann coupling of **2a** or **2b**[5] in the presence of activated Cu powder and DMF for 72 hours produced the bis(oxazoline) (**3a**) or (**3b**).

Scheme 1

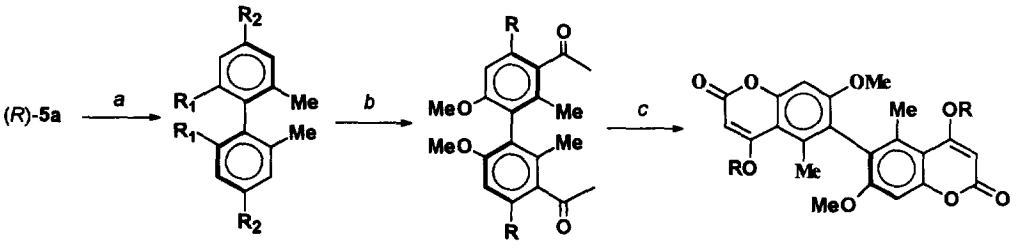


Reagents and conditions: a. activated Cu powder, DMF, reflux, 72h; b. TFA, H_2O, THF, r.t; Ac_2O, py., r.t; 51% for **4a** from **2a** and 60% for **4b** from **2b**; c. **4a**→**5a** or **4b**→**5b**, LAH, THF, r.t; 80% for **5a** and 87% for **5b**; **5a**→**6a** or **5b**→**6b**, (S)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride, 4-DMAP, Et_3N, CH_2Cl_2,r.t.

Because the bis(oxazoline) (**3a**) or (**3b**) was unstable in acidic media, it was converted directly to **4a** or **4b** by treatment with TFA/H_2O followed by acetylation [6]. LAH reduction of **4a** or **4b** in THF at room temperature gave the dicarbinol (**5a**) or (**5b**). The diastereomeric excess of **5a** and **5b** were determined to be 83% and 90% by the examination of the ^1H NMR spectra of their corresponding (*S*)-Mosher's ester (**6a**) and (**6b**).

The optically pure dicarbinol (**5a**) and (**5b**) were obtained by recrystallization from acetyl acetate [7]. With the enantiomerically pure dicarbinol (**5a**) or (**5b**) in hand, our efforts were then made to complete the synthesis of the optically pure Isokotanin A (Scheme 2).

Scheme 2



(*R*)-**7a** R_1=R_2=OMe
(*R*)-**8a** R_1=R_2=OH

(*R*)-**9a** R=OMe
(*R*)-**10a** R=OH
(*R*)-**11a** R=OCOOMe

(*R*)-**12a** R=H
(*R*)-(+)-**1a** R=Me

Reagents and conditions: a. **5a**→**7a**,10% Pd/C, cat. TFA, Ethanol, 54%; **7a**→**8a**, BBr_3, CH_2Cl_2, -78°C→r.t, 74%; b. 7a→9a, $(CH_3CO)_2O$, $TiCl_4$, CH_2Cl_2, r.t, 78%;, **9a**→**10a** ,$TiCl_4$, benzene, reflux, 96%;**10a**→**11a**, ClCOOMe, py., 55°C, 90%; c. **11a**→**12a**, t-BuOK, t-BuOH, 60°C, 89%; **12a**→(*R*)-(+)-**1a** ,NaH, HMPA, r.t; $(CH_3)_2SO_4$, HMPA, r.t, 64%.

The biaryl (**7a**) was prepared from **5a** by catalytic hydrogenation in the presence of 10% Pd/C and a catalytic amount of TFA in ethanol [8]. **7a** was acetylated with $(CH_3CO)_2O/TiCl_4$ in CH_2Cl_2 to afford **9a**, which was selectively demethylated with $TiCl_4$ / benzene to give **10a** [9]. The carbonate (**11a**) generated from the phenol (**10a**) and methyl chloroformate in pyridine ,was subjected to the treatment of t-BuOK in t-BuOH to afford the desired cyclized product **12a**. Then **12a** was methylated with NaH/HMPA/$(CH_3)_2SO_4$ [10] to give the optically pure (+)-Isokotanin A [$[\alpha]^{24}_D$ +22.4 (c 0.3, $CHCl_3$), lit.[1] $[\alpha]^{24}_D$ +21.4 (c 0.22, $CHCl_3$)] in 64% yield[11]. In the same manner, the optically pure (-)-Isokotanin A [$[\alpha]^{24}_D$ -22.0 (c 0.3, $CHCl_3$)] was obtained from **5b**.

In order to assign the absolute configuration of the naturally occurring (+)-Isokotanin A , (+)-**7a** was demethylated in the presence of BBr_3 to afford (+)-2,2',4,4'-tetrahydroxy-6, 6'-dimethyl biphenyl (**8a**) [$[\alpha]^{24}_D$ +38.7 (c 0.9, EtOH), lit.[4] $[\alpha]^{25}_D$ +39.4 (c 0.5, EtOH)], the absolute configuration of which was known in literature as a*R* [4] (Scheme 2). Accordingly, (+)-**7a** was determined to be a*R* and (-)-**7b** to be a*S*. This assignment was also in accordance with Meyers' conclusion that the (*S*)-bromo-oxazoline generally induced the formation of the (*S*)-biaryl[3a]. Therefore, the absolute of the naturally occurring (+)-Isokotanin A is determined to be a*R*.

In summary, we have accomplished the first asymmetric synthesis of optically pure (+)- and (-)-Isokotanin A. The obtainment of both (+) and (-) isomers of Isokotanin A allowed us to assign the absolute configuration of the naturally occurring (+)-Isokotanin A as a*R*.

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6. (*R*)-**4a**. $[\alpha]^{24}_D$ +4.6 (c 1.0, $CHCl_3$). $[\alpha]^{24}_D$ -6.2 (c 1.0, benzene). FT-IR (film): 3295, 1730, 1650 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.27-7.23 (m, 6H), 7.17-7.14 (m, 4H), 6.98 (d, 2H, J=2.38Hz), 6.57 (d, 2H, J=2.36Hz), 6.25-6.15 (d, 2H, J=8.51Hz), 5.17-5.07 (m, 2H), 4.40-4.17 (m,4H), 3.83 (s, 6H), 3.57 (s, 6H), 1.94 (s, 6H). ^{13}C NMR (100MHz, $CDCl_3$) δ 169.73, 167.61, 159.46, 158.35, 138.39, 131.73, 128.62, 127.70, 126.64, 119.68, 105.57, 102.69, 66.45, 56.09, 55.45, 52.24, 23.19 ppm. HRMS m/z calcd. for $C_{38}H_{40}N_2O_{10}$ 684.2684, found 684.2694. (*S*)-**4b**. $[\alpha]^{24}_D$ -64.3 (c 0.5, $CHCl_3$). FT-IR (film) : 3390, 1716, 1654 cm^{-1} . ^1H NMR (300MHz,$CDCl_3$) δ 7.10 (d, 2H, J=2.14Hz), 6.68 (d, 2H, 2.13Hz), 5.53-5.50 (d, 2H, J=8.51Hz), 4.18-4.05 (m,4H), 3.88 (s, 6H), 3.75-3.72 (m, 2H), 3.66 (s, 6H), 1.95 (s, 6H), 0.79-0.76 (t, 12H, J=4.6Hz, 6.2Hz) ppm. ^{13}C NMR (100MHz, $CDCl_3$) δ 177.39, 169.92, 168.39, 163.23, 150.91, 132.60, 119.20, 105.66, 102.43, 65.78, 56.15, 55.51, 58.51, 53.20, 28.29, 23.10, 19,34, 19.01 ppm. HRMS m/z calcd. for $C_{32}H_4N_2O_{10}$ (M^+) 616.2997, found 616.2995.
7. (*R*)-**5a**. m.p 144-145°C. $[\alpha]^{24}_D$ +62.5 (c 1.10, $CHCl_3$). FT-IR (KBr) : 3242 cm^{-1} . ^1H NMR (300MHz,$CDCl_3$) δ 6.72 (d, 2H, J=2.74Hz), 6.52 (d, 2H, J=2.34Hz), 4.22 (d,4H, J=2.64Hz), 3.87 (s,6H), 3.69 (s, 6H), 1.95 (s, 2H, disappeared in D_2O) ppm . ^{13}C NMR (100MHz,$CDCl_3$) δ 166.52, 158.22, 142.19, 116.36, 105.49, 98.79, 56.01, 55.39 ppm. HRMS m/z calcd. for $C_{18}H_{22}O_6$ (M^+) 334.1417, found 334.1433. Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.67; H, 6.51. (*S*)-**5b**. $[\alpha]^{24}_D$ -62.8 (c 0.97, $CHCl_3$).
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9. (*R*)-**10a**. $[\alpha]^{24}_D$ +29.3 (c 0.5, $CHCl_3$). FT-IR (KBr): 3420, 1620 cm^{-1}. ^1H NMR (300MHz,$CDCl_3$) δ 6.41 (s, 2H), 3.71 (s, 6H), 2.63 (s, 6H), 2.15 (s, 6H) ppm. HRMS m/z calcd. for $C_{20}H_{22}O_6$ (M^+) 358.1417, found 358.1430. Anal. calcd. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.18. Found: C, 66.72; H, 6.38.
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11. (*R*)-**1a**. m.p 240-242 °C (dec.). $[\alpha]^{24}_D$ +22.4 (c 0.3, $CHCl_3$). FT-IR (KBr): 3418, 2942, 2884, 1721, 1607, 1594, 1557, 1455, 1367, 1253, 1170, 976, 807 cm^{-1}. ^1H NMR (300MHz,$CDCl_3$) δ 6.78 (s, 2H), 5.60 (s,2H), 3.94 (s, 6H), 3.72 (s, 6H), 2.23 (s, 6H). ^{13}C NMR (75.5MHz, $CDCl_3$) δ 170.07, 163.02, 160.17, 156.31, 137.21, 123.46, 108.12, 97.46, 87.97, 56.00, 18.73 ppm . MS m/z (EI, 70ev): 439 (27.5, M^++1), 438 (100, M^+), 423 (4.0), 410 (17.6), 392 (12.2), 364 (7.9), 219 (10.4), 191 (18.2), 69 (49.7), 55 (51.0), 44 (24.0). HRMS m/z calcd. for $C_{24}H_{22}O_8$ (M^+) 438.1314, found 438.1263.

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