Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 9, pp. 1369–1372, 1997

Printed in Great Britain
PII: S0957-4166(97)00117-1
0957-4166/97 $17.00 + 0.00

The first asymmetric synthesis of the naturally occurring (+)-Kotanin and the assignment of its absolute configuration

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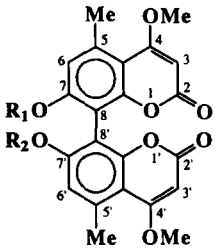
Abstract: The first asymmetric synthesis of the naturally occurring (+)-Kotanin is described. The key steps involve the intramolecular oxidative coupling of the cyanocuprate intermediate and the Fries rearrangement. The absolute configuration of (+)-Kotanin was assigned as a*S* by CD spectroscopic method. © 1997 Elsevier Science Ltd

In 1971, the fungal metabolites Kotanin **1** and demethylkotanin **2** were isolated as the first enantiomerically pure 8,8′-bicoumarins from *Aspergillus clavatus* by Büchi and coworkers[1]. Several years later, Cutler and coworkers[2] isolated another optically active 8,8′-bicoumarin named as Orlandin **3** from *Aspergillus niger*. Since then other two groups of optically active bicoumarins, *i.e.*, Desertorins[3] and Isokotanins[4] were isolated from *Emericella desertorum* and *Aspergillus Alliaceus*, respectively.



1 Kotanin $R_1 = R_2 = Me$
2 Demethylkotanin $R_1 = H$, $R_2 = Me$
3 Orlandin $R_1 = R_2 = H$

Wheat coleoptile and chick bioassays indicated that the biological activity of Orlandin **3** in plants, and of Kotanin **1** in chick, is intimately associated with the 7,7′-hydroxyl groups. Orlandin **3** was nontoxic to day-old cockerels but significantly inhibited wheat coleoptile growth. Kotanin **1** was inactive in the coleoptile elongation but toxic to chicks[2]. This result indicated that the bicoumarin structure offers an interesting model to determine functional group activity in plant and animal bioassays.

The optical activity of those bicoumarins was caused by the restricted rotation around the carbon–carbon single bond connecting the two aryl monomers. Although racemic Kotanin was synthesized by Büchi *et al.*[1a], the stereochemistry of it still remained unsolved for over twenty years. As a continuation of our efforts in this area, we report here the first asymmetric synthesis of the naturally occurring (+)-Kotanin, in which the asymmetric intramolecular oxidative coupling of the cyanocuprate intermediate of **8** developed by Lipshutz's group[5] and the Fries rearrangement of **15** were employed as the key steps. The absolute configuration of (+)-Kotanin was assigned as a*S* based on the comparison of the CD Cotton effects of the intermediate **16** with that of the known compound[6].

As shown in Scheme 1, 1,4-di-*O*-benzyl-L-threitol **4**[7] was converted to its monosilyl ether **5**. Mitsunobu reaction of **5** with 2-bromo-3-methoxy-5-methylphenol[8] gave **6** in 85% yield. Cleavage of

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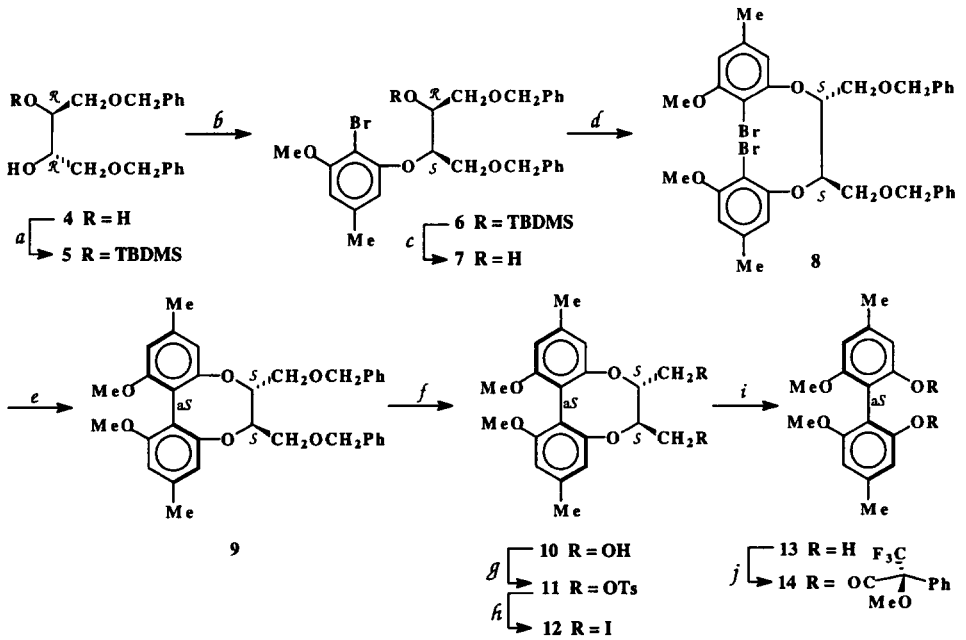
the silyl ether of **6** with *n*-Bu_4NF in THF gave **7** in 91% yield, which was followed by treatment with 2-bromo-3-methoxy-5-methylphenol again to afford **8**[9] in 54% yield. Treatment of **8** with *n*-BuLi followed by addition of CuCN–TMEDA (1:3) led to formation *in situ* of a higher order cyanocuprate intermediate, which transformed to **9**[10] upon exposure to dry oxygen at −78°C in 60% yield. Catalytic hydrogenation of **9** gave the threitol **10** in 90% yield. The threitol **10** was converted to the ditosylate **11** in 92% yield, which upon treatment with NaI gave the diiodide **12** in 96% yield. Reduction of **12** by activated zinc powder in ethanol provided the biphenol **13** in 80%. The enantiomeric excess of **13** was determined to be 82% by the examination of the ^1H NMR spectra of its corresponding (*S*)-Mosher's ester **14**. The enantiomerically pure **13**[11] was obtained by recrystallization from ethyl acetate and hexane.



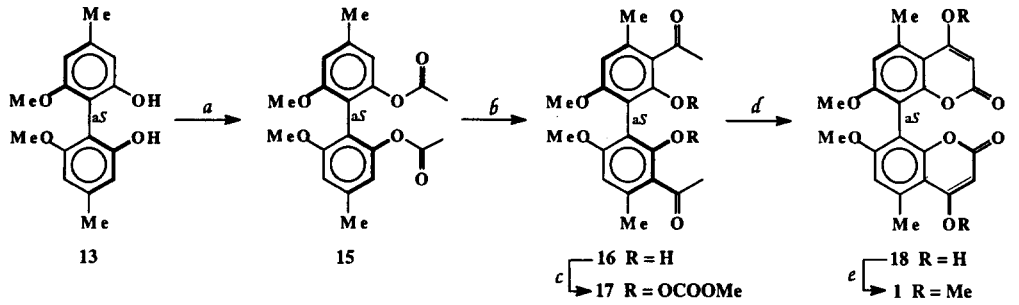
Reagents and conditions: a. TBDMSCl, imidazole, DMF, r.t, 24 h, 84%; b. 2-bromo-3-methoxy-5-methylphenol, DEAD, *n*-Bu_3P, THF, r.t, 24 h, 85%; c. *n*-Bu_4NF, THF, 2 h, 91%; d., 2-bromo-3-methoxy-5-methylphenol, DEAD, *n*-Bu_3P, THF, r.t, 42 h, 54%; e. *n*-BuLi, THF, -78°C, 1 h; CuCN-TMEDA(1:3), -78°C→ -40°C, 1 h; dry O_2, -78°C, 4 h, 60%; f. 10% Pd/C, H_2, EtOAc, 12 h, 90%; g. TsCl, py., 0 °C, 8 h, 92%; h. NaI, acetone, reflux, 3 h, 96%; i. activated Zn powder, EtOH, reflux, 1 h, 80%; j. (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 4-DMAP, Et_3N, CH_2Cl_2, r.t, 24 h, 90%.

Scheme 1.

Subsequently, our efforts were made to complete the synthesis of **1** (Scheme 2).

The diacetate **15**, generated from **13** on treatment with acetic anhydride in pyridine, underwent Fries rearrangement promoted by $TiCl_4$ as Lewis acid to afford **16**[12] in 68% yield. The dicarbonate **17** prepared from **16** and methyl chloroformate in pyridine, was subjected to treatment of *t*-BuOK in *t*-BuOH to afford the desired cyclized product **18**. Then the crude **18** was directly methylated with NaH/HMPA/$(CH_3)_2SO_4$ to give the naturally occurring (+)-Kotanin **1**[13] [$[\alpha]^{20}_D$ +38.4 (c 0.44, $CHCl_3$); lit.[1b] $[\alpha]^{23}_D$ +40.0 (c 1.65, $CHCl_3$)] in 42% yield.

The CD Cotton effects of (+)-2,2′-dihydroxy-3,3′-diacetyl-4,4′-dimethyl-6,6′-dimethoxybiphenyl **16** were in accordance with that of (a*S*)-(+)-2,2′-dihydroxy-3,3′-diacetyl-4,4′,6,6′-tetramethoxybiphenyl **19**, which exhibits positive first and negative second Cotton effects at the ^1L_a transition region[6]. Accordingly, the absolute configuration of the biaryls **9**, **10**, **11**, **12**, **13**, **15**, **16**, **17**, **18** and the naturally occurring (+)-Kotanin **1** were all assigned as a*S*. This assignment was also



Reagents and conditions: a. $(CH_3CO)_2O$, py., 2 h, 93%; b. $TiCl_4$, benzene, reflux, 4 h, 68%; c. ClCOOMe, py., 4-DMAP, 50 °C, 8 h, 85%; d. *t*-BuOK, *t*-BuOH, 60°C, 2 h; e. NaH, HMPA, rt.; $(CH_3)_2SO_4$, HMPA, r.t., 20 min, 42% (**17**→**1**).

Scheme 2.

in agreement with Lipshutz's conclusion[5] that the (2*S*,3*S*)-tetraether generally induced the formation of (a*S*)-biaryl in the coupling process (**8**→**9**).

The absolute configuration of the naturally occurring (+)-Isokotanin A, which belongs to 6,6′-bicoumarins, was determined to be a*R* by us[14], but that of the naturally occurring (+)-Kotanin, which was belong to 8,8′-bicoumarins, was established as a*S*. The biosynthetic passway of (+)-Isokotanin A and (+)-Kotanin remains as an interesting issue.

In summary, we have accomplished the first asymmetric synthesis of the naturally occurring (+)-Kotanin and assigned its absolute configuration as a*S* by CD spectra.

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6. (a*R*)-**19**. $[\alpha]^{20}_D$ −27.6 (c 0.56, $CHCl_3$). CD (EtOH) λ_{ext} 298 nm (Δε −3.29), 276 (Δε +4.60), 241 (Δε −1.34), 235 (Δε −0.26), 229 (Δε −2.63), 212 (Δε +8.67). for (a*S*)-**19**. $[\alpha]^{19}_D$ +27.2 (c 0.40, $CHCl_3$). CD (EtOH) λ_{ext} 297 nm (Δε +3.38), 275 (Δε −2.03), 240 (Δε +3.78), 235 (Δε +2.43), 230 (Δε +3.78), 211 (Δε −6.21).
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9. **8**, $[\alpha]^{22}_D$ −0.74 (c 4.34, $CHCl_3$). FT-IR (film): 3064, 3030, 3005, 2980, 2863, 1587, 1496, 1457, 1412, 1367, 1326, 1236, 1112, 1040, 910, 813, 738, 699, 626, 573, 531, 462 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.12–7.27 (m, 10H), 6.79 (s, 2H), 6.09 (s, 2H), 5.12 (t, *J*=3.6Hz, 2H), 4.39, 4.35 (AB, J_{AB}=12.0Hz, 4H), 4.16 (dd, *J*=4.1, 10.2Hz, 2H), 3.95 (dd, *J*=4.8, 10.3Hz, 2H), 3.32 (s, 6H), 2.02 (s, 6H) ppm. MS m/z (EI, 70 ev): 700(M^+), 619, 593, 513, 297, 267, 227, 181, 138, 108, 91(100), 77. Calcd. for $C_{34}H_{36}O_6Br_2$: C, 58.30; H, 5.18. Found: C, 58.49; H, 5.32.

10. (a*S*)-**9**, $[\alpha]^{22}_D$ −12.0 (c 0.68, $CHCl_3$). FT-IR (film): 3031, 2932, 2860, 1606, 1566, 1497, 1455, 1407, 1367, 1311, 1222, 1099, 948, 880, 738, 699, 583 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.38 (m, 10H), 6.70 (d, *J*=1.0Hz, 2H), 6.60 (d, *J*=1.0Hz, 2H), 4.61, 4.59 (AB, J_{AB}=12.1Hz, 4H), 4.10 (t, *J*=2.1Hz, 2H), 3.78 (s, 6H), 3.74 (dd, *J*=0.8, 10.9Hz, 2H), 3.62 (tt, *J*=3.3, 10.9Hz, 2H), 2.37 (s, 6H) ppm. ^1H NMR (300 MHz, C_6D_6) δ 7.30–7.32 (m, 4H), 7.15–7.18 (m, 6H), 6.99 (s, 2H), 6.46 (s, 2H), 4.43 (s, 4H), 4.35 (m, 2H), 3.50–3.62 (m, 4H), 3.42 (s, 6H), 2.23 (s, 6H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.393, 157.912, 139.388, 138.173, 128.433, 127.807, 127.699, 115.167, 114.589, 108.320, 85.099, 73.719, 70.744, 55.911, 21.820 ppm. MS m/z (EI, 70 ev): 541, 540(M^+,10.76), 432, 401, 341, 324, 311, 285, 256, 213, 195, 175, 151, 129, 105, 91(100), 77. HRMS calcd. for $C_{34}H_{36}O_6$(M^+): 540.2513, found 540.2475.

11. (a*S*)-**13**, m.p. 122–123°C (EtOAc/hexane). $[\alpha]^{22}_D$ −143.2 (c 0.66, $CHCl_3$). FT-IR (KBr): 3477, 3426, 2944, 2850, 1615, 1573, 1465, 1334, 1318, 1199, 1164, 1101, 1099, 1003, 938, 836, 812, 589, 562, 510, 470 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 6.74 (s, 2H), 6.15 (s, 2H), 5.18 (s, 2H), 3.20 (s, 6H), 2.15 (s, 6H) ppm. MS m/z (EI, 70 ev): 276, 275, 274(M^+,100), 259, 243, 228, 213, 199, 188, 177, 162, 151, 141, 128, 115, 105, 91, 77. Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.95; H, 6.65.

12. (a*S*)-**16**, m.p. 217–218°C ($CHCl_3$/EtOH). $[\alpha]^{22}_D$ +109.2 (c 0.70, $CHCl_3$). CD (EtOH) λ_{ext} 335nm (Δε +3.71), 310 (Δε +2.17), 297 (Δε +3.10), 274 (Δε −6.82), 227 (Δε +22.32), 210 (Δε −32.89). FT-IR (KBr): 3503, 3370, 3011, 2978, 2941, 2850, 2739, 2687, 1600, 1495, 1464, 1420, 1400, 1349, 1271, 1214, 1183, 1162, 1110, 1044, 953, 874, 822, 610, 586, 537 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 14.10 (s, 2H), 6.10 (s, 2H), 3.34 (s, 6H), 2.07 (s, 6H), 2.04 (s, 6H) ppm. MS m/z (EI, 70 ev): 360, 359, 358(M^+, 43.38), 343(100), 325, 301, 259, 255, 241, 213, 193, 164, 141, 128, 115, 91, 77. Calcd. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.18. Found: C, 67.32; H, 6.18.

13. (a*S*)-**1**, m.p. >300°C ($CHCl_3$/EtOH). $[\alpha]^{20}_D$ +38.4 (c 0.44, $CHCl_3$). FT-IR (KBr): 2928, 2853, 1711, 1611, 1588, 1457, 1412, 1365, 1330, 1259, 1204, 1136, 1125, 1204, 1136, 1125, 1097, 1054, 1032, 973, 838, 809, 733, 580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 2H), 5.51 (s, 2H), 3.93 (s, 6H), 3.78 (s, 6H), 2.70 (s, 6H) ppm. MS m/z (EI, 70ev): 440, 439, 438(M^+, 24.60), 410, 409, 408, 407(100), 379, 293, 265, 219, 165, 139, 111, 91, 69, 57, 43. HRMS calcd. for $C_{24}H_{22}O_8$(M^+): 438.1315, found 438.1342.

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(Received in Japan 9 December 1996; accepted 4 March 1997)