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The First Synthesis of Optically Pure Biscarbazoles and Determination of Their Absolute Configurations

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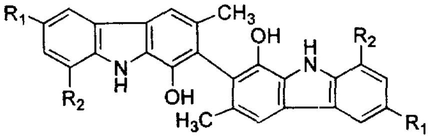
Abstract: Optically pure dimeric *O*-demethylmurrayafoline A (**1**) and its 6,6'-dimethoxyl analog **2** were synthesized *via* the resolution of their corresponding camphorsulfonates of the racemates. The absolute configurations of (+)-**1**, (+)-**2** and (-)-**1**, (-)-**2** were assigned as (a*R*) and (a*S*), respectively, by the X-ray analysis and CD spectrum. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Amination; Cyclization; Oxidative coupling; Resolution; X-Ray crystallography

A broad range of dimeric carbazole alkaloids with diverse biological activities have been isolated from different natural sources over the past decades [1]. For example, clausenamine-A (**3**) was isolated from the stem and root bark of *Clausena excavata* [2], which is used as folk medicine for detoxication caused by the poisonous snakebite in China. Recently, dimeric *O*-demethylmurrayafoline A (**1**) was found to exhibit antiplasmodial activity against *P.falciparum in vitro* [3].



1. $R_1 = R_2 = H$
2. $R_1 = OMe$ $R_2 = H$
3. $R_1 = R_2 = OMe$

Due to the restricted rotation around the central biaryl axis, **1**, **2** and **3** are structurally atropisotopic. However, little attention has been paid to the relationship between the stereochemistry and the biological activity [3]. To our knowledge, there is no report of the synthesis of optically pure biscarbazole [4]. Herein, we report the first synthesis of the optically pure (*R*)-**1** and (*S*)-**1**, in which the regioselective oxidative coupling of synthetic *O*-demethylmurrayafoline A (**9**) and the enantioresolution of (±)-**1** were employed as the key steps. The absolute configurations were established on the bases of the X-ray crystallographic analysis and CD spectrum.

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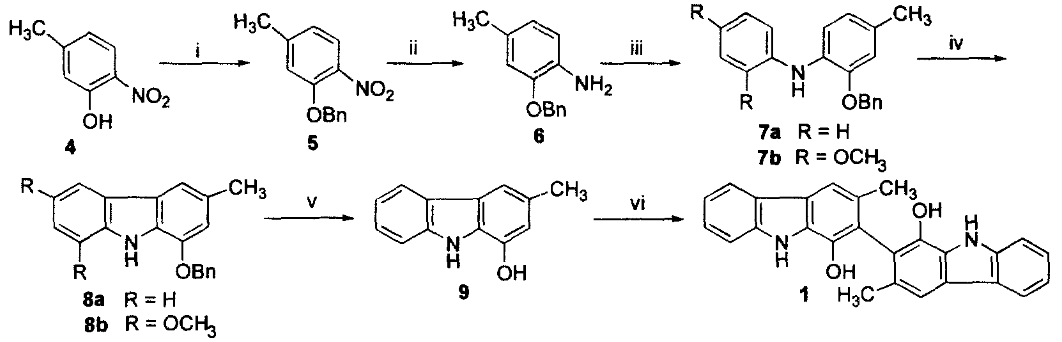
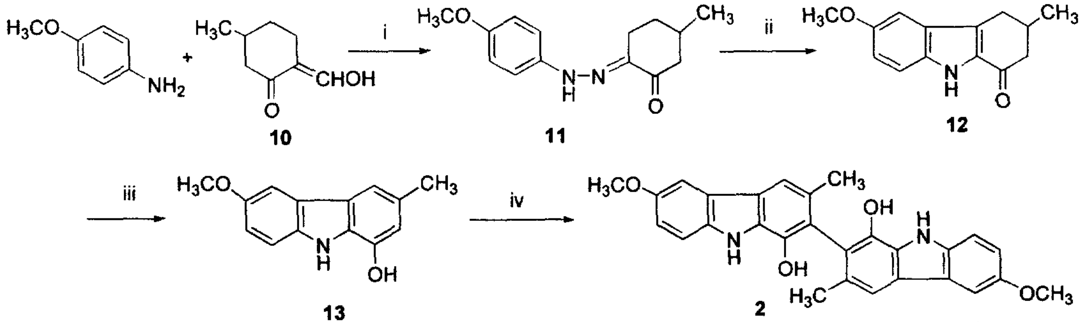
Scheme 1



Reagents and conditions: i) $PhCH_2Br$, NaOH, DMSO, 86%; ii) Fe, H_2O, NH_4Cl, reflux, 83%; iii) Pd_2(dibenzylideneacetone)$_3$, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 18-C-6, *t*-BuONa, THF, 40°C, iodobenzene for **7a**, 93%, 2,4-dimethoxy-1-iodobenzene for **7b**, 77%; iv) $Pd(OAc)_2$, HOAc, reflux, 32%; v) 10% Pd/C, H_2, 73%; vi) $(t\text{-}BuO)_2$, chlorobenzene, reflux, 87%.

As shown in Scheme 1, the hydroxyl group of **4** was protected as the benzyl ether, and the resulting product **5** was reduced by ferrum. When compound **6** was subjected to Goldberg coupling reaction [5a,b] and Ullmann coupling reaction [5c], the desired product was all obtained in poor yields. Finally, amination of **6** was achieved under Buchwald condition [5d,e] in 93% yield. Cyclization of the *N*-phenyl-2-benzyloxy-4-methylaniline (**7a**) through refluxing $Pd(OAc)_2$ in acetic acid gave **8a** in 32% yield [6]. The low yield of the cyclization is possible to be caused by the electron-donating effects of the methyl and the benzyloxyl substitution in the benzene ring. Catalytic hydrogenation of **8a** afforded the *O*-demethylmurrayafoline A (**9**) in 73% yield. Oxidative coupling of the phenolic monomer **9** was completed by aerial treatment of **9** with $(t\text{-}BuO)_2$ in chlorobenzene to provide the racemic dimeric *O*-demethyl-murrayafoline A (**1**) in 87% yield [7]. The desired site of coupling was confirmed by the disappearance of the signal of 2-H in the ^1H NMR spectrum and the analysis of X-ray crystallography.

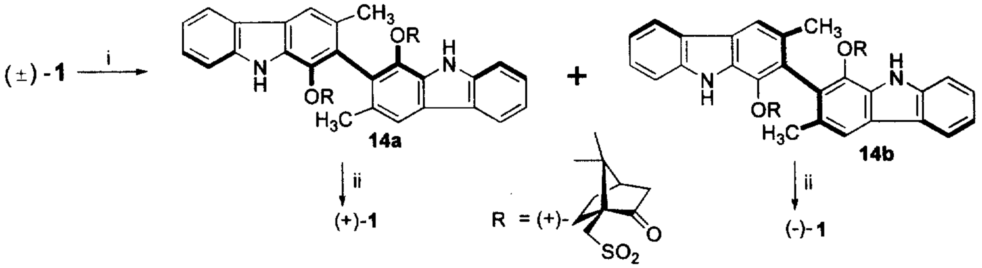
Scheme 2



Reagents and conditions: i) HCl, $NaNO_2$, CH_3COONa, 54%; ii) HOAc, HCl, reflux, 44%; iii) 10% Pd/C, 220-240°C, 73%; iv) $(t\text{-}BuO)_2$, chlorobenzene, reflux, 82%.

After accomplishment of the synthesis of racemic dimeric *O*-demethylmurrayafoline A (**1**), we attempted to synthesize clausenamine-A (**3**) in a similar manner. However, the cyclization of **7b** with palladium acetate failed to afford the desired product **8b**, probably due to the electron donating of the methoxyl group which decreases the reaction activity. Thus, another approach to the analog of **1** was taken as a model study (Scheme 2). The Japp-Klingemann condensation [4] of *p*-methoxybenzenediazonium chloride with **10** resulted in hydrazone **11**, which cyclized to give **12**. Treatment of **12** with 10% Pd/C in a sealed tube under evacuated condition furnished **13** in 73% yield. The next oxidative coupling of **13** provided **2** in 82% yield.

Scheme 3



Reagents and conditions: i) Et_3N, (+)-camphorsulfonyl chloride, CH_2Cl_2, reflux, 94%, then chromatographic separation of **14a** and **14b** (silica gel, eluant: CH_2Cl_2-$CHCl_3$-Et_2O = 50:1:2); ii) KOH, EtOH, rt, (+)-**1**, 73.2%, (-)-**1**, 94%.

Resolution of (±)-**1** was accomplished by silica gel column chromatography of their corresponding (+)-camphorsulfonates **14a** and **14b** with CH_2Cl_2:$CHCl_3$:Et_2O (50:1:2) as the eluant (Scheme 3). The first eluted ester was **14b** (46%, m.p. 132-134°C, $[\alpha]^{21}_D$ +15.2° (c 0.48, $CHCl_3$)), followed by **14a** (48%, m.p. 177-179°C, $[\alpha]^{21}_D$ +3.75° (c 0.1, $CHCl_3$)). ^1H NMR spectrum of **14a** shows two well-separated sets of AB system signals of the methylene group (-CH_2SO_2-) at 3.48 (2H, d, *J* = 14.8Hz) and 2.23 (2H, d, *J* = 14.8Hz) ppm, while those of **14b** were at 3.13 (2H, d, *J* = 14.9Hz) and 2.53 (2H, d, *J* = 14.8Hz) ppm.

Recrystallization of **14a** from ethanol provided a colorless prism for X-ray diffraction (Figure 1). The absolute stereochemistry of the **14a** was determined as (a*R*) by correlation with the known absolute configuration of (+)-camphorsulfonate ester moiety in it [9]. Treatment of **14a** and **14b** with KOH in EtOH afforded optically pure (*R*)-**1** (73.2%, $[\alpha]^{21}_D$ +29.9° (c 0.67, $CHCl_3$)) and (S)-**1** (94%, $[\alpha]^{21}_D$ -39° (c 0.1, $CHCl_3$)) respectively [11].

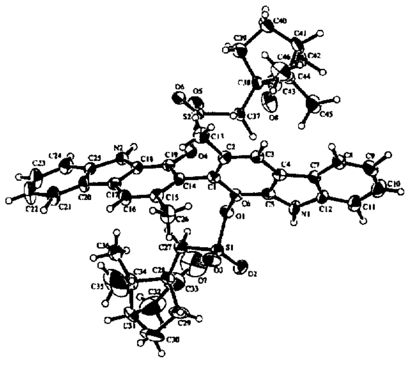


Figure 1: Single-crystal X-ray structure of **14a**

The structure of (+)-**1** was confirmed by the CD spectrum [12] of (+)-**1** which showed the first (positive) cotton effect at 256.6 nm and the second (negative) one at 227.4 nm, while its enantiomer (-)-**1** showed the first (negative) cotton effect at 257.4 nm and the second (positive) one at 227.6 nm [12]. (±)-**2** was subjected to the same procedure to afford optically pure (+)-**2** (57%, $[\alpha]^{21}_D$ +44.3° (c 0.09, $CHCl_3$)) and (-)-**2** (90%, $[\alpha]^{21}_D$ -44.7° (c 0.13, $CHCl_3$)), respectively [11]. The structure of (+)-**2** was confirmed as a*R* by the CD spectrum [12] of (+)-**2** which showed the first (positive) cotton effect at 256.4 nm and the second (negative) one at 228.6 nm, while its enantiomer (-)-**2** gave the first (negative) cotton effect at 258.4 nm and the second (positive) one at 229 nm.

In summary, we have accomplished the first synthesis of the optically pure (*R*)- and (*S*)-dimeric *O*-demethylmurrayafoline A (**1**) and established the absolute configuration of (+)-**1** as a*R* by X-ray analysis and CD spectrum. Therefore, the configurations of (-)-**1** and (-)-**2** should be a*S*, and (+)-**2** as a*R*.

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9. X-ray structure analysis: $C_{46}H_{48}N_2S_2O_8$.EtOH, Mr = 867.08, orthorhombic, space group $P2_12_12_1$, a = 16.763(3), b = 23.657(8), c = 11.572(1) Å, V = 4590(1) Å^3, Z = 4, Dx = 1.255 gcm^{-3}, MoKa (λ = 0.71069 Å), μ = 1.73 cm^{-1}, F(000) = 1840.00, T = 293 K. The structure was solved by direct method and expanded using Fourier techniques[10]. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1Ez, U.K.
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11. (a*R*)-**1**: m.p. > 260°C. ^{1}H NMR (300MHz, $CDCl_3$) 8.28 (b, 2H, -NH), 8.09 (d, *J* = 7.9 Hz, 2H), 7.70 (s, 2H), 7.43 (m, 4H), 7.26 (m, 2H), 2.17 (s, 6H). FT-IR (KBr): 3508, 3409, 2922, 1614, 1564, 1251 cm^{-1}. UV (Ethanol): 296.4, 252.4, 224.4 nm. MS m/z (EI, 70ev): 392, 391(100), 197, 196. HRMS calcd. for $C_{26}H_{20}N_2O_2$ (M+): 392.1526, found 392.1513.
    (a*S*)-**1**: m.p. > 260°C. ^{1}H NMR (300MHz, $CDCl_3$) 8.28 (b, 2H, -NH), 8.09 (d, *J* = 8.0 Hz, 2H), 7.71 (s, 2H), 7.47 (m, 4H), 7.26 (m, 2H), 2.18 (s, 6H). FT-IR (KBr): 3510, 3422, 2925, 1615,1564,1253 cm^{-1}. UV (Ethanol): 295.2, 253.6, 224.8 nm. MS m/z (EI, 70ev): 392, 391(100), 197, 196. HRMS calcd. for $C_{26}H_{20}N_2O_2$ (M+): 392.1526, found 392.1531.
    (a*R*)-**2**: m.p. > 260°C. ^{1}H NMR (300MHz, $CDCl_3$) 8.13 (b, 2H, -NH), 7.66 (s, 2H), 7.55 (d, *J* = 2.4Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.11 (dd, *J* = 8.8, 2.4Hz, 2H), 5.12 (s, 2H, -OH), 3.96 (s, 6H, $-OCH_3$), 2.17 (s, 3H, $-CH_3$). FT-IR (KBr): 3529, 3414, 2924, 1564 cm^{-1}, 1212. UV (Ethanol): 302.0, 254.0, 226.0, 203.2 nm. MS m/z (EI, 70ev): 453, 452 (M^+), 227, 226. HRMS calcd. for $C_{28}H_{24}N_2O_4$ (M+): 452.1737, found 4520.1738.
    (a*S*)-**2**: m.p. > 260°C. ^{1}H NMR (400MHz, $CDCl_3$) 8.10 (b, 2H, -NH), 7.65 (s, 2H), 7.55 (d, *J* = 2.4 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.10 (dd, *J* = 8.8, 2.5 Hz, 2H), 3.95 (s, 6H, $-OCH_3$), 2.17 (s, 3H, $-CH_3$). FT-IR (KBr): 3520, 3412, 2924, 1561, 1465, 1213 cm^{-1}. UV (Ethanol): 302.0, 253.6, 226.8, 203.6 nm. MS m/z (EI, 70ev): 453, 452 (M^+), 227, 226. HRMS calcd. for $C_{28}H_{24}N_2O_4$ (M+): 452.1737, found 4520.1738.
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