JOC*Note*

Total Synthesis of Two Naturally Occurring Bicyclo[3.2.1]octanoid Neolignans

Mingyi Wang,† Anxin Wu,‡ Xinfu Pan,* and Hongfang Yang†

Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

panxf@lzu.edu.cn

Received November 14, 2001

Abstract: The first total syntheses of the racemates of naturally occurring macrophyllin-type bicyclo[3.2.1]octanoid neolignans, kadsurenin C **3** and kadsurenin L **4**, were accomplished starting from vanillin and resorcinol. The acid-catalyzed rearrangement of hydrobenzofuranoid neolignans into bicyclo[3.2.1]octanoid neolignans was used as the key step.

The bicyclo[3.2.1]octanoid neolignans constitute an important class of neolignan compounds, which are further subdivided into the guianin-type **1** and the macrophyllin-type **2** (Figure 1).[1] Among the known bicyclo[3.2.1]octanoid neolignans, macrophyllin-type neolignans are less common than guianin-type neolignans.[2] Most of the isolated macrophyllin-type neolignans, however, have excellent PAF (platelet-activating factor)[3] antagonistic activities, and it was therefore important to devise an efficient synthetic route to this class of compounds. Two macrophyllin-type bicyclo[3.2.1]octanoid neolignans with significant PAF antagonistic activities are kadsurenin C **3** and kadsurenin L **4**, which are isolated from *Piper kadsura* (Choisy) Ohwi.[4] Their structures were determined on the basis of spectral analysis and chemical derivatization. In this paper, the first total syntheses of the racemates of kadsurenin C **3** and kadsurenin L **4** starting from vanillin and resorcinol are described.

The published approaches for the syntheses of bicyclooctanoid neolignans almost always adopt the cycloaddition strategy pioneered by Büchi et al.,[5] which was further developed by Engler et al.[6] In most cases, the cycloaddition strategy was used for the syntheses of the guianin-type neolignans and their analogues. Only one

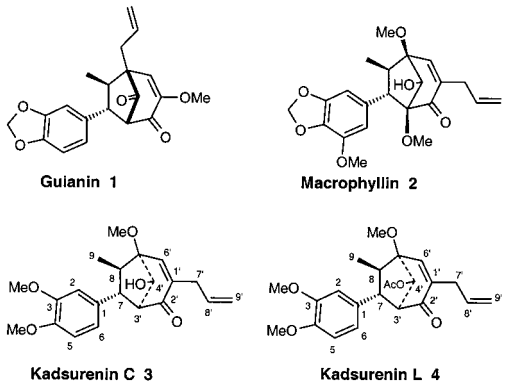
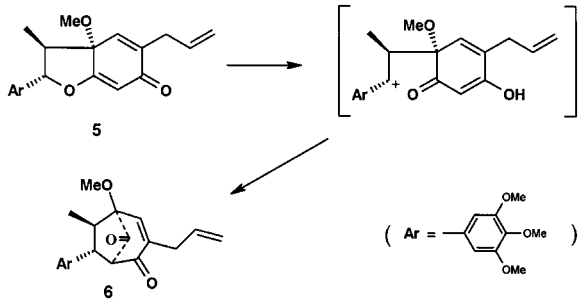


FIGURE 1.

SCHEME 1



report[7] afforded macrophyllin-type bicyclooctane products, and their absolute configuration (C-4′) was different from the desired target molecules. Apparently, the cycloaddition strategy could not be used for the syntheses of kadsurenin C **3** and kadsurenin L **4**, and in fact, our attempt to adopt this strategy also failed.

Gottlieb et al.[8] reported the acid-catalyzed rearrangement of mirandin-A **5** into bicyclo[3.2.1]octene **6** through an intermediate benzylic cation in 76% yield (Scheme 1). Comparison of **6** with methyl kadsurenin K **10** indicated that they have identical stereochemistry, and as it happens, the precursor of methyl kadsurenin K **10** is kadsurenone **9b**,[9] which is a hydrobenzofuranoid neolignan with specific antagonistic activity of PAF. Consequently, it was anticipated that the target molecules could be synthesized according to this strategy, and the retrosynthetic analysis is presented in Scheme 2.

Recently, we reported an efficient method for the preparation of cinnamyl aryl ethers.[10] The same method could also be utilized for the synthesis of 3,4-dimethoxycinnamyl 3-(allyloxy)phenyl ether **7** on a large scale and in good yield (67%, lit.[11] 23%). The cyclization of **7** in *N*,*N*-diethylaniline was carried out in a sealed tube at 225 °C for 12 h to stereoselectively afford the *trans*-dihydroben-

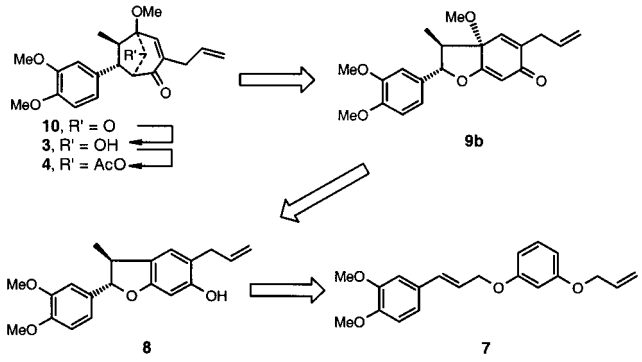
† Present address: Department of Chemistry, Center for Heterocyclic Compounds, University of Florida, Gainesville, FL 32611-7200.

‡ Present address: Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742.

(1) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191.
(2) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183; **1997**, *14*, 43.
(3) Demopoulos, C. A.; Pinckard, R. N.; Hanahan, D. J. *J. Biol. Chem.* **1979**, *254*, 9355.
(4) (a) Han, G. Q.; Dai, P.; Xu, L.; Wang, S. C.; Zheng, Q. T. *Chin. Chem. Lett.* **1992**, *3*, 521. (b) Ma, Y.; Han, G. Q.; Liu, Z. J. *Yaoxue Xuebao* **1993**, *28*, 307.
(5) (a) Büchi, G.; Mak, C. P. *J. Am. Chem. Soc.* **1977**, *99*, 8073. (b) Büchi, G.; Chu, P. S. *J. Org. Chem.* **1978**, *43*, 3717.
(6) Engler, T. A.; Wei, D.; Letavic, M. A. *Tetrahedron Lett.* **1993**, *34*, 1429.
(7) Mortlock, S. V.; Seckington, J. K.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2305.
(8) De Alvarenga, M. A.; Brocksom, B U.; Gottlieb, O. R.; Toshida, M.; Filho, R. B.; Figliuolo, R. *J. Chem. Soc., Chem. Commun.* **1978**, 831.
(9) Chang, M. N.; Han, G. Q.; Arison, B. H.; Springer, J. P.; Hwang, S. B.; Shen, T. Y. *Phytochemistry* **1985**, *24*, 2079.
(10) Wang, M. Y.; Wu, A. X.; Pan, X. F. *J. Chem. Res., Synop.* **1998**, 168.

10.1021/jo011077o CCC: $22.00
Published on Web 06/26/2002

SCHEME 2



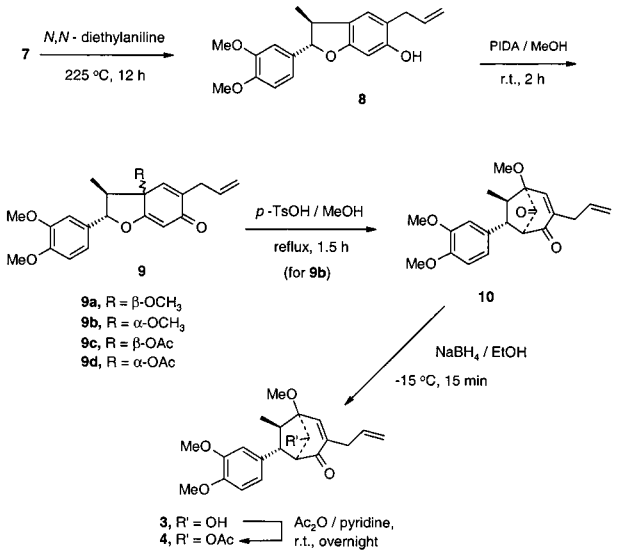
zofuran **8** in 40% yield. The thermal reaction apparently involved two Claisen rearrangements, followed by an abnormal Claisen rearrangement (1,5-homosigmatropic hydrogen shift).[12] Following a literature method,[11] oxidation of dihydrobenzofuran **8** in methanol gave the oxidative methoxylation products **9a** and **9b**. Using lead tetraacetate as an oxidant was unsatisfactory, since the major products were not **9a** and **9b** (15% and 9%, respectively) but were the epimeric acetates **9c** and **9d** (40%). With phenyliodonium diacetate (PIDA)[13] as an oxidant, however, it was found that the yields of **9a** and **9b** were substantially increased to 50% and 20%, respectively, whereas the yields of **9c** and **9d** dropped sharply to less than 5%. The acid-catalyzed rearrangement of a mixture of **9a** and **9b** in methanol afforded the desired bicyclo[3.2.1]octane skeleton **10** (73%) from **9b**. However, the same procedure employing pure **9a** did not give any rearrangement products, and the starting material was recovered. This suggests that the rearrangement might be controlled by the relative configuration of the tetrasubstituted sp^3 carbon atom. Selective reduction of **10** with sodium borohydride in ethanol at −15 °C provided **3** in 85% yield, which was reacted with acetic anhydride in pyridine at room temperature to give **4** in 90% yield (Scheme 3). The structures of **10**, **3**, and **4** were supported by ^{1}H NMR and ^{13}C NMR spectroscopic comparisons with literature data,[4b] and the stereochemistry at C-4′ was assigned by analogy with the work of Gottlieb.[8] The spectral data of **3** and **4** are consistent with those reported.[4]

The successful syntheses of kadsurenin C **3** and kadsurenin L **4** through rearrangement of the hydrobenzofuran to bicyclooctane neolignans indicates that this route may have general utility in the convenient syntheses of many members of the neolignan group.

Experimental Section

Melting points were determined on a micro-melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR were recorded with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. Column chromatography was conducted on silica gel H (200−400 mesh) and with 60−90 °C petroleum ether in the eluent. Compounds **7** and **8** were prepared according to literature methods.[10,11b]

SCHEME 3



***rac*-Denudatin B (9a) and *rac*-Kadsurenone (9b)**. To a solution of dihydrobenzofuran **8** (500 mg, 1.5 mmol) in dry MeOH (10 mL) was dropwise added a solution of PIDA (1.0 g, 3.1 mmol) in dry MeOH (15 mL) at room temperature. After the addition, the reaction mixture was stirred for 2 h and then evaporated to dryness. The residue was purified by flash column chromatography on silica gel H (200 mesh; petroleum ether−ethyl acetate, 4:1 to 2:1, v/v) to afford a yellow oil (420 mg). The crude product was purified by column chromatography on silica gel H (400 mesh; petroleum ether−ethyl acetate−acetone, 8:1.5:0.5, v/v). The first eluted compound was **9a**,[11b] obtained as a colorless oil (270 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.7 Hz, CH_3), 2.18−2.22 (1H, m, H-3), 3.13 (3H, s, OCH_3), 3.09−3.24 (2H, m, CH_2CH=CH_2), 3.89 (6H, s, 2 × Ar−OCH_3), 5.12−5.17 (2H, m, CH_2CH=CH_2), 5.36 (1H, d, J = 9.5 Hz, H-2), 5.82 (1H, s, H-7), 5.88 (1H, m, CH_2CH=CH_2), 6.27 (1H, s, H-4), 6.78−6.90 (3H, m, ArH). EIMS (m/z): 356 (M^+).

The second component eluted was obtained as a light yellow oil and identified as **9b**[11b] (110 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 7.6 Hz, CH_3), 2.65−2.71 (1H, m, H-3), 3.04 (3H, s, OCH_3), 3.10−3.15 (2H, m, CH_2CH=CH_2), 3.89 and 3.90 (6H, 2s, 2 × Ar−OCH_3), 5.12 (2H, d t, J = 2.0, 17.0 Hz, CH_2CH=CH_2), 5.23 (1H, s, H-2), 5.85 (1H, m, CH_2CH=CH_2), 5.89 (1H, s, H-7), 6.21 (1H, s, H-4), 6.84−6.89 (2H, m, ArH), 7.02 (1H, d, J = 0.5 Hz, ArH). HRMS (FAB) calcd for $C_{21}H_{24}O_5$ [M + 1] 357.1702. Found 357.1700.

***rac*-Methyl Kadsurenin K (10)**. A solution of **9b** (50 mg, 0.14 mmol) in dry MeOH (5 mL) containing a catalytic amount of *p*-toluenesulfonic acid was refluxed vigorously for 1.5 h. The residue obtained on removal of MeOH was purified by column chromatography on silica gel H (400 mesh; petroleum ether−ethyl acetate, 4:1, v/v) to afford pure **10**[4b] as a colorless oil (36.5 mg, 73%). IR (film): ν_{max} 2931, 2846, 1671, 1623, 1516, 1259, 1138 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.0 Hz, H-9), 2.44−2.50 (2H, m, H-7, H-8), 3.10−3.13 (2H, m, H-7′), 3.53 (1H, s, H-3′), 3.64 (3H, s, OCH_3-5′), 3.86 (6H, s, 2 × Ar−OCH_3), 5.16−5.20 (2H, m, H-9′), 5.83−5.90 (1H, m, H-8′), 6.58 (1H, d, J = 1.8 Hz, H-2), 6.66 (1H, dd, J = 2.0, 8.1 Hz, H-6), 6.79 (1H, d, J = 8.2 Hz, H-5), 7.06 (1H, s, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8 (C-1), 110.0 (C-2), 147.1 (C-3), 149.3 (C-4), 111.4 (C-5), 119.3 (C-6), 45.3 (C-7), 48.8 (C-8), 13.7 (C-9), 140.4 (C-1′), 194.4 (C-2′), 69.9 (C-3′), 202.2 (C-4′), 89.3 (C-5′), 148.4 (C-6′), 32.7 (C-7′), 133.7 (C-8′), 118.2 (C-9′), 54.0 (OCH_3-5′), 55.9 (OCH_3-3), 55.9 (OCH_3-4). EIMS (m/z): 356 (M^+). HRMS (FAB) calcd for $C_{21}H_{24}O_5$ [M + 1] 357.1702. Found 357.1728.

***rac*-Kadsurenin C (3)**. To a solution of **10** (18 mg, 0.05 mmol) in dry EtOH (15 mL) was dropwise added a solution of $NaBH_4$

(11) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brooker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309. (b) Ponpipom, M. M.; Bugianesi, R. L.; Brooker, D. R.; Yue, B. Z.; Hwang, S. B.; Shen, T. Y. *J. Med. Chem.* **1987**, *30*, 136.

(12) Schmid, E.; Frater, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1625.

(13) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891.

(25 mg, 0.06 mmol) in dry EtOH (5 mL) at −15 °C. After the addition, the reaction mixture was stirred at −15 °C for 15 min and then water was added to quench the reaction. The products were extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water, sat. $NaHCO_3$, and sat. NaCl and dried over Na_2SO_4. The crude oily product obtained on removal of the solvent was purified by preparative TLC (hexanes−ethyl acetate, 2:1, v/v) to give **3**[4b] as a light yellow oil (15.3 mg, 85%). IR (film): ν_{max} 3455 (br), 2950, 2931, 1681, 1590, 1515, 1461, 1363, 1264, 1236, 1128, 1101, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 6.9 Hz, H-9), 2.38 (1H, d, J = 8.1 Hz, H-7), 2.64−2.69 (1H, m, H-8), 3.01−3.05 (2H, m, H-7′), 3.09 (1H, s, H-3′), 3.46 (3H, s, OCH_3-5′), 3.87 (6H, s, 2 × Ar−OCH_3), 4.22 (1H, s, H-4′), 5.13−5.17 (2H, m, H-9′), 5.80−5.88 (1H, m, H-8′), 6.76 (1H, d, J = 8.2 Hz, H-5), 6.85 (1H, s, H-6′), 6.88 (1H, d, J = 8.2 Hz, H-6), 7.13 (1H, s, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6 (C-1), 110.8 (C-2), 147.8 (C-3), 149.0 (C-4), 111.8 (C-5), 120.7 (C-6), 51.8 (C-7), 46.7 (C-8), 13.1 (C-9), 139.8 (C-1′), 198.8 (C-2′), 53.6 (C-3′), 75.5 (C-4′), 89.8 (C-5′), 148.4 (C-6′), 32.5 (C-7′), 134.5 (C-8′), 117.4 (C-9′), 62.0 (OCH_3-5′), 55.8 (OCH_3-3), 55.8 (OCH_3-4). EIMS (*m*/*z*): 358 (M^+). HRMS (FAB) calcd for $C_{21}H_{26}O_5$ [M + 1] 359.1858. Found 359.1868.

***rac*-Kadsurenin L (4)**. To a solution of **3** (10 mg, 0.028 mmol) in dry pyridine (1 mL) was added freshly distilled Ac_2O (0.1 mL) at 0 °C. After the addition, the reaction mixture was stirred at 0 °C to room temperature overnight. The excess solvents were removed *in vacuo*, and the residue was dissolved in EtOAc (10 mL), washed with 2 N HCl and water, and dried over anhydrous Na_2SO_4. Purification through preparative TLC gave pure **4**,[4b] which was recrystallized from ethyl ether−hexane to give colorless crystals (10.1 mg, 90%), mp 136−137 °C. IR (KBr): ν_{max} 2961, 2933, 1736, 1681, 1599, 1515, 1460, 1412, 1370, 1321, 1300, 1252, 1233, 1160, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (3H, d, J = 6.5 Hz, H-9), 2.18 (3H, s, $-OCOCH_3$), 2.43 (1H, d, J = 8.0 Hz, H-7), 2.74−2.80 (1H, m, H-8), 3.00 (1H, s, H-3′), 3.03−3.05 (2H, m, H-7′), 3.38 (3H, s, OCH_3-5′), 3.87 and 3.88 (6H, 2s, 2 × Ar−OCH_3), 5.14−5.18 (2H, m, H-9′), 5.32 (1H, s, H-4′), 5.80−5.90 (1H, m, H-8′), 6.80 (1H, d, J = 5.1 Hz, H-5), 6.85−6.87 (3H, m, H-2, H-6, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3 (C-1), 111.1 (C-2), 147.9 (C-3), 148.7 (C-4), 111.3 (C-5), 120.1 (C-6), 51.3 (C-7), 46.3 (C-8), 13.2 (C-9), 140.0 (C-1′), 197.6 (C-2′), 54.1 (C-3′), 75.1 (C-4′), 88.4 (C-5′), 148.9 (C-6′), 32.4 (C-7′), 133.7 (C-8′), 117.7 (C-9′), 60.7 (OCH_3-5′), 55.9 (OCH_3-3), 55.9 (OCH_3-4), 21.2 and 169.1 ($-OCOCH_3$). EIMS (*m*/*z*): 400 (M^+). HRMS (FAB) calcd for $C_{23}H_{28}O_6$ [M] 400.1886. Found 400.1830.

Acknowledgment. We thank Dr. Yuxin Cui for obtaining the NMR spectra of compounds **3** and **4**. Many thanks are also due to Dr. Suoming Zhang for discussions. Financial support was provided by the National Science Foundation of China (No. 20172023) and is highly appreciated.

Supporting Information Available: NMR spectra of **3**, **4**, **9b**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO011077O