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Article

Ramberg-Bäcklund Rearrangement Approaches to the Synthesis of Natural Bibenzyls

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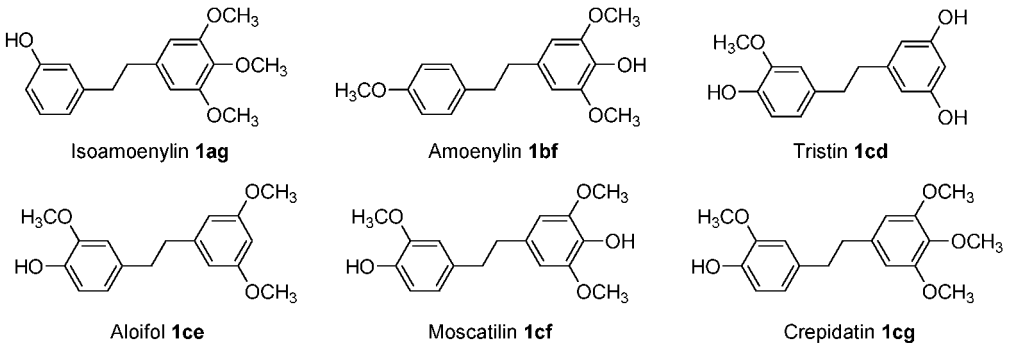
The Ramberg-Bäcklund rearrangement has been successfully utilized to convert readily available α- and α′-hydrogen bearing substituted dibenzyl sulfones into corresponding stilbene derivatives, which is conveniently followed by hydrogenation in the presence of 10% Pd/C to afford the natural bibenzyls.

Keywords bibenzyl, sulfone, Ramberg-Bäcklund rearrangement, biological activity

Introduction

Bibenzyls (dihydrostilbenes) are the important natural products and have attracted considerable interests due to their biological activities.[1] Some bibenzyls, especially some termed combretastatins, are reported to exhibit pronounced antimitotic and antileukemic activities and have been tested as cytotoxic agents so far against a series of cancer cell lines. The activity of this kind of natural antimitotics depends on their ability to interact with tubulin, the predominant protein component of microtubules, which make up the mitotic spindle. They are capable of inhibiting microtubule assembly at nanomolar concentration and share a common binding site on tubulin with the well-known antimitotic agents colchicines, podophyllotoxin, and steganancin.[2] Structure-activity relationship analyses of this series of natural products and their analogues have shown that the phenolic functional groups are essential for antitumor activity.[3] There is a clear structure-activity correlation between bridge length (the number of methylene units separating the aryl moieties) with biological potency, and the two-carbon bridge analogues, *i.e.* bibenzyls, have the maximum activity, while the one-carbon and three-carbon bridge analogues are somewhat less potent.[4] The occurrence of the bibenzyls in nature in limited amount in rather inaccessible plant species, has increased the need for good synthetic methods. Many synthetic methodologies have been developed for the preparation of bibenzyls and their derivatives, and most are through the hydrogenation of stilbene derivatives, which are usually obtained by means of Wittig olefination.[2,5] Medarde reported a versatile approach to the synthesis of the families of combretastatins and their analogues utilizing a common lithiated 1,3-dithiane intermediate reacting with benzylbromo-derivatives.[6] Bracher described a convenient approach to natural bibenzyls starting from a styrene and a phenolic building block by a hydroboration/palladium catalyzed

Scheme 1 Structures of natural bibenzyls **1**



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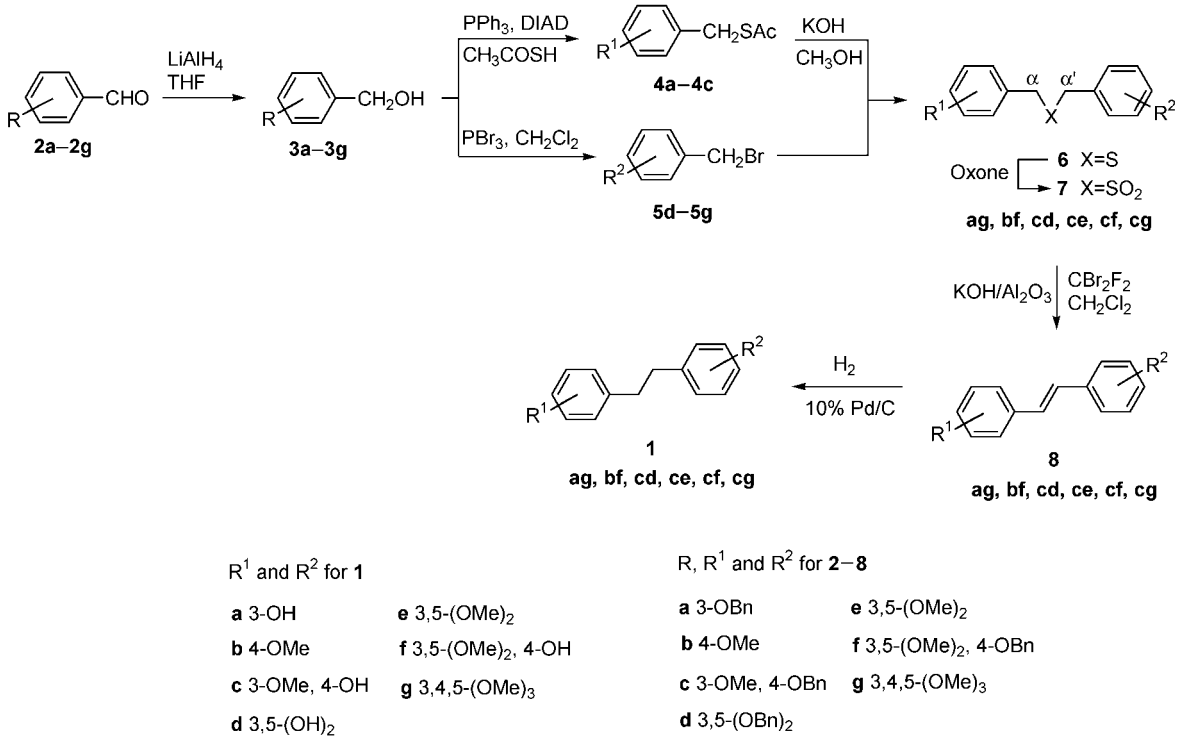
Scheme 2 Synthesis of natural bibenzyls **1**



R^1 and R^2 for **1**

a 3-OH **e** 3,5-$(OMe)_2$
b 4-OMe **f** 3,5-$(OMe)_2$, 4-OH
c 3-OMe, 4-OH **g** 3,4,5-$(OMe)_3$
d 3,5-$(OH)_2$

R, R^1 and R^2 for **2**−**8**

a 3-OBn **e** 3,5-$(OMe)_2$
b 4-OMe **f** 3,5-$(OMe)_2$, 4-OBn
c 3-OMe, 4-OBn **g** 3,4,5-$(OMe)_3$
d 3,5-$(OBn)_2$

cross-coupling protocol to give the lunularic acid and lunularine.[7] Recently Hudlicky and co-workers efficiently obtained the bibenzyl product designated combretastatin B-1 via coupling of biocatalytically generated *p*-bromomethoxycatechol with trimethoxyphenylacetylene under Suzuki-Miyaura conditions.[8] We recently reported a new protocol of Ramberg-Bäcklund reaction to transform the α- and α′-hydrogen bearing sulfones into alkenes directly.[9] The previous finding that sulfones were smoothly transformed into alkenes in excellent yield prompted us to be interested in using our procedure to synthesize six natural bibenzyls, isoamoenylin (**1ag**),[10] amoenylin (**1bf**),[10] tristin (**1cd**),[11] aloifol (**1ce**),[11] moscatilin (**1cf**)[12] and crepidatin (**1cg**)[13] (Scheme 1). In this paper the synthesis of them as well as full details of their preparation will be reported.

Results and discussion

In our previous studies on the synthesis of polyenes, we reported the successful application of our procedure to the formation of conjugated trienes from diallylic sulfones,[9b] conjugated tetraenes from allylic dienylic sulfones[9d] and linear and cyclic enediynes from dipropargylic sulfones.[9e] Our synthetic method was also applied to the synthesis of natural products containing a triene unit such as galbanolenes.[9f,9g] The procedure reported here involves the preparation of the vital intermediates substituted stilbenes **8**. The single bond products bibenzyls **1** are obtained by hydrogenation of **8** in the presence of 10% Pd/C conveniently. This retrosynthetic approach relied on the synthesis of dibenzyl sulfones **7**, which were in turn prepared from substituted benzaldehyde.

As shown in Scheme 2, we used commercially available benzaldehydes or their benzylic derivatives **2** as starting materials, which could be easily reduced by $LiAlH_4$ in THF to give the corresponding benzyl alcohols **3** directly. These alcohols **3** can be either converted to thiol acetates **4** via the Mitsunobu reaction[14] with thioacetic acid in the presence of Ph_3P and DIAD (diisopropyl azodicarboxylate) or the corresponding benzyl bromides **5** by reaction with PBr_3 in CH_2Cl_2 respectively. *In situ* cleavage of the acetyl moiety of **4** with KOH in CH_3OH followed by alkylation of the resulting thiols with benzyl bromide **5** provided the unsymmetrical sulfides **6** ($R^1 \neq R^2$) in good yields (Table 1). All of these sulfides **6** were oxidized by oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in the mixture of MeOH, CH_2Cl_2 and H_2O (1 ∶ 1 ∶ 0.01) to give the corresponding sulfones **7** in high yields (Table 1). It is noteworthy that oxidation of these sulfides **6** by oxone in CH_2Cl_2 according to our previous procedure[9] was very slow, when methanol and a little of water was added to the reaction system, the oxidation underwent fast. Treatment of the sulfones **7** with CF_2Br_2 in the presence of KOH/Al_2O_3 in CH_2Cl_2 gave the substituted stilbenes **8** mainly with *trans*-isomer (>95%) in good yields. The *trans* geometries of the stilbenes were assigned by the characteristic ^1H NMR coupling constants of the olefinic protons (Table 2). Catalytic hydrogenation of stilbenes **8** in the presence of 10% Pd/C in EtOAc-MeOH (3 ∶ 1) conducted reduction of the double bond as well as the removal of the benzyl protecting groups simulta-

neously to afford the bibenzyls **1** conveniently. All of these bibenzyls, isoamoenylin (**1ag**),[10] amoenylin (**1bf**),[10] tristin (**1cd**),[11] aloifol (**1ce**),[11] moscatilin (**1cf**)[12] and crepidatin (**1cg**)[13] were identified by their spectral data and further corroborated by comparison of their physical and spectroscopic properties to those reported in the literature. To the best of our knowledge, except for the previous preparation of **1cg**,[6a] other bibenzyls **1** were synthesized herein for the first time. It is worth pointing out that the ^{1}H NMR spectra of bibenzyls **1** showed signals (singlet in $CDCl_3$ or CD_3OD, multiplet in CD_3COCD_3) for four benzylic methylene protons at δ 2.68—2.82, which are typical of the four benzylic methylene protons of bibenzyls.[15]

Conclusion

In summary, we have successfully explored the Ramberg-Bäcklund rearrangement as a key step to synthesize six natural bibenzyls. This methodology offers a rapid, convergent and practically simple route to the series of natural products and their analogues. The synthetic transformation utilizes readily available benzaldehydes as starting materials. The synthetic route is facile and the reactions can be performed on molar scales. This study may eventually offers many possibilities to design and synthesize bibenzyl derivatives which can be evaluated for their biological activities and the structure-activity relationships. Other application of our investigation will be reported in due course.

Experimental

General methods and materials

Melting points were measured on a Kofler apparatus and were uncorrected. IR spectra were recorded on a Nicolet 670 FT-IR spectrophotometer and reported in wavenumbers (cm^{-1}). The ^{1}H and ^{13}C NMR data were recorded on a Avance-200, a Mercury Plus-300 or a

Table 1 Data of dibenzyl sulfides **6** and dibenzyl sulfones **7**

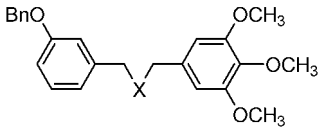
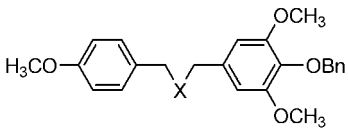
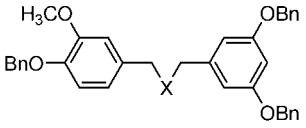
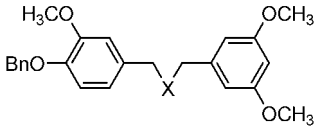
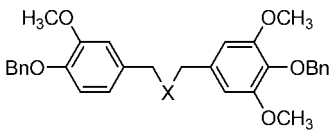
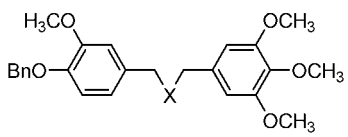
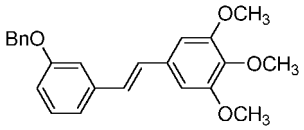
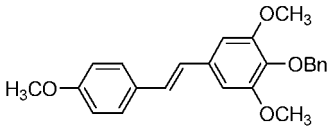
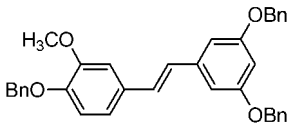
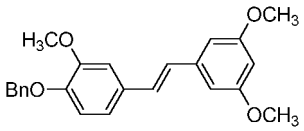
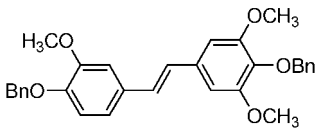
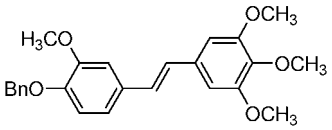
Entry	Structure	Yield	δ_H and δ_C of CH_2XCH_2	IR ν/cm^{-1}	HRMS
6ag (X=S)		83%	3.53 (s, 2H), 35.8 3.58 (s, 2H), 36.0	2937, 1591, 1238, 1127, 734, 697	$C_{24}H_{26}O_4SNa$ [M+Na]$^+$ 433.1444, found 433.1449
7ag (X=SO_2)		88%	4.04 (s, 2H), 58.0 4.14 (s, 2H), 58.2	2974, 1588, 1303, 1128, 881, 794, 692	$C_{24}H_{27}O_6S$ [M+H]$^+$ 443.1523, found 443.1547
6bf (X=S)		82%	3.56 (s, 2H), 35.1 3.60 (s, 2H), 36.0	2934, 1588, 1242, 1127, 833, 731, 697	$C_{24}H_{26}O_4SNa$ [M+Na]$^+$ 433.1444, found 433.1437
7bf (X=SO_2)		92%	4.03 (s, 2H), 57.4 4.07 (s, 2H), 58.0	2975, 1511, 1303, 1124, 833, 739, 672	$C_{24}H_{30}NO_6S$ [M+NH_4]$^+$ 460.1788, found 460.1783
6cd (X=S)		93%	3.62 (s, 2H), 35.5 3.63 (s, 2H), 35.8	2909, 1588, 1318, 1123, 848, 747, 698	$C_{36}H_{38}NO_4S$ [M+NH_4]$^+$ 580.2516, found 580.2520
7cd (X=SO_2)		96%	4.02 (s, 2H), 57.5 4.05 (s, 2H), 58.1	2909, 1588, 1318, 1132, 848, 747, 698	$C_{36}H_{38}NO_6S$ [M+NH_4]$^+$ 612.2414, found 612.2402
6ce (X=S)		91%	3.57 (s, 2H), 35.4 3.60 (s, 2H), 35.8	2938, 1592, 1258, 1155, 856, 747, 690	$C_{24}H_{30}NO_4S$ [M+NH_4]$^+$ 428.1890, found 428.1896
7ce (X=SO_2)		90%	4.05 (s, 2H), 57.8 4.07 (s, 2H), 58.3	2975, 1599, 1301, 1154, 852, 742, 696	$C_{24}H_{27}O_6S$ [M+H]$^+$ 443.1523, found 443.1531
6cf (X=S)		86%	3.59 (s, 2H), 36.0 3.62 (s, 2H), 36.5	2938, 1712, 1508, 1223, 1128, 734, 698	$C_{31}H_{36}NO_5S$ [M+NH_4]$^+$ 534.2309, found 534.2316
7cf (X=SO_2)		93%	4.06 (s, 2H), 57.8 4.09 (s, 2H), 58.0	2936, 1592, 1302, 1126, 856, 739, 699	$C_{31}H_{36}NO_7S$ [M+NH_4]$^+$ 566.2207, found 566.2206
6cg (X=S)		87%	3.52 (s, 2H), 35.6 3.56 (s, 2H), 36.0	2937, 1508, 1231, 1127, 853, 740, 699	$C_{25}H_{28}O_5SNa$ [M+Na]$^+$ 463.1550, found 463.1560
7cg (X=SO_2)		92%	4.04 (s, 2H), 58.0 4.10 (s, 2H), 58.0	2935, 1590, 1510, 1296, 1130, 747, 699	$C_{25}H_{29}O_7S$ [M+H]$^+$ 473.1629, found 473.1661

Table 2 Data of stilbenes **8**

Entry	Structure	Yield	δ_H of CH=CH	*J*/Hz	IR ν/cm^{-1}	HRMS
8ag		84%	7.03 (d, 1H) 7.08 (d, 1H)	16.2 16.2	2938, 1418, 1128, 815, 749	$C_{24}H_{25}O_4$ [M+H]$^+$ 377.1747, found 377.1751
8bf		78%	6.91 (d, 1H) 7.00 (d, 1H)	16.0 16.0	2935, 1510, 1246, 1126, 831, 734	$C_{24}H_{25}O_4$ [M+H]$^+$ 377.1747, found 377.1742
8cd		86%	6.94 (s, 1H) 6.99 (s, 1H)	16.2 16.2	3029, 1590, 1159, 733, 698	$C_{36}H_{33}O_4$ [M+H]$^+$ 529.2373, found 529.2392
8ce		85%	6.95 (d, 1H) 7.01 (d, 1H)	16.5 16.5	2936, 1593, 1512, 1153, 849, 735	$C_{24}H_{25}O_4$ [M+H]$^+$ 377.1747, found 377.1753
8cf		81%	6.88 (d, 1H) 6.95 (d, 1H)	16.2 16.2	2937, 1510, 1245, 1130, 850, 698	$C_{31}H_{31}O_5$ [M+H]$^+$ 483.2166, found 483.2157
8cg		80%	6.89 (d, 1H) 6.95 (d, 1H)	16.1 16.1	2938, 1580, 1418, 1128, 815, 749	$C_{25}H_{27}O_5$ [M+H]$^+$ 407.1853, found 407.1853

Bruker-400 MHz spectrometer. The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Mass spectral (MS) data were obtained on a V.G.ZAB-HS mass spectrometer. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEX II 47e mass spectrometer. Column chromatography was generally performed on silica gel (200—300 mesh) and TLC inspections on silica gel GF_{254} plates, if not noted especially below. 4-Hydroxy-3,5-dimethoxybenzaldehyde was prepared according to literature methods.[16]

Benzyl alcohols 3 A solution of individual benzaldehydes **2** (10 mmol) in THF (25 mL) was added dropwise to a well-stirred suspension of $LiAlH_4$ (10 mmol) in THF. The reaction mixture was stirred at r.t. for 2 h and then quenched by water (10 mL), extracted with ethyl acetate (3×25 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was evaporated *in vacuo* and flash chromatography of the residue over silica gel [petroleum ether (boiling range 60—90 ℃)-ethyl acetate, 2∶1] afforded the corresponding benzyl alcohols **3**. All of these products were easily characterized by comparison with their analogues.[17]

Thiol acetates 4 A solution of DIAD (10 mmol) in dry C_6H_6 (10 mL) was added to a stirred solution of Ph_3P (10 mmol) in C_6H_6 (50 mL) at 0 ℃. The resulting red solution was kept at 0 ℃ for 15 min and then a precooled (0 ℃) mixture of the individual benzyl alcohol **3a**—**3c** (10 mmol) and CH_3COSH (10 mmol) in dry C_6H_6 (10 mL) was added in one portion. The mixture was stirred at r.t. for 1 h and the solvent was removed *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether-ethyl acetate, 10∶1) afforded thiol acetates **4**. These products can be easily characterized by comparison with their analogues.[18]

Benzyl bromides 5 PBr_3 (10 mmol) was added to a well-stirred solution of the individual benzyl alcohol **3d**—**3g** (10 mmol) in dry CH_2Cl_2 (50 mL) at 0 ℃. The stirring was continued for 2 h at 0 ℃ for 1 h. The reaction mixture was poured into ice-water (200 mL), extracted with diethyl ether (3×50 mL). The ether layers were combined and dried with $MgSO_4$. The solvent was evaporated and flash chromatography of the residue (petroleum ether-ethyl acetate, 10∶1) gave the desired benzyl bromide **5**. All of these products were easily characterized by comparison with their analogues.[17]

General procedure for the preparation of sulfides 6 The individual thiol acetate **4** (5.1 mmol) was added to a solution of KOH (5.1 mmol) in methanol (10 mL). After being stirred at 0 ℃ for 30 min, the solvent was evaporated *in vacuo* and the solvent was changed to benzene (10 mL). To this well-stirred thiol solution was then dropwise added the individual benzyl bromides **5** (5 mmol) over a period of 5 min and the stirring was continued for 1 h at r. t.. The solvent was removed *in vacuo* and flash chromatography of the residue (petroleum ether-CH_2Cl_2, 10∶1) afforded the unsymmetrical sulfide **6**. These six dibenzyl sulfides were easily characterized by their spectra, especially by the ^1H and ^{13}C NMR signals for α- and α′- benzylic methylene at δ_H 3.52—3.63 and δ_C 35.1—36.5 (Table 1).

General procedure for the preparation of sulfones 7 The individual sulfide **6** (5 mmol) was dissolved in the mixture of CH_2Cl_2-CH_3OH-H_2O (1∶1∶0.01, 10 mL). To this well-stirred solution the oxone (25 mmol) was added and the reaction mixture was stirred at r. t. for 30 min. Then the mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layer was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. The crude product was flash chromatographed (petroleum ether-CH_2Cl_2, 2∶1) to give the sulfone **7**. These six dibenzyl sulfones were easily characterized by their ^1H and ^{13}C NMR spectra, especially by the ^1H and ^{13}C NMR signals for α- and α′-benzylic methylene at δ_H 4.02—4.14 and δ_C 57.4—58.3 (Table 1).

General procedure for the preparation of stilbenes 8 A solution of the individual sulfones **7** (4 mmol) in dry CH_2Cl_2 (10 mL) was added to a well-stirred suspension of KOH/Al_2O_3 (10 mmol of KOH) in CBr_2F_2/CH_2Cl_2 (1∶10, 10 mL). The reaction mixture was stirred for 12 h at r. t.. Then KOH/Al_2O_3 was removed by filtering and the solution was evaporated *in vacuo*. Flash chromatography of the residue over silica gel (petroleum ether-CH_2Cl_2, 10∶1) afforded the following stilbene **8**. These six stilbenes were easily characterized by their spectra, especially by the ^1H NMR signals for two benzylic methine protons of the double bond at δ_H 6.88—7.03 and 6.95—7.08 with coupling constants (J=16.0—16.5 Hz) which revealed the *trans* geometries of the stilbenes (Table 2).

General procedure for the preparation of bibenzyls 1 A solution of the individual stilbenes **8** (3 mmol) in EtOAc-MeOH (3∶1, 25 mL) was hydrogenated under hydrogen atmosphere (10% Pd/C, 20 mg). The reaction mixture was filtered through a short column of silica gel and the filtrate was concentrated *in vacuo* to give the crude bibenzyl **1**. Flash chromatography of the residue over silica gel (petroleum ether-acetone, 2∶1) afforded the bibenzyl **1**. The spectral data (IR, NMR and MS) for the natural products **1ag**,[10] **1bf**,[10] **1cd**,[11] **1ce**,[11] **1cf**[12] and **1cg**[13] were identical with those in the literatures respectively.

3′-Hydroxy-3,4,5-trimethoxybibenzyl (isoamoenylin 1ag) Colorless oil, yield 94%; ^1H NMR (CD_3OD, 400 MHz) δ: 2.79 (s, 4H, CH_2CH_2), 3.71 (s, 3H, 4-OCH_3), 3.73 (s, 6H, 3,5-OCH_3), 4.87 (br.s, 1H, OH), 6.39 (s, 2H, 2,6-H), 6.60—6.63 (m, 3H, 2′,4′,6′-H), 7.21 (t, J=7.5 Hz, 1H, 5′-H); ^{13}C NMR (CD_3OD, 100 MHz) δ: 38.8 (CH_2), 39.0 (CH_2), 56.5 (3,5-OCH_3), 61.1 (4-OCH_3), 106.9, 113.7, 116.5, 120.9, 130.2, 137.1, 139.2, 144.5, 154.1, 158.3; IR (film) ν: 3402, 2936, 1591, 1125, 782, 698 cm^{-1}; MS (70 eV) *m/z* (%): 288 (M^+, 20), 181 (100), 107 (6), 77 (4).

4-Hydroxy-3,4′,5-trimethoxybibenzyl (amoenylin 1bf) Colorless oil, yield 89%; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.77 (s, 4H, CH_2CH_2), 3.80 (s, 3H, 4′-OCH_3), 3.85 (s, 6H, 3,5-OCH_3), 5.48 (br s, 1H, OH), 6.38 (s, 2H, 2,6-H), 7.10 (d, J=8.5 Hz, 2H, 2′,6′-H), 7.10 (d, J=8.5 Hz, 2H, 3′,5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 37.1 (CH_2), 38.2 (CH_2), 55.1 (4′-OCH_3), 56.1 (3,5-OCH_3), 105.1, 113.6, 129.3, 132.7, 132.7, 133.6, 146.7, 157.7; IR (film) ν: 3443, 2935, 1513, 1242, 1114, 827 cm^{-1}; MS (70 eV) *m/z* (%): 288 (M^+, 24), 167 (100), 121 (43), 91 (3), 77 (4).

3′-Methoxy-3,4′,5-trihydroxybibenzyl (tristin 1cd) Colorless oil, yield 91%; ^1H NMR (CD_3COCD_3, 300 MHz) δ: 2.68—2.81 (m, 4H, CH_2CH_2), 3.80 (s, 3H, 3′-OCH_3), 6.21 (d, J=1.8 Hz, 1H, 4-H), 6.24 (d, J=1.8 Hz, 2H, 2,6-H), 6.66 (dd, J=8.1 Hz and 1.8 Hz, 1H, 6′-H), 6.74 (d, J=8.1 Hz, 1H, 5′-H), 6.80 (d, J=1.8 Hz, 1H, 2′-H), 7.54 (s, 1H, 4′-OH), 8.37 (s, 2H, 3,5-OH); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 42.5 (CH_2), 43.6 (CH_2), 60.7 (3′-OCH_3), 105.6, 112.3, 117.4, 120.1, 126.1, 138.7, 149.7, 149.9, 152.6, 163.8; IR (film) ν: 3346, 2941, 1603, 1515, 1151, 840 cm^{-1}; MS (70 eV) *m/z* (%): 260 (M^+, 8), 137 (100), 123 (6), 77 (5).

4′-Hydroxy-3,3′,5-trimethoxybibenzyl (aloifol 1ce) Colorless oil, yield 94%; ^1H NMR (CD_3OD, 300 MHz) δ: 2.81 (s, 4H, CH_2CH_2), 3.74 (s, 6H, 3,5-OCH_3), 3.81 (s, 3H, 3′-OCH_3), 4.70 (br.s, 1H, OH), 6.30 (d, J=2.4 Hz, 1H, 4-H), 6.32 (d, J=2.4 Hz, 2H, 2,6-H), 6.63 (d, J=7.8 Hz, 1H, 6′-H), 6.64 (s, 1H, 2′-H), 6.76 (d, J=7.8 Hz, 1H, 5′-H); ^{13}C NMR (CD_3OD, 75 MHz) δ: 36.7 (CH_2), 37.9 (CH_2), 54.3 (3,5-OCH_3), 54.9 (3′-OCH_3), 97.2, 106.0, 111.3, 114.2, 120.2, 132.8, 143.5, 143.7, 146.6, 160.1; IR (film) ν: 3442, 1599, 1514, 1462, 924, 831, 692 cm^{-1}; MS (70 eV) *m/z* (%): 288 (M^+, 6), 151 (6), 137 (100), 91 (5), 77 (8).

4,4′-Dihydroxy-3,3′,5-trimethoxybibenzyl (moscatilin 1cf) Colorless solid, yield 90%; m.p. 82—83 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.82 (s, 4H, CH_2CH_2), 3.84 (s, 9H, 3,3′,5-OCH_3), 5.46 (s, 1H, OH), 5.57 (s, 1H, OH), 6.36 (s, 2H, 2,6-H), 6.62 (d, J=2.1 Hz, 1H, 2′-H), 6.68 (dd, J=8.1 Hz and 2.1 Hz, 1H, 6′-H), 6.84 (d, J=8.1 Hz, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.8 (CH_2), 38.4 (CH_2), 55.7 (3'-OCH_3), 56.1 (3,5-OCH_3), 104.9, 111.1, 114.1, 120.9, 132.6, 132.8, 133.6, 143.6, 146.1, 146.7; IR (KBr) ν: 3447, 2938, 1516, 1214, 1114, 821, 797, 733 cm^{-1}; MS (70 eV) *m/z* (%): 304 (M^+, 76), 167 (100), 137 (74).

4′-Hydroxy-3,3′,4,5-tetramethoxybibenzyl (crepidatin 1cg) Colorless solid, yield 93%; m.p. 98—99 ℃; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.80 (s, 4H,

CH_2CH_2), 3.76 (s, 3H, 4-OCH_3), 3.78 (s, 6H, 3,5-OCH_3), 3.81 (s, 3H, 3′-OCH_3), 5.96 (s, 1H, OH), 6.35 (s, 2H, 2,6-H), 6.59 (d, J=1.8 Hz, 1H, 2′-H), 6.65 (dd, J=7.8 Hz and 1.8 Hz, 1H, 6′-H), 6.82 (d, J=7.8 Hz, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 37.6 (CH_2), 38.6 (CH_2), 55.7 (3′-OCH_3), 55.9 (3,5-OCH_3), 60.7 (4-OCH_3), 105.5, 111.3, 114.3, 120.9, 133.4, 136.1, 137.5, 143.8, 146.4, 152.9; IR (KBr) ν: 3432, 2926, 1589, 1458, 1124, 813, 781 cm^{-1}; MS (70 eV) *m/z* (%): 318 (M^+, 12), 182 (12), 181 (100), 137 (30), 77 (5).

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