Total Synthesis of (+)-Machaeriols B and C and of Their Enantiomers with a Cannabinoid Structure

by **Hee Jin Lee**[a]), **Yong Rok Lee***[a]), and **Sung Hong Kim**[b])

[a]) School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea (phone: +82-53-810-2529; fax: +82-53-810-4631; e-mail: yrlee@yu.ac.kr)

[b]) Analysis Research Division, Daegu Center, Korea Basic Science Institute, Daegu 702-701, Korea

An efficient and concise synthesis of the biologically interesting (+)-machaeriol B (**2**) and its enantiomer **5** was accomplished from *O*-phenylhydroxylamine (**7**) in four steps (*Scheme 2*). In addition, the first total synthesis of natural (+)-machaeriol C (**3**) and its enantiomer **6** was achieved from the readily available ester **15** in eight steps (*Scheme 4*). The key strategies in the syntheses of **2** and **5** involved benzofuran formation through a [3,3]-sigmatropic rearrangement and *trans*-hexahydrodibenzopyran formation by a domino aldol-type/hetero-*Diels–Alder* reaction. In the case of **3** and **6**, the key steps were stilbene formation by a *Horner–Wadsworth–Emmons* reaction and *trans*-hexahydrodibenzopyran formation by domino reactions.

Introduction. – (+)-Machaeriols A (**1**), B (**2**), C (**3**), and D (**4**), bearing the cannabinoid structure, were recently isolated from the bark of the *Machaerium multiflorum* spruce (*Fig.*) located in Loreto and Peru [1]. They have been reported to have potential *in vitro* antimicrobial activity against *Staphylococcus aureus* (IC_{50} [μg/ml]: **1**, 15.0; **2**, 5.0; **3**, 0.7; **4**, 25.0) and methicillin-resistant *S. aureus* (IC_{50} [μg/ml]: **1**, 10.0; **2**, 4.5; **3**, 0.7; **4**, 30.0) [1]. They also showed potent *in vitro* antimalarial activity against *Plasmodium falciparum* D6 (IC_{50} (**3**) = 3.0 μg/ml) and W2 clones (IC_{50} (**3**) = 3.7 μg/ml) [1]. These important biological activities have led to the development of a variety of synthetic approaches to these natural products. The first syntheses of machaeriol A (**1**) and machaeriol B (**2**) were reported by *Avery* and co-workers starting from phloroglucinol (= benzene-1,3,5-triol) through a hetero *Diels–Alder* cyclization and *Suzuki* coupling reaction as the key steps with 34% (7 steps) and 32% (7 steps) overall yields, respectively [2]. Another total synthesis of (+)-machaeriol A (**1**) was accomplished starting from the synthesized enol silyl ether of α,β-epoxycyclohexanone through an S_N2' reaction to an aryl cyanocuprate as the key step with an overall yield of 26% (10 steps) [3]. Recently, (+)-machaeriol D (**4**) was also synthesized starting from 4-bromo-2,4-dihydroxybenzoic acid in 12% overall yield (17 steps) by *She*, *Pan*, and co-workers [4]. Although synthetic approaches to (+)-machaeriols A (**1**), B (**2**), and D (**4**) have been reported, there is still a demand for a more concise and efficient method for synthesizing these biologically interesting natural products. In particular, no total synthesis of natural (+)-machaeriol C (**3**) or its enantiomer **6** has been reported thus far.

Results and Discussion. – We developed a new and useful methodology for preparing a variety of benzopyrans using the ethylenediamine diacetate (EDDA)

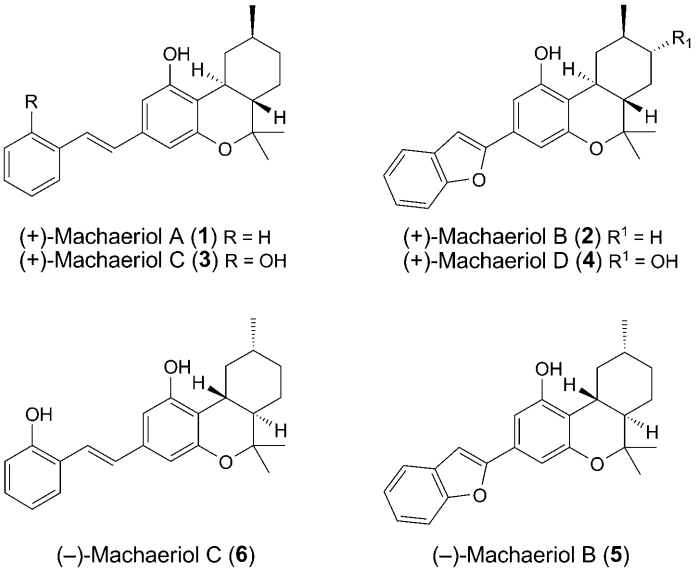


Figure. *Natural products* **1**–**4** *isolated from* Machaerium multiflorum *and unnatural products* **5**–**6** *with cannabinoid structure*

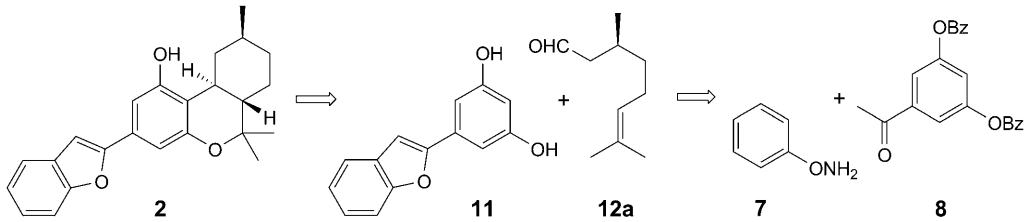
catalyzed reactions of resorcinols (= benzene-1,3-diols) to α,β-unsaturated aldehydes [5]. These reactions involve cycloadditions through 6π-electrocyclization or hetero-*Diels–Alder* reactions [5]. This methodology provides a rapid route for the synthesis of benzopyran derivatives with a variety of substituents on the pyranyl moiety.

Recently, we also developed a new and useful methodology for preparing a variety of cannabinoid analogues by the reaction of resorcinols with optically pure citronellals (= 3,7-dimethyloct-6-enals) in the presence of EDDA and Et_3N as a co-catalyst [6]. By using this methodology as a key-step, we described the synthesis of (+)-machaeriol A (**1**) starting from 3,5-dimethoxybenzaldehyde [7]. As an extension of our work, we now report the total syntheses of natural (+)-machaeriols B (**2**) and C (**3**) and of their unnatural enantiomers (−)-machaeriols B (**5**) and C (**6**), respectively.

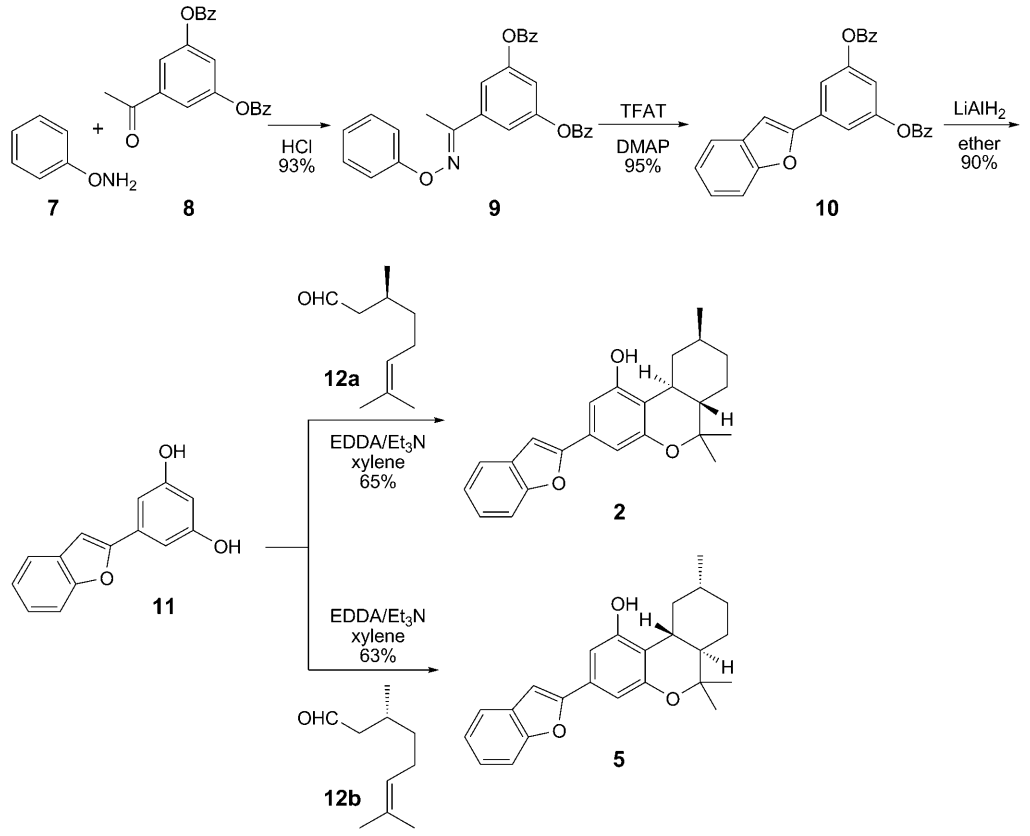
Scheme 1 shows the retrosynthetic analysis for (+)-machaeriol B (**2**). (+)-Machaeriol B (**2**) can be prepared from stemofuran A (**11**) and (−)-(3*S*)-citronellal (**12a**) through a hetero-*Diels–Alder* reaction. Stemofuran A (**11**) can be readily generated from *O*-phenylhydroxylamine (**7**) and 3,5-bis(benzoyloxy)acetophenone (= 1-[3,5-bis(benzoyloxy)phenyl]ethanone; **8**).

Scheme 2 shows a concise synthetic approach to natural (+)-machaeriol B (**2**) and its unnatural enantiomer **5**. The precursor **11** for the total syntheses of **2** and **5** was obtained by a known method [8]. Thus, the condensation of *O*-phenylhydroxylamine (**7**) with 3,5-bis(dibenzoyloxy)acetophenone (**8**) in the presence of conc. HCl in EtOH gave the oxime ether **9** in 93% yield. The latter was treated with trifluoroacetyl triflate ($CF_3C(=O)OS(=O)_2CF_3$ = TFAT, 5.0 equiv.) and *N*,*N*-dimethylpyridin-4-amine (DMAP, 3.0 equiv.) in CH_2Cl_2 at room temperature to afford the desired cycloadduct

Scheme 1. *Retrosynthetic Analysis for Natural (+)-Machaeriol B* (**2**)



Scheme 2. *Total Synthesis of Natural (+)-Machaeriol B* (**2**) *and Its Enantiomer* **5**



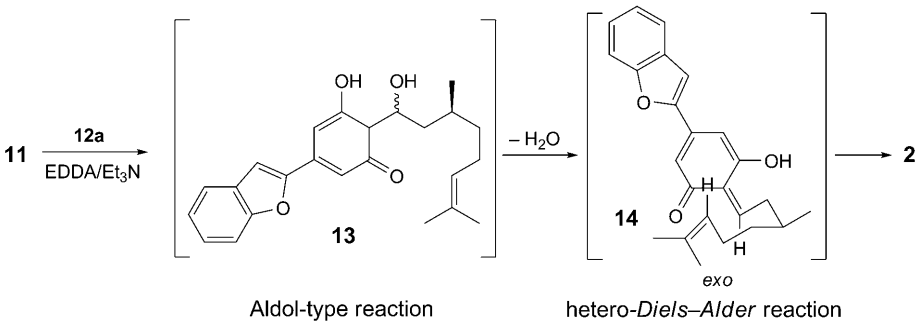
10 in 95% yield and as the sole product, *via* a [3,3]-sigmatropic rearrangement which is the well-known oxa-variant of *Fischer*'s indole synthesis. Removal of the two benzoyl groups from **10** with $LiAlH_4$ in ether at room temperature afforded stemofuran (**11**) in 90% yield. Stemofuran (= 5-(benzofuran-2-yl)benzene-1,3-diol; **11**), bearing a benzofuran moiety, was isolated from *Stemona collinsae*, distributed mainly in southeast Asia [9]. This plant has been used in traditional medicine in China and Japan to treat

inflammatory-related diseases [10], with the extracts from the fleshy tuberous roots still used to treat respiratory disorders, including pulmonary tuberculosis, antiasthmatic, and bronchitis. The extracts also kill insects and worms [11]. Benzofuranylbenzenediol **11** has also been shown to have potent antibacterial and antifungal activity [9].

Then the formation of the hexahydrodibenzopyran moiety of **2** and **5** from **11** in the presence of EDDA/Et_3N was investigated (*Scheme 2*). Treatment of **11** with (−)-(*S*)-citronellal (**12a**; $[\alpha]_D^{25} = -15.0$ (neat)) in the presence of EDDA (20 mol-%)/Et_3N (2.0 ml) in refluxing xylene gave (+)-machaeriol B (**2**) in 65% yield. (synthetic **2**: $[\alpha]_D^{25} = +113.1$ ($c = 0.14$, MeOH); [1b]: $[\alpha]_D^{25} = +113.7$ ($c = 0.53$, MeOH)). The spectroscopic data of the synthetic **2** are in good agreement with the reported data [1b]. Conversely, the corresponding treatment of **11** with (+)-(*R*)-citronellal (**12b**; $[\alpha]_D^{25} = +12.5$, neat) gave (−)-machaeriol B (**5**) in 63% yield (synthetic **5**: $[\alpha]_D^{25} = -99.7$ ($c = 0.45$, MeOH)).

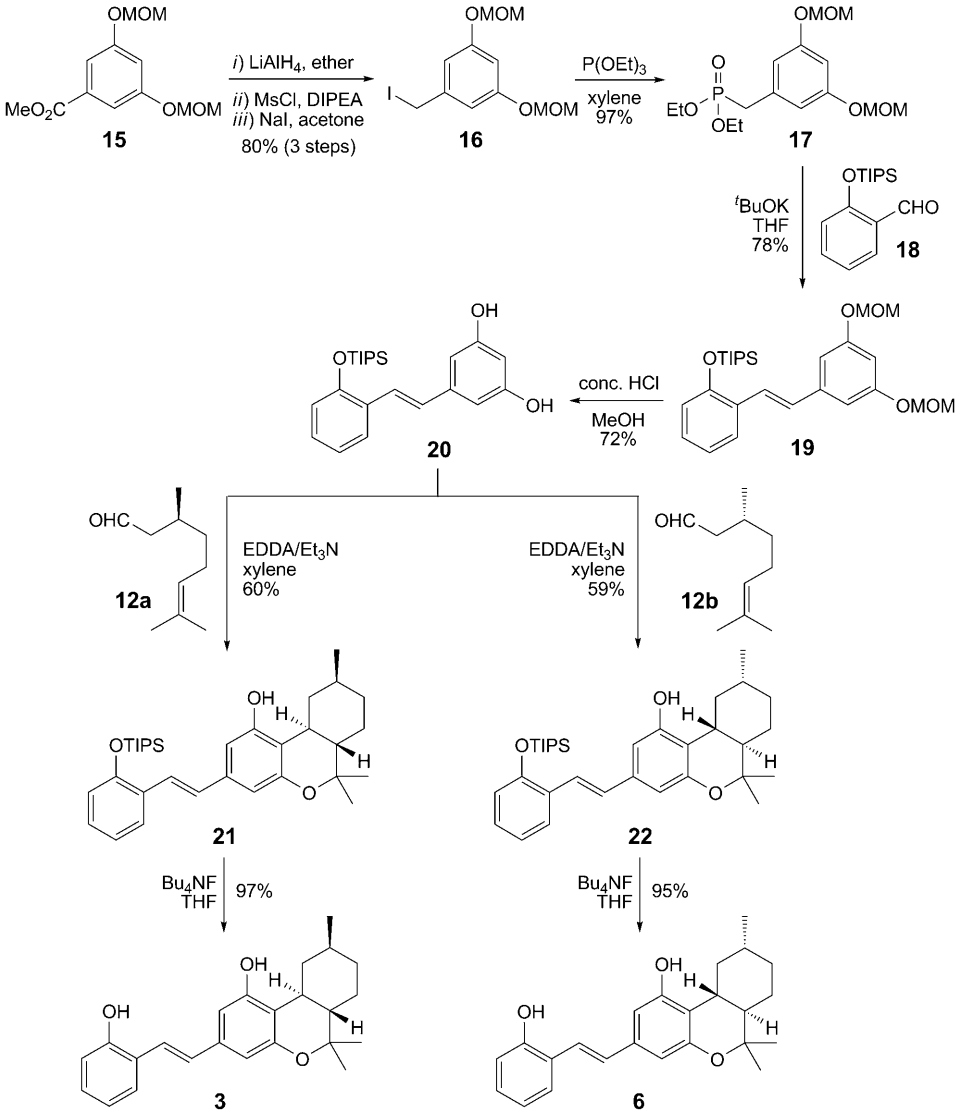
Scheme 3 shows the mechanism for the formation of (+)-machaeriol B (**2**) through a domino aldol-type/hetero-*Diels–Alder* reaction. Citronellal **12a** was first protonated at the aldehyde function by EDDA and then attacked by stemofuran (**11**) to yield an intermediate **13**. *Shigemasa* and co-workers first suggested such a process for the formation of aldol-type products in a $Ca(OH)_2$-mediated reaction of resorcinol with enals [12]. The dehydration of intermediate **13** in the presence of EDDA/Et_3N afforded *o*-quinone methide **14**. The stereospecificity of the formation of product **2** might be explained by the pseudo-equatorial conformation of the Me group of **14** in the coplanar structure of the chair-like transition state. In the subsequent hetero-*Diels–Alder* reaction of *o*-quinone methide **14**, the *exo*-transition state must be energetically more favorable than the *endo*-transition state [13]. This is in good agreement with *Marino* and *Dax* [14] and *Korthals* and *Wulff* [15], who reported the syntheses of hexahydrocannabinol and hexahydrodibenzopyran by the intramolecular hetero-*Diels–Alder* cycloaddition of an *o*-quinone methide.

Scheme 3. *Mechanism for the Formation of (+)-Machaeriol B* (**2**)



Next, the syntheses of natural (−)-machaeriol C (**3**) and its enantiomer **6** were achieved as shown in *Scheme 4*. The readily available ester **15** [16] was converted into the corresponding iodide **16** by the sequence of reduction, mesylation, and iodination in 80% yield (3 steps). Compound **16** was then treated with triethyl phosphite in xylene at 100° to give phosphonate **17** in 97% yield [17]. The *Horner–Wadsworth–Emmons*

Scheme 4. *Total Synthesis of Natural (+)-Machaeriol C* (**3**) *and Its Enantiomer* **6**



reaction of **17** with benzaldehyde **18** [18] (prepared from salicylaldehyde) in the presence of potassium *tert*-butoxide in THF, gave the desired coupling product **19** in 78% yield. Removal of the two protecting $MeOCH_2$ groups of **19** with conc. HCl in MeOH at room temperature afforded diol **20** in 72% yield. Reaction of compound **20** with (−)-(*S*)-citronellal (**12a**) in the presence of EDDA (20 mol-%)/Et_3N (2.0 ml) in

refluxing xylene gave adduct **21** (60%). Removal of the silyl protecting group with Bu_4NF afforded (+)-machaeriol C (**3**) in 97% yield (synthesized **3**: $[\alpha]_D^{25} = +118.2$ ($c =$ 0.34, MeOH); [1b]: $[\alpha]_D^{25} = +117.4$ ($c = 1.01$, MeOH)). The spectroscopic data of the synthetic **3** was in agreement with the reported data [1b]. The corresponding treatment of **20** with (+)-(*R*)-citronellal (**12b**; $[\alpha]_D^{25} = +12.5$, neat) (→**22** (59%)), followed by deprotection provided unnatural (−)-machaeriol C (**6**) in 95% yield (synthetic **6**: $[\alpha]_D^{25} = -104.0$ ($c = 0.26$, MeOH)).

Conclusions. – Efficient and concise syntheses of the biologically interesting (+)-machaeriol B (**2**) and its enantiomer **5** were carried out starting from *O*-phenylhydroxylamine (**7**) and 3,5-bis(benzoyloxy)acetophenone (**8**). Additionally, the first total synthesis of natural (+)-machaeriol C (**3**) and its enantiomer **6** was accomplished from readily available ester **15**. The key strategies in the syntheses of **2** and **5** involved the benzofuran formation of oxime ether **9** through a [3,3]-sigmatropic rearrangement which is the well-known oxa-variant of *Fischer*'s indole synthesis, and the *trans*-hexahydrodibenzopyran formation of stemofuran (**11**) by a domino aldol-type/hetero-*Diels–Alder* reaction. In the case of (+)-machaeriol C (**3**) and its enantiomer **6**, the key steps were stilbene formation by a *Horner–Wadsworth–Emmons* reaction and *trans*-hexahydrodibenzopyran formation by a domino reaction. These synthetic routes are expected to be widely used in the synthesis of other natural products including cannabinoid analogues.

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Experimental Part

General. All experiments were carried out under N_2. Column chromatography (CC): silica gel *9385* (*Merck*). Thin-layer chromatography (TLC): pre-coated silica gel plates (Art. *5554*) with a fluorescent indicator. FT-IR Spectra: *Jasco-FTIR-5300* spectrophotometer. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-ARX-300* spectrometer; $CDCl_3$ or CD_3OD solns.; δ in ppm rel. to the solvent chemical shift, *J* in Hz. EI-MS (70 eV) and HR-MS: the spectra were carried out at the Korea Basic Science Institute; in *m/z*.

(1E)-1-[3,5-Bis(benzoyloxy)phenyl]ethanone O-Phenyloxime (**9**). To a soln. of *O*-phenylhydroxylamine (**7**; 0.327 g, 3.0 mmol) in EtOH (10 ml) were added 3,5-bis(benzoyloxy)acetophenone (**8**; 1.080 g, 3.0 mmol) and conc. HCl soln. (0.10 ml) at r.t. After being stirred at r.t. for 10 h, the mixture was concentrated and the residue purified by CC (SiO_2, hexane/AcOEt 10:1): 1.259 g (93%) of **9**. White solid. M.p. 87–88°. IR (KBr): 3461, 3098, 1740, 1593, 1483, 1453, 1431, 1335, 1312, 1265, 1202, 1134, 1082, 1067, 1024, 953, 901, 878, 762. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.42 (*d*, *J* = 8.1, 4 H); 7.86–7.84 (*m*, 2 H); 7.80 (*d*, *J* = 2.0, 2 H); 7.76–7.71 (*m*, 4 H); 7.53–7.46 (*m*, 5 H); 7.28–7.22 (*m*, 1 H); 2.67 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 164.7; 159.3; 156.0; 151.4; 138.2; 133.8; 130.2; 129.3; 129.1; 128.6; 122.4; 117.3; 117.1; 114.9; 13.2. EI-MS: 451 (2, M^+), 360 (6), 359 (32), 358 (72), 105 (100), 94 (5), 77 (25). HR-MS: 451.1417 (M^+, $C_{28}H_{21}NO_5^+$; calc. 451.1420).

5-(Benzofuran-2-yl)benzene-1,3-diol 1,3-Dibenzoate (**10**). To a soln. of **9** (0.902 g, 2.0 mmol) in CH_2Cl_2 (20 ml) were added DMAP (0.734 g, 6.0 mmol) and TFAT (2.460 g, 10.0 mmol) at r.t. After being stirred at r.t. for 10 h, the mixture was diluted with H_2O (30 ml) and extracted with CH_2Cl_2 (3 × 40 ml). The org. layer was washed with brine (30 ml), dried ($MgSO_4$), and concentrated, and the residue purified by CC (SiO_2, hexane/AcOEt 5:1): 0.826 g (95%) of **10**. White solid. M.p. 148–150°. IR (KBr): 3097, 1744, 1620, 1599, 1451, 1258, 1130, 1063, 1024, 953, 882, 800, 747. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.27–8.25 (*d*, *J* = 8.1, 4 H); 7.71–7.67 (*m*, 4 H); 7.64–7.52 (*m*, 6 H); 7.36–7.22 (*m*, 3 H); 7.11 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 164.7; 155.0; 154.0; 151.8; 133.9; 132.7; 130.3; 129.1; 128.9; 128.7; 124.9; 123.2; 121.2;

115.7; 111.3; 102.9. EI-MS: 434 (46, M^+), 358 (4), 330 (3), 106 (8), 105 (100), 77 (24). HR-MS: 434.1151 (M^+, $C_{28}H_{18}O_5^+$; calc. 434.1154).

Stemofuran A (=*5-(Benzofuran-2-yl)benzene-1,3-diol*; **11**). A suspension of $LiAlH_4$ (0.228 g, 6.0 mmol) in dry Et_2O (20 ml) was cooled to 0° and treated dropwise with **10** (0.651 g, 1.5 mmol) in dry Et_2O (5 ml). After stirring at r.t. for 2 h, the mixture was quenched at 0° by the addition of H_2O (30 ml) and 2N HCl (50 ml). The mixture was extracted with AcOEt (3 × 40 ml), the org. layer washed with brine (30 ml), dried ($MgSO_4$), and concentrated, and the residue purified by CC (SiO_2, hexane/AcOEt 3:1): 0.306 g (90%) of **11**. Yellow solid. M.p. 181–182°. IR (KBr): 3331, 1620, 1579, 1449, 1358, 1246, 1148, 999, 953, 853, 833, 801, 748. ^{1}H-NMR (CD_3OD, 300 MHz): 7.46 (*d*, *J* = 8.0, 1 H); 7.38 (*d*, *J* = 8.0, 1 H); 7.18–7.06 (*m*, 2 H); 6.93 (*d*, *J* = 1.5, 1 H); 6.74 (*d*, *J* = 1.5, 2 H); 6.20 (*t*, *J* = 1.5, 1 H); 4.78 (br. *s*, 2 H). ^{13}C-NMR (CD_3OD, 75 MHz): 160.0; 157.4; 156.1; 133.4; 130.5; 125.3; 124.0; 121.9; 111.8; 104.5; 104.1; 102.3. EI-MS: 226 (100, M^+), 197 (11), 181 (2), 169 (3), 152 (4), 151 (3), 150 (4), 141 (4), 139 (3), 115 (5), 113 (5). HR-MS: 226.0631 (M^+, $C_{14}H_{10}O_3^+$; calc. 226.0630).

(+)-Machaeriol B (=*(6a*S*,9*S*,10a*S*)-3-(Benzofuran-2-yl]-6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol*; **2**). To a soln. of **11** (0.101 g, 0.4 mmol) and (−)-(*S*)-citronellal (**12a**; $[\alpha]_D^{25}$ = −15.0, neat; 0.136 g, 0.9 mmol) in xylene (10 ml) was added ethylenediamine diacetate (0.016 g) and Et_3N (2 ml) at r.t. The mixture was stirred in refluxing xylene for 48 h. The solvent was evaporated and the oily residue purified by CC (SiO_2, hexane/AcOEt 5:1): 0.104 g (65%) of **2**. Brown solid. M.p. 92–93°. $[\alpha]_D^{25}$ = +113.1 (*c* = 0.14, MeOH). IR (KBr): 3393, 2922, 1622, 1564, 1452, 1422, 1358, 1250, 1142, 1040, 965, 883, 902, 750. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.51 (*d*, *J* = 7.4, 1 H); 7.44 (*d*, *J* = 7.8, 1 H); 7.25–7.15 (*m*, 2 H); 6.90 (*d*, *J* = 1.5, 1 H); 6.86 (*s*, 1 H); 6.77 (*d*, *J* = 1.5, 1 H); 5.11 (*s*, 1 H); 3.05 (*d*, *J* = 12.9, 1 H); 2.49 (*dd*, *J* = 13.0, 11.1, 1 H); 1.85–1.82 (*m*, 2 H); 1.68–1.56 (*m*, 1 H); 1.51–1.42 (*m*, 1 H); 1.38 (*s*, 3 H); 1.13–1.05 (*m*, 2 H); 1.07 (*s*, 3 H); 0.93 (*d*, *J* = 6.6, 3 H); 0.87–0.76 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 156.0; 155.8; 155.2; 130.0; 129.7; 124.5; 123.3; 121.3; 114.4; 111.5; 107.5; 104.4; 101.6; 77.9; 49.5; 39.2; 36.1; 35.9; 33.3; 28.5; 28.1; 23.0; 19.5. EI-MS: 362 (100, M^+), 347 (7), 320 (5), 319 (22), 279 (14), 277 (12), 263 (70), 240 (7), 239 (39), 226 (13). HR-MS: 362.1885 (M^+, $C_{24}H_{26}O_3^+$; calc. 362.1882).

(−)-Machaeriol B (=*(6a*R*,9*R*,10a*R*)-3-(Benzofuran-2-yl)-6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol*; **5**). As described for **2** with **11** (0.100 g, 0.4 mmol) and (+)-(*R*)-citronellal (**12b**; $[\alpha]_D^{25}$ = +12.5, neat; 0.136 g, 0.9 mmol): 0.101 g (63%) of **5**. Brown solid. M.p. 181–182°. $[\alpha]_D^{25}$ = −99.7 (*c* = 0.45, MeOH).

1-(Iodomethyl)-3,5-bis(methoxymethoxy)benzene (**16**). To a suspension of $LiAlH_4$ (0.417 g, 11.0 mmol) in Et_2O (40 ml) at 0° was added dropwise ester **15** (2.563 g, 10.0 mmol) in Et_2O (3 ml). The mixture was stirred at r.t. for 3 h and then quenched by addition of ice water (30 ml). The mixture was acidified with 2N HCl (30 ml) and extracted with AcOEt (3 × 40 ml), the org. layer washed with H_2O (30 ml) and brine (30 ml), dried ($MgSO_4$), and concentrated, and the residue purified by CC (SiO_2, hexane/AcOEt 5:1): 2.191 g (95%) of 3,5-bis(methoxymethoxy)benzenemethanol. Liquid. IR (neat): 2955, 2830, 2732, 1702, 1600, 1465, 1389, 1297, 1214, 1153, 1084, 1033, 927, 856, 726. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.88 (*s*, 1 H); 7.18 (*s*, 2 H); 6.94 (*s*, 1 H); 5.18 (*s*, 4 H); 3.46 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 191.6; 158.7; 138.4; 111.1; 110.4; 90.4; 56.2.

Methanesulfonyl chloride (0.916 g, 8.0 mmol) was added dropwise to a soln. of the above benzenemethanol (1.789 g, 7.8 mmol) and *N*,*N*-diisopropylethylamine (2.012 g, 15.6 mmol) in CH_2Cl_2 (30 ml) at 0°. The mixture was stirred at r.t. for 10 h and then quenched by addition of H_2O (30 ml). The mixture was extracted with AcOEt (3 × 40 ml) and the combined org. layer washed with NH_4Cl soln. (30 ml), H_2O (30 ml), and brine (30 ml), dried ($MgSO_4$), and concentrated. The resulting residue and NaI (3.507 g, 23.4 mmol) were stirred in acetone (50 ml) for 10 h. After solvent evaporation, the oily residue was purified by CC (SiO_2, hexane/AcOEt 5:1): 2.188 g (83%) of **16**. Liquid. IR (neat): 3022, 2935, 1601, 1457, 1364, 1179, 1151, 1024, 967, 867, 808, 744. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.70 (*s*, 2 H); 6.60 (*s*, 1 H); 5.12 (*s*, 4 H); 4.35 (*s*, 2 H); 3.45 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 158.2; 141.2; 110.0; 104.4; 94.4; 56.0; 5.2. HR-FAB-MS: 339.0091 ($[M + H]^+$, $C_{11}H_{16}IO_4^+$; calc. 339.0093).

{[3,5-Bis(methoxymethoxy)phenyl]methyl}phosphonic Acid Diethyl Ester (**17**). To a soln. of **16** (2.025 g, 6.0 mmol) in xylene (10 ml) was added triethyl phosphite (1 ml) at r.t. The mixture was heated at 100° for 7 h. After removal of the solvent, the oily residue was purified by CC (SiO_2, hexane/AcOEt 1:1): 2.024 g (97% of **17**). Liquid. IR (neat): 3457, 2982, 1602, 1464, 1400, 1150, 1029, 965, 857, 792.

^{1}H-NMR ($CDCl_3$, 300 MHz): 6.61–6.58 (*m*, 3 H); 5.10 (*m*, 4 H); 4.05–3.95 (*m*, 4 H); 3.42 (*s*, 6 H); 3.01 (*d*, *J*(P,H) = 21.6, 2 H); 1.26–1.21 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 158.1; 133.6; 111.1; 103.4; 94.3; 62.1; 55.9; 33.9 (*d*, *J*(C,P) = 138.1); 16.2. EI-MS: 348 (100, M^+), 318 (28), 317 (22), 316 (94), 315 (27), 287 (42), 271 (25), 232 (24), 229 (20), 160 (21). HR-MS: 348.1335 (M^+, $C_{15}H_{25}O_7P^+$; calc. 348.1338).

(E)-3′,5′-Bis(methoxymethoxy)-2-[(triisopropylsilyl)oxy]stilbene (= *1,3-Bis(methoxymethoxy)-5-{(1*E*)-2-{2-{(tris(1-methylethyl)silyl]oxy}phenyl}ethenyl}benzene*; **19**). To a soln. of **17** (1.045 g, 3.0 mmol) and aldehyde **18** (0.891 g, 3.2 mmol) in THF (30 ml) was added ^{t}BuOK (0.717 g, 6.4 mmol) at 0°. The mixture was stirred at 0° for 30 min and then quenched by addition of H_2O (30 ml). The mixture was extracted with AcOEt (3 × 30 ml), the combined org. layer washed with NH_4Cl soln. (30 ml), H_2O (30 ml), and brine (30 ml), dried ($MgSO_4$), and concentrated, and the oily residue purified by CC (SiO_2, hexane/AcOEt 4:1): 1.180 g (78%) of **19**. Liquid. IR (neat): 2949, 2867, 1596, 1481, 1265, 1149, 1082, 1035, 922, 756, 684. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.59 (*d*, *J* = 7.5, 1 H); 7.56 (*d*, *J* = 16.5, 1 H); 7.12 (*dd*, *J* = 7.8, 7.5, 1 H); 6.98 (*d*, *J* = 16.5, 1 H); 6.93 (*dd*, *J* = 8.1, 7.8, 1 H); 6.88 (br. *s*, 2 H); 6.84 (*d*, *J* = 8.1, 1 H); 6.63 (br. *s*, 1 H); 5.18 (*s*, 4 H); 3.49 (*s*, 6 H); 1.37–1.30 (*m*, 3 H); 1.16–1.11 (*m*, 18 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 158.5; 153.7; 140.2; 128.6; 127.9; 126.0; 124.6; 121.2; 119.1; 107.8; 104.3; 94.5; 56.0; 18.1; 17.7; 13.0. EI-MS: 472 (100, M^+), 429 (15), 397 (31), 367 (18), 365 (18), 353 (13), 337 (10), 335 (13), 323 (16), 251 (14), 237 (14), 235 (36), 165 (17), 161 (13), 145 (19), 131 (35), 117 (10), 103 (31), 75 (34), 61 (14). HR-MS: 472.2646 (M^+, $C_{27}H_{40}O_5Si^+$; calc. 472.2645).

(E)-2-[(Triisopropylsilyl)oxy]stilbene-3′,5′-diol (= *5-{(1*E*)-2-{2-{[Tris(1-methylethyl)silyl]oxy}phenyl}ethenyl}benzene-1,3-diol*; **20**). To a soln. of **19** (0.993 g, 2.1 mmol) in MeOH (10 ml) was added conc. HCl soln. (5 drops), and the mixture was stirred at r.t. for 10 h. After removal of the solvent, the oily residue was diluted with H_2O (30 ml) and the mixture extracted with AcOEt (3 × 40 ml). The combined org. layer was washed with sat. $NaHCO_3$ soln. (30 ml), H_2O (30 ml) and brine (30 ml), dried ($MgSO_4$), and concentrated and the oily residue was purified by CC (SiO_2, hexane/AcOEt 4:1): 0.581 g (72%) of **20**. Liquid. IR (neat): 3392, 2946, 2865, 1597, 1482, 1485, 1344, 1264, 1152, 1003, 920, 833, 680. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.54 (*d*, *J* = 7.8, 1 H); 7.48 (*d*, *J* = 16.5, 1 H); 7.10 (*dd*, *J* = 8.1, 7.8, 1 H); 6.90 (*d*, *J* = 16.5, 1 H); 6.87 (*dd*, *J* = 8.1, 7.2, 1 H); 6.82 (*d*, *J* = 7.2, 1 H); 6.55 (*d*, *J* = 2.1, 2 H); 6.25 (*t*, *J* = 2.1, 1 H); 1.35–1.28 (*m*, 3 H); 1.13–1.11 (*m*, 18 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 157.0; 153.7; 140.7; 128.6; 128.1; 127.7; 126.2; 124.8; 121.1; 119.1; 106.0; 102.0; 18.0; 13.0. EI-MS: 384 (78, M^+), 342 (27), 341 (100), 300 (11), 299 (48), 257 (11), 255 (13), 251 (18), 217 (19), 189 (14), 175 (12), 165 (11), 161 (23), 143 (9), 135 (8), 59 (8). HR-MS: 384.2122 (M^+, $C_{23}H_{32}O_3Si^+$; calc. 384.2121).

*(6a*S*,9*S*,10a*S*)-6a,7,8,9,10,10a-Hexahydro-6,6,9-trimethyl-3-{(1*E*)-2-{2-{(tris(1-methylethyl)silyl]oxy}-phenyl}ethenyl}-6*H*-dibenzo[*b,d*]pyran-1-ol* (**21**). As described for **2**, with **20** (0.231 g, 0.5 mmol), (−)-(*S*)-citronellal (**12a**; $[\alpha]_D = -15.0°$, neat; 0.154 g, 1.0 mmol) xylene (10 ml), ethylenediamine diacetate (0.018 g), and Et_3N (2 ml). CC (SiO_2, hexane/AcOEt 15:1) gave 0.156 g (60%) of **21**. Liquid. $[\alpha]_D^{25} = +84.$ 6, (*c* = 0.60, MeOH). IR (neat): 3412, 2945, 2866, 1614, 1567, 1481, 1455, 1263, 1141, 918, 880, 750, 685. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.54 (*d*, *J* = 7.8, 1 H); 7.44 (*d*, *J* = 16.5, 1 H); 7.10 (*dd*, *J* = 7.8, 7.5, 1 H); 6.92 (*dd*, *J* = 7.5, 7.2, 1 H); 6.87 (*d*, *J* = 16.5, 1 H); 6.83 (*d*, *J* = 7.2, 1 H); 6.57 (br. *s*, 1 H); 6.42 (br. *s*, 1 H); 4.98 (br. *s*, 1 H); 3.07 (*d*, *J* = 12.6, 1 H); 2.50 (*dd*, *J* = 12.6, 10.8, 1 H) 1.87–1.84 (*m*, 2 H); 1.69–1.58 (*m*, 1 H); 1.52–1.44 (*m*, 1 H); 1.40 (*s*, 3 H); 1.37–1.28 (*m*, 3 H); 1.15–1.09 (*m*, 2 H); 1.14 (*d*, *J* = 7.2, 18 H); 1.09 (*s*, 3 H); 0.95 (*d*, *J* = 6.3, 3 H); 0.90–0.78 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 155.4, 155.1, 153.5; 137.4; 128.4; 128.2; 127.9; 126.3; 123.7; 121.1; 119.0; 112.6; 108.9; 105.1; 76.6; 49.1; 38.9; 35.7; 35.5; 32.9; 28.0; 27.7; 22.6; 19.0; 18.1; 13.0. EI-MS: 520 (100, M^+), 478 (31), 477 (80), 472 (19), 354 (13), 353 (43), 341 (14), 311 (17), 189 (16), 161 (23), 149 (15), 129 (28), 83 (11), 81 (13), 71 (14), 69 (240), 57 (21). HR-MS: 520.3376 (M^+, $C_{33}H_{48}O_3Si^+$; calc. 520.3373).

(+)-Machaeriol C (= *(6a*S*,9*S*,10a*S*)-6a,7,8,9,10,10a-Hexahydro-3-[(1*E*)-2-(2-hydroxyphenyl)ethenyl]-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol*; **3**). To a soln. of **21** (0.104 g, 0.2 mmol) in THF (10 ml) was added 1M Bu_4NF in THF (0.6 ml), and the mixture was stirred at r.t. for 5 h. The mixture was quenched by addition of sat. NH_4Cl soln. (30 ml) and extracted with AcOEt (3 × 40 ml). The combined org. layer was washed with H_2O (30 ml) and brine (30 ml), dried ($MgSO_4$), and concentrated, and the oily residue purified by CC (SiO_2, hexane/AcOEt 5:1): 0.071 g (97%) of **3**. Brown solid. M.p. 105–106°. $[\alpha]_D^{25} = +118.2$ (*c* = 0.34, MeOH). IR (KBr): 3409, 2925, 1612, 1569, 1453, 1422, 1263, 1092, 1039, 870, 806, 746. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.43 (*d*, *J* = 7.5, 1 H); 7.22 (*d*, *J* = 16.2, 1 H); 7.08 (*dd*, *J* = 7.5, 7.2,

1 H); 6.88 (*dd*, *J* = 7.8, 7.2, 1 H); 6.85 (*d*, *J* = 16.2, 1 H); 6.76 (*d*, *J* = 7.8, 1 H); 6.56 (br. *s*, 1 H); 6.41 (br. *s*, 1 H); 5.28 (br. *s*, 2 H); 3.04 (*d*, *J* = 12.3, 1 H); 2.47 (*dd*, *J* = 12.3, 11.1, 1 H); 1. 84 – 1.81 (*m*, 2 H); 1.71 – 1.52 (*m*, 1 H); 1.50 – 1.41 (*m*, 1 H); 1.37 (*s*, 3 H); 1.12 – 1.02 (*m*, 2 H); 1.05 (*s*, 3 H); 0.92 (*d*, *J* = 6.6, 3 H); 0.81 – 0.69 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 155.7, 155.6; 153.5; 137.5; 129.9; 129.1; 127.5; 125.2; 123.2; 121.6; 116.5; 113.5; 109.3; 105.8; 77.9; 49.6; 39.3; 36.1; 35.9; 33.3; 28.5; 28.2; 23.0; 22.5; 19.5. EI-MS: 364 (82, M^+), 355 (27), 346 (12), 321 (28), 279 (32), 241 (43), 221 (25), 167 (40), 150 (11), 149 (100), 147 (17), 129 (12), 73 (10), 71 (13), 69 (10), 57 (17). HR-MS: 364.2042 (M^+, $C_{24}H_{28}O_3^+$; calc. 364.2038).

*(6a*R*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-6,6,9-trimethyl-3-{(1*E*)-2-{2-{[tris(1-methylethyl)silyl]oxy}phenyl}ethenyl}-6*H*-dibenzo[*b,d*]pyran-1-ol* (**22**). As described for **2**, with **20** (0.154 g, 0.4 mmol), (+)-(*R*)-citronellal (**12b**; $[\alpha]_D = +12.5$, neat; 0.123 g, 0.8 mmol), xylene (10 ml), ethylenediamine diacetate (0.014 g), and Et_3N (2 ml). CC (SiO_2, hexane/AcOEt 15 : 1) gave 0.123 g (59%) of **22**. Liquid. $[\alpha]_D^{25} = -74.4$ ($c = 0.65$, MeOH).

(−)-Machaeriol C (= *(6a*R*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-3-[(1*E*)-2-(2-hydroxyphenyl)ethenyl]-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol*; **6**). As described for **3**, with **22** (0.102 g, 0.2 mmol), THF (10 ml), and 1M Bu_4NF in THF (0.6 ml). CC (SiO_2, hexane/AcOEt 5 : 1) gave 0.064 g (95%) of **6**. $[\alpha]_D^{25} = -104.0$ ($c = 0.26$, MeOH).

REFERENCES

[1] a) I. Muhammad, X.-C. Li, M. R. Jacob, B. L. Tekwani, D. C. Dunbar, D. Ferreira, *J. Nat. Prod*. **2003**, *66*, 804; b) I. Muhammad, X.-C. Li, D. C. Dunbar, M. A. ElSohly, I. A. Khan, *J. Nat. Prod*. **2001**, *64*, 1322.

[2] A. G. Chittiboyina, C. R. Reddy, E. B. Watkins, M. A. Avery, *Tetrahedron Lett.* **2004**, *45*, 1689.

[3] Q. Huang, Q. Wang, J. Zheng, J. Zhang, X. Pan, X. She, *Tetrahedron* **2007**, *63*, 1014.

[4] Q. Wang, Q. Huang, B. Chen, J. Lu, H. Wang, X. She, X. Pan, *Angew. Chem., Int. Ed.* **2006**, *45*, 3651.

[5] Y. R. Lee, J. H. Choi, S. H. Yoon, *Tetrahedron Lett*. **2005**, *46*, 7539; Y. R. Lee, W. K. Lee, S. K. Noh, W. S. Lyoo, *Synthesis* **2006**, 853; Y. R. Lee, D. H. Kim, *Synthesis* **2006**, 603; X. Wang, Y. R. Lee, *Tetrahedron Lett*. **2007**, *48*, 6275; X. Wang, Y. R. Lee, *Synthesis* **2007**, 3044; Y. R. Lee, L. Xia, *Synthesis* **2007**, 3240; Y. R. Lee, J. H. Kim, *Synlett* **2007**, 2232; Y. R. Lee, Y. M. Kim, *Helv. Chim. Acta* **2007**, *90*, 2401; Y. R. Lee, X. Li, J. H. Kim, *J. Org. Chem*. **2008**, *73*, 4313; Y. R. Lee, T. V. Hung, *Tetrahedron* **2008**, *64*, 7338.

[6] Y. R. Lee, L. Xia, *Tetrahedron Lett*. **2008**, *49*, 3283.

[7] L. Xia, Y. R. Lee, *Synlett* **2008**, 1643.

[8] O. Miyata, N. Takeda, T. Naito, *Org. Lett*. **2004**, *6*, 1761; N. Takeda, O. Miyata, T. Naito, *Eur. J. Org. Chem*. **2007**, 1491.

[9] T. Pacher, C. Seger, D. Engelmeier, S. Vajrodaya, O. Hofer, H. Greger, *J. Nat. Prod*. **2002**, *65*, 820.

[10] 'Pharmacopoeia of the People's Republic of China', English edition, Ed. Pharmacopoeia of the People's Republic of China, Chemical Industry Press, Beijing, 2000, Vol. 1, p. 199.

[11] R. S. Xu, in 'Studies in Natural Products Chemistry', Ed. Atta-ur-Rahman, Elsevier Science Publishers, Amsterdam, 2000, Vol. 21, p. 729; K. Sakata, K. Aoki, C. F. Chang, A. Sakurai, S. Tamura, S. Murakoshi, *Agric. Biol. Chem.* **1978**, *42*, 457; M. Terada, M. Sano, A. I. Ishii, H. Kino, S. Fukushima, T. Noro, *Nippon Yakurigku Zasshi* **1982**, *79*, 93; T. L. Do, in 'Vietnamese Traditional Medical Plants and Drugs', 3rd edn., Publishing House of Medicine, Hanoi, 2001, p. 180; V. C. A. Vo, in 'Dictionary of Traditional Vietnamese Medicinal Plants', Bio-Pharmaceutical Publisher, Hanoi, 2001, p. 162.

[12] H. Saimoto, K. Yoshida, T. Murakami, M. Morimoto, H. Sashiwa, Y. Shigemasa, *J. Org. Chem*. **1996**, *61*, 6768.

[13] J. J. Talley, *J. Org. Chem*. **1985**, *50*, 1695.

[14] J. P. Marino, S. L. Dax, *J. Org. Chem*. **1984**, *49*, 3671.

[15] K. A. Korthals, W. D. Wulff, *J. Am. Chem. Soc.* **2008**, *130*, 2898.

[16] T. Katoh, O. Ohmori, K. Iwasaki, M. Inoue, *Tetrahedron* **2002**, *58*, 1289.

[17] G. Chen, W. Shan, Y. Wu, L. Ren, J. Day, Z. Ji, *Chem. Pharm. Bull*. **2005**, *53*, 1587.

[18] Y. Ito, T. Aoyama, T. Shioiri, *Synlett* **1997**, 1163.

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