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FIRST TOTAL SYNTHESES OF NEW PHENYLPROPANOID LIGNANS, (±)-AGLACIN K STEREOISOMER AND (±)-ARBORONE

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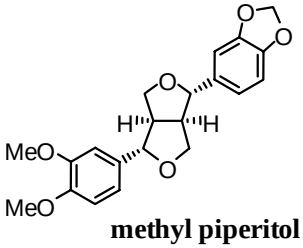
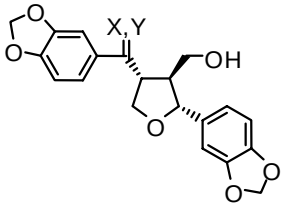
Abstract – An efficient and convergent process is described for the first preparation of new phenylpropanoid lignans, (±)-aglacin K stereoisomer and (±)-arborone, isolated from the stem bark of *Algaia cordata* and the stems of *Piper arborescens*, respectively. The key substituted tetrahydrofuran rings were constructed through chemoselective hydrogenation of functionalized lactol derivatives, which were in turn elaborated via requisite reverse stereoselective addition of organometallic reagent to the amide-aldehyde intermediates derived from a terpene lactone.

The lignan class of natural products displays a wide variety of constitution based on phenolic and *O*-heterocyclic substructures[1] and an equally wide range of biological activities. Especially, those attributed to the tetrahydrofuran series are diverse and include many activities such as antitumor promotion, antiallergic, antihypertensive, antimitotic, stress reducing, *c*AMP phosphodiesterase inhibitory, Ca^{2+} and PAF antagonist, insecticidal and toxicity enhancement activities[2] together with use as constituents of folk medicines.[1,3] Due to their interesting activity as well as unique structural characteristics, they have been the subject of an extensive synthetic effort which has culminated in numerous syntheses.[4] However, most methods were concerned with the construction of 2,5-disubstituted furans, while few focused on tri- and tetrasubstituted derivatives,[5] although the synthesis of this type of compounds includes interesting and often unsolved problems of stereocontrol. In spite of these facts, they serve as good templates for the construction of pharmacologically important furanoid groups and exhibit various degrees of potency and specificity.[6] We have also recently succeeded in the development of novel and stereoselective syntheses of biologically active furanoid natural products such as methyl piperitol

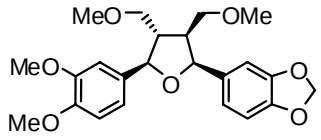
(**1**),[7a] sesaminone (**2a**) (*trans,trans* structure), its derivative (**2b**)[7b] (trisubstituted tetrahydrofurans, respectively), virgatusin (**3**)[7c] and goniothalesdiol (**4**)[7d] (tetrasubstituted tetrahydrofuran, respectively) employing Lewis acid induced deoxygenation of the lactol precursors exploited in this laboratory (Figure 1). On the other hand, new phenylpropanoid lignans, aglacin K (**5**) and arborone (**6**) (*cis,trans* structure), possessing a characteristic substitution pattern such as a di- or trisubstituted tetrahydrofuran ring have been isolated in 2004 from the stem bark of *Algaia cordata* Hiern collected from Kalimantan, Indonesia as one of the chemical constituents,[8a] and in 2005 from the stems of *Piper arborescens* Roxb. (Piperaceae) mainly distributed throughout Lanyu Island of Taiwan and the Philippines,[8b] respectively. The relative stereochemistry of **5** and **6** were determined from ^{1}H NMR and ^{13}C NMR spectra assisted with 2D NMR experiments. Since these two compounds are expected to be a rich source of compounds that might be useful for the development of new pharmaceutical agents containing insecticidal, cytotoxic, and potent anti-platelet aggregation activities, these would capture hereafter the interest as attractive and useful targets for synthesis. With these considerations in mind, we wish to communicate the details of the first and convergent syntheses of (±)-aglacin K (**5**) stereoisomer and (±)-arborone (**6**) by means of requisite reverse stereoselective addition of organometallic reagent followed by chemoselective hydrogenation of functionalized lactol derivatives elaborated from a common terpene lactone.



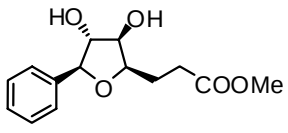
methyl piperitol (1)



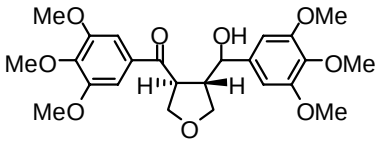
sesaminone (2a): X, Y = O
4-epidihydrosesamin (2b): X, Y = H



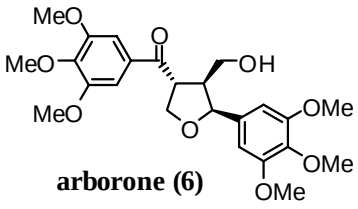
virgatusin (3)



goniothalesdiol (4)



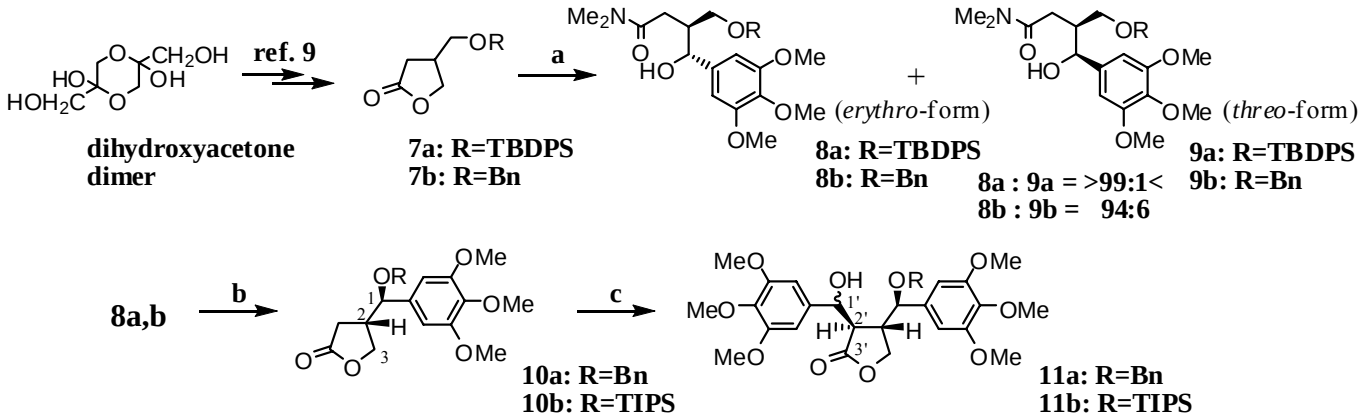
aglacin K (5)



arborone (6)

Figure 1. Furan Lignans

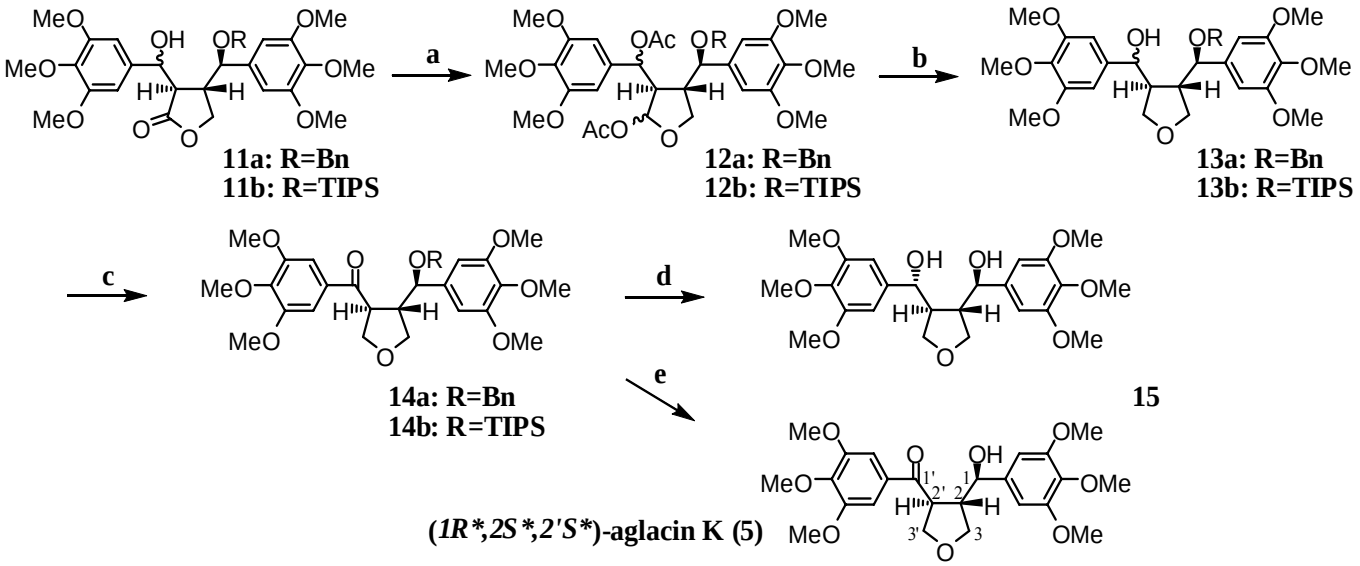
As shown in Scheme 1, the starting terpene lactones **7** prepared from dihydroxyacetone dimer according to our procedure[9] were converted to the *erythro*-amide alcohols **8** as a predominant product together with minor isomers *threo*-**9** via the subsequent reactions of aminolysis, Swern oxidation followed by the nucleophilic addition of organolithium reagent.[10] These were then submitted to the secondary alcohol-protection, deprotection of the primary alcohol part, and cyclization sequence to give the 1-substituted lactone derivatives **10**.[7a] Coupling reaction of **10** thus obtained with 3,4,5-trimethoxy-benzaldehyde in the presence of LiHMDS at low temperature provided the 2,2'-*trans* adducts **11** as a sole product in 93% (**11a**) and 94% (**11b**), respectively.[11]



Scheme 1 *Reagents and conditions*: (a) i, Me_2NH, MeOH; ii, $(COCl)_2$, DMSO, THF then Et_3N, -78 to 45 °C; iii, 5-bromo-1,2,3-trimethoxybenzene, BuLi, Et_2O, -78 °C; 33% (three steps) (**8a**), trace (**9a**); 39% (three steps) (**8b**), 2.5% (**9b**); (b) for (**8a**): i, BnBr, Ag_2O, AcOEt, 86%; ii, Bu_4NF, THF, 98%; iii, *p*-TsOH, toluene, 93% (**10a**); for (**8b**): i, TIPSOTf, 2,6-lutidine, CH_2Cl_2, 92%; ii, H_2, 5% Pd/C, MeOH, 90%; iii, PPTS, toluene, 45 °C; 82% (**10b**); (c) 3,4,5-trimethoxybenzaldehyde, LiHMDS, THF; -78 °C; 93% (**11a**) (*trans* only); 94% (**11b**) (*trans* only).

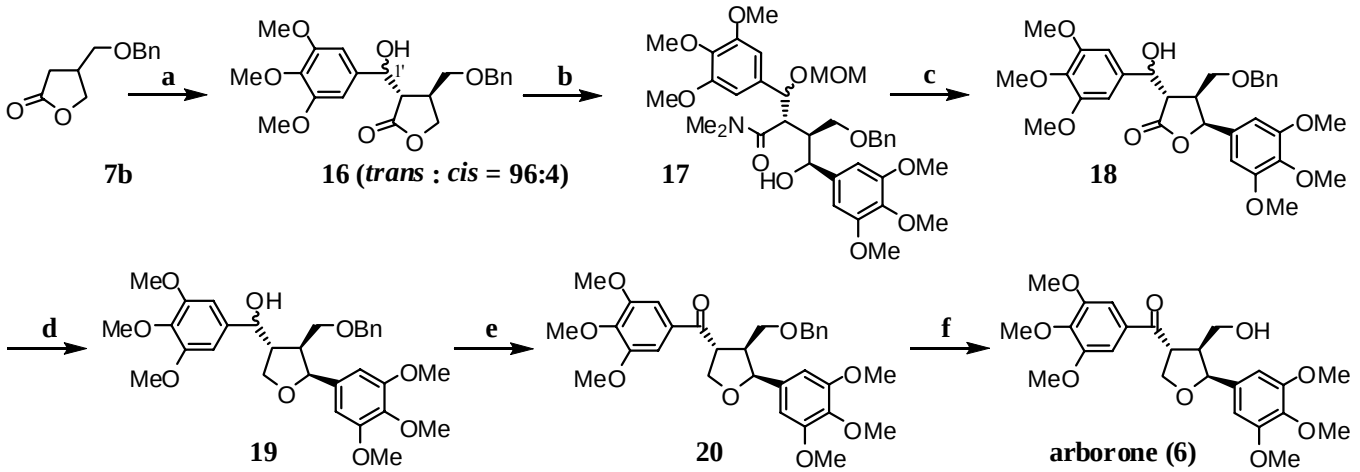
With these compounds in hand, we focused our research on the synthesis of aglacin K (**5**) (Scheme 2). To begin with, we investigated the conversion of this lactone ring to the corresponding tetrahydrofuran skeleton through Lewis acid-mediated hydrogenation of its lactol intermediate. Whereas direct hydrogenation of those lactols derived from DIBAL-H reduction of **11** as well as their MOM-hydroxyl protected derivatives with Et_3SiH in the presence of BF_3OEt_2 disappointingly yielded the inseparable mixture even at low temperature,[12] use of the diacetates **12** fortunately brought about the chemoselective hydrogenation products, which were hydrolyzed to give the desired tetrahydrofurans **13** as a predominant product. After TPAP-NMO oxidation[13] of **13**, the obtained ketone **14a** was at first hydrogenated with Pd/C under H_2 atomosphere to afford the diol **15** as the main product in moderate yield ascribed to over-reduction of the carbonyl function. However, **15** was interestingly identified to be the C_2-symmetrical structure based on its spectral data.[14] On the other hand, reaction of **14b** with Bu_4NF smoothly desilylated and accomplished the first synthesis of (±)-aglacin K (**5**) stereoisomer in 74% isolated yield. The spectral data of synthetic **5** were slightly different from those of the reported natural product.[8a,15] Since the stereochemical features of **5** have been unambiguously characterized through our synthetic process described here, we thus concluded that the unknown relative configurations of natural aglacin K should be (*1S*,2S*,2'S**).

In light of the above outcome, we turned our attention to the synthesis of the next target compound, (±)-arborone (**6**),[8b] which contains the similar carbon framework to that of sesaminone (**2a**), but with the relatively different stereochemistry. When the *trans*-lactone **16** obtained from coupling reaction of the common monoterpene lactone **7b** with 3,4,5-trimethoxy-benzaldehyde[16] was successively subjected to reactions of aminolysis and Swern oxidation after MOM-protection followed by the nucleophilic addition of organolithium reagent in a similar manner, it reversely provided the desired *threo*-type of amide alcohol **17** in contrast to the reaction giving *erythro*-**8** (shown in Scheme 1) as a single isomer.[17] After



Scheme 2 *Reagents and conditions*: (a) i, DIBAL-H, toluene, -78 °C; ii, Ac_2O, Et_3N, CH_2Cl_2; 60% (two steps) (**12a**); 57% (two steps) (**12b**); (b) i, Et_3SiH, BF_3OEt, CH_2Cl_2; ii, K_2CO_3, MeOH; 65% (two steps) (**13a**); 63% (two steps) (**13b**); (c) TPAP, NMO, MS4A, CH_2Cl_2; 75% (**14a**); 88% (**14b**); (d) H_2, 5% Pd/C, MeOH; 41% (from **14a**); (e) Bu_4NF, THF; 74% (from **14b**).

cyclization to the lactone **18**, the beneficial synthetic sequence consisting of DIBAL-H reduction, acetylation, and the chemoselectively reductive deoxygenation followed hydrolysis was applied to this synthetic process, fortunately leading to the trisubstituted furan **19** containing the desired relative configuration sequence in satisified yield (Scheme 3). Finally, the ketone **20** oxidized under Swern oxidation conditions was submitted to deprotection with Pd (black) to complete the first synthesis of (±)-arborone (**6**) in 85% yield. The spectral data of synthesized **6**[18] were completely identical to those of the reported values in all respects.[8b]



Scheme 3 *Reagents and conditions*: (a) 3,4,5-trimethoxybenzaldehyde, LiHMDS, THF, -78 °C; 96%; (b) i, MOMCl, *i*-Pr_2NEt, CH_2Cl_2; 93%; ii, Me_2NH, MeOH; 88%; iii, $(COCl)_2$, DMSO, THF then Et_3N, -78 to 45 °C; iv, 5-bromo-1,2,3-trimethoxybenzene, BuLi, Et_2O, -78 °C; 59% (two steps); (c) *p*-TsOH, toluene; 85%; (d) i, DIBAL-H, toluene, -78 °C; 89%; ii, Ac_2O, Et_3N, CH_2Cl_2; 98%; iii, Et_3SiH, BF_3OEt_2, CH_2Cl_2, -78 to 40 °C; 77%; iv, K_2CO_3, MeOH; 80%; (e) $(COCl)_2$, DMSO, THF then Et_3N, -78 to 45 °C, 84%; (f) Pd(black), HCO_2H, 47 °C; 85 %.

In summary, this work constitutes the first and convergent syntheses of new phenylpropanoids, (±)-aglacin K stereoisomer and (±)-arborone, by means of requisite reverse stereoselective addition of organolithium reagent followed by chemoselective hydrogenation of functionalized lactol derivatives, which were elaborated from the common terpene lactone. In addition, it verifies the structure proposed in the literature for these compounds. Synthetic strategy described here will be widely applicable to the synthesis of other important phenylpropanoid lignan natural products.

ACKNOWLEDGEMENTS

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10. These results can be explained in terms of the thermodynamically more stable Cram's non-chelation model based on our previous results.[7b]
11. The ratios of stereoisomers at C-1', on the contrary, were 65:35 (for **11a**) and 54:46 (for **11b**), respectively (determined by ^{1}H NMR analysis). S. Yamauchi and M. Yamaguchi, *Biosci. Biotechnol. Biochem*., 2003, **67**, 838.
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14. Spectral data for **15**. ^{1}H NMR ($CDCl_3$): δ 6.60 (s, 4H), 4.46 (d, 2H, *J*= 9.3 Hz), 4.15-4.08 (m, 2H), 3.88 (s, 12H), 3.85 (s, 6H), 3.58 (dd, 2H, *J*= 7.5, 9.4 Hz), 3.42 (dd, 2H, *J*= 7.0, 9.4 Hz), 2.68-2.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 152.6, 136.3, 133.1, 102.9, 84.3, 62.9, 61.2, 56.3, 51.5. Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.06; H, 6.94. Found: C, 61.95; H, 7.11.
15. Spectral data for synthetic **5**. ^{1}H NMR ($CDCl_3$): δ 7.21 (s, 2H), 6.98 (s, 1H), 5.63 (s, 1H), 5.20-5.15 (m, 1H), 4.15-3.96 (m, 2H), 3.95-3.86 (m, 20H), 3.64 (s, 1H), 3.31-3.27 (m, 1H), 2.32 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 195.6, 154.1, 153.1, 149.6, 133.2, 130.3, 124.5, 106.7, 106.2, 73.4, 73.3, 64.7, 62.0, 61.0, 60.9, 56.3, 56.1, 54.2, 44.0. IR (thin film): 3387, 2943, 1678, 1581, 1416, 1335, 1126 cm^{-1}. Anal. Calcd for $C_{24}H_{30}O_9$: C, 62.33; H, 6.54. Found: C, 62.16; H, 6.63.
16. The ratio of stereoisomers at C-1' was estimated to be 52:48 (by ^{1}H NMR analysis).
17. These results could be also reasonably explained with the aid of the thermodynamically more stable Cram's non-chelation model.[10]
18. Spectral data for syntheitc **6**. ^{1}H NMR ($CDCl_3$): δ 7.43 (s, 2H), 6.55 (s, 2H), 5.02 (d, 1H, *J*= 5.9 Hz), 4.44 (t, 1H, *J*= 7.7 Hz), 4.36-4.24 (m, 2H), 3.94 (s, 3H), 3.93 (s, 6H), 3.85 (s, 6H), 3.84 (s, 3H), 3.46-3.42 (m, 2H), 2.90 (dq, 1H, *J*= 2.2, 6.4, 12.5 Hz), 1.39 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 198.5, 153.4, 153.2, 143.0, 137.1, 133.6, 131.3, 106.4, 102.5, 81.5, 69.0, 62.0, 61.0, 60.9, 56.4, 56.2, 49.7, 48.7. IR (thin film): 3436, 2928, 1589, 1508, 1418, 1358, 1128, 1003 cm^{-1}. Anal. Calcd for $C_{24}H_{30}O_9$: C, 62.33; H, 6.54. Found: C, 62.45; H, 6.39.