HETEROCYCLES, Vol. 65, No. 3, 2005, pp. 519 - 522
Received, 30th November, 2004, Accepted, 21st January, 2005, Published online, 21st January, 2005

A NEW SYNTHETIC ENTRY TO FUROFURANOID LIGNANS, METHYL PIPERITOL AND FARGESIN

Hidemi Yoda,* Yuji Suzuki, Daisuke Matsuura, and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan; e-mail: tchyoda@ipc.shizuoka.ac.jp

Abstract – An efficient and general process is described for the preparation of the unsymmetrically substituted diequatorial and axial-equatorial furofuran lignans, methyl piperitol and fargesin. The synthetic strategy is based on a stereoselective manner by nucleophilic addition of organometallic reagent to the monoterpene lactone elaborated from dihydroxyacetone dimer followed by condensation with the corresponding aromatic aldehyde counter part.

Natural lignans, a class of phenylpropanoid, display 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 furofuran series (Figure) 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] Their unique structural complexity containing the bisfuran component as well as the equatorial or axial stereochemistry of the substituents coupled with diverse and potentially useful characteristics make them inviting targets for synthesis.[3]

Although much effort as described above has been devoted to developing efficient methods for syntheses of the furofuran series of lignans, very few synthetic strategies for natural methyl piperitol (**1**) and fargesin (**2**)[4] themselves have been reported.[5] In this connection we have also recently disclosed the total syntheses of dibenzylbutyrolactone-type lignans, (-)-hinokinin[6a] and (-)-enterolactone,[6b] and tri- and tetrasubstituted tetrahydrofuran lignans, (-)-sesaminone[6c] and (-)-virgatusin,[6d] the latter was the first example of the asymmetric total synthesis. Herein we wish to communicate a new and expeditious synthetic pathway for the preparation of the unsymmetrically substituted diequatorial and axial-equatorial furofuran lignans (**1**) and (**2**) starting from the monoterpene lactone, a crucial key compound for the synthesis of many kinds of lignans, developed in this laboratory.

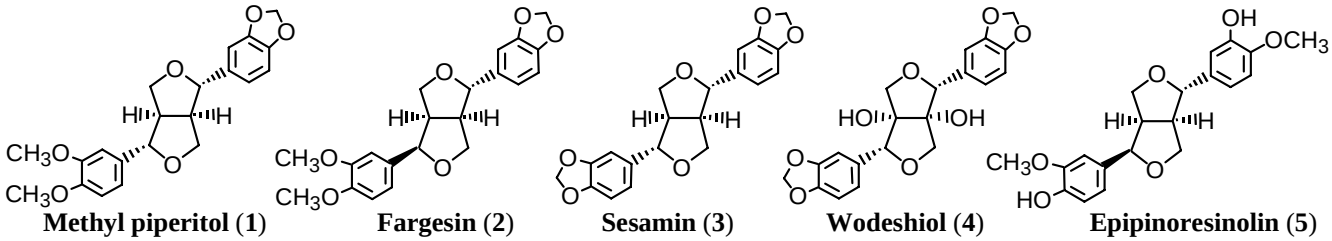
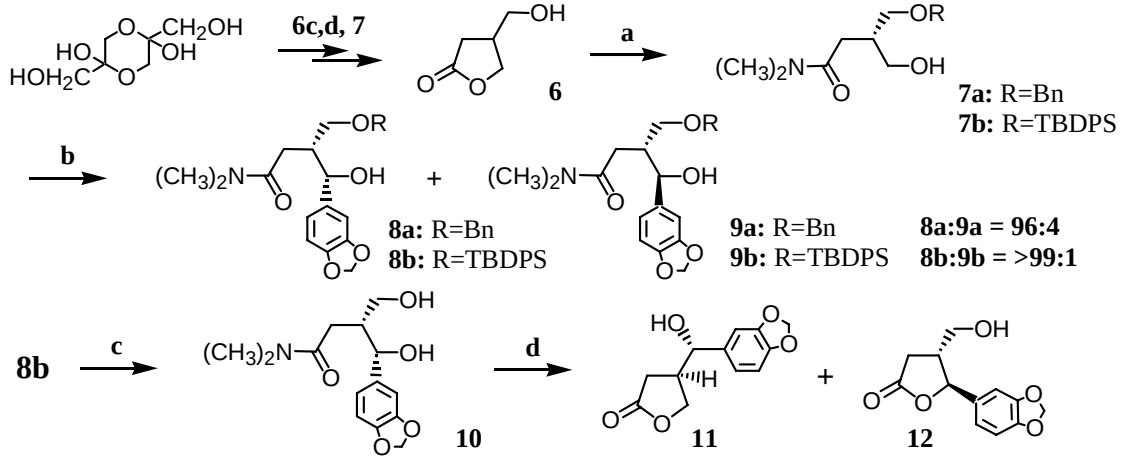


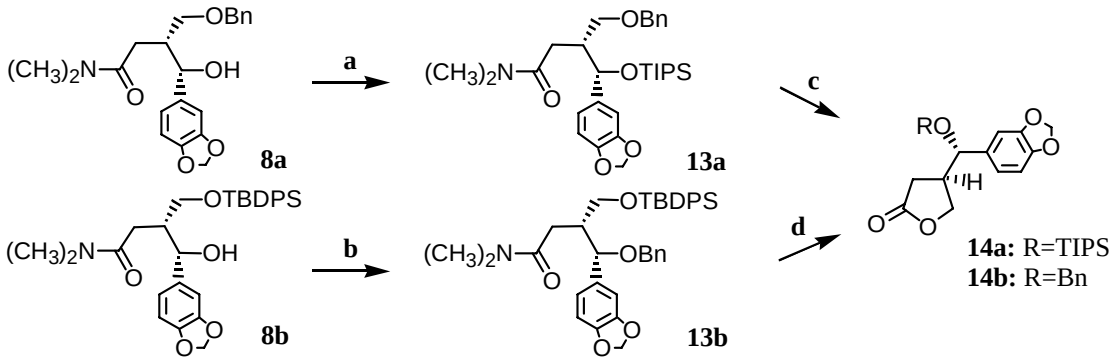
Figure. Furofuran Lignans.

As shown in Scheme 1, the key monoterpene lactone (**6**) prepared from dihydroxyacetone dimmer according to our preceding procedure[6c,d,7] was protected with the benzyl or *tert*-butyldiphenylsilyl (TBDPS) group and treated with dimethylamine to give the amide alcohols (**7**). Then, Swern oxidation of **7a** and **7b** followed by nucleophilic addition of piperonyl Grignard reagent *in situ* at 0 °C afforded the corresponding amide alcohols (**8a**) and (**8b**) as a predominant product, respectively (**8a**:**9a** = 96:4, **8b**:**9b** = >99:1, isolated ratio). These results can be explained in terms of the thermodynamically more stable Cram's non-chelation model based on our previous results.[6c] Initial experiments have been performed with **8b** in expectation of the direct preparation of the non-protected β-substituted hydroxylactone (**11**). Thus, subsequent reactions of desilylation and cyclization under mild acidic conditions gave the desired lactone (**11**) *via* the diol (**10**) in 33% yield (two steps), but disappointingly accompanied with the β,γ-disubstituted lactone (**12**) as a major component (66%) after chromatographic separation.



Scheme 1. Reagents and conditions: (a) 1. BnBr, Ag_2O, $CH_3CO_2C_2H_5$; 2. $(CH_3)_2NH$, 73% (**7a**) (2 steps); 1. TBDPSCl, CH_2Cl_2, imidazole; 2. $(CH_3)_2NH$, 96% (**7b**) (2 steps); (b) 1. $(COCl)_2$, DMSO, THF then $(C_2H_5)_3N$, -78 to -45 °C; 2. 3,4-methylenedioxyphenylmagnesium bromide, THF, 0 °C, 75% (**8a**), 3% (**9a**) (2 steps), 76% (**8b**), trace (**9b**) (2 steps); (c) $(C_4H_9)_4NF$, THF, 99%; (d) *p*-TsOH, toluene, 33% (**11**), 66% (**12**).

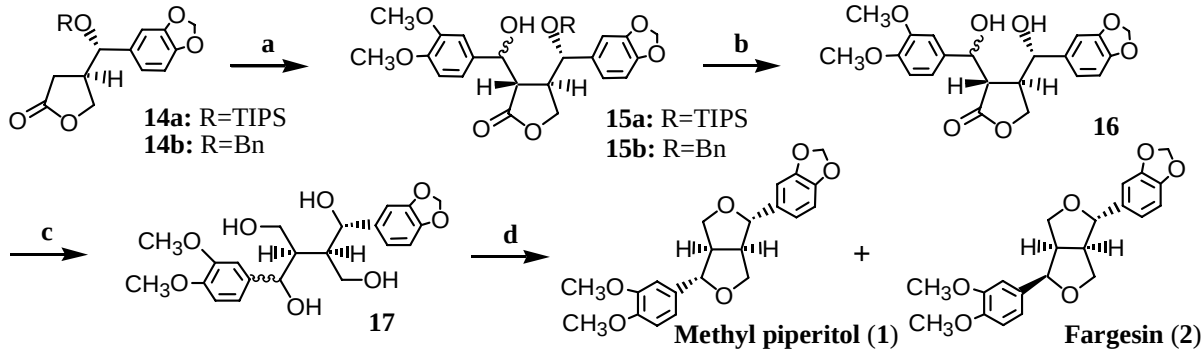
In light of the above outcome, we turned our attention to another synthetic route for the target natural product. An attempt to obtain the different hydroxyl-protected lactones of **11** is outlined in Scheme 2. Protection of the hydroxyl group of **8a** with TIPSOTf and debenzylation followed by cyclization yielded the TIPS-lactone (**14a**). On the other hand, the silylated amide alcohol (**8b**) was reversely subjected to the successive reactions of benzylation, desilylation and cyclization, leading to the desired benzyl-lactone (**14b**) in satisfactory yield.



Scheme 2. Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 86%; (b) BnBr, Ag_2O, $CH_3CO_2C_2H_5$, 75%; (c) 1. 5% Pd/C, H_2, CH_3OH; 2. PPTS, toluene, 45 °C, 88% (**14a**) (2 steps); (d) 1. $(C_4H_9)_4NF$, THF; 2. *p*-TsOH, toluene, 81% (**14b**) (2 steps).

With these two intermediates in hand, we then focused our research on the synthesis of methyl piperitol (**1**) and fargesin (**2**) (Scheme 3). **14a** and **14b** thus obtained were effected by coupling reaction with 3,4-dimethoxybenzaldehyde in the presence of LiHMDS[8] at low temperature, respectively. We were delighted to find that these reactions smoothly brought about the desired α,β-*trans* adduct (**15a**) or (**15b**) alone[6c,7,9] based on their spectral data, including the almost equivalent amount of stereoisomers at the benzyl position in each case (determined by ^{1}H NMR spectrum). Then, these two compounds (**15a**) and (**15b**) were independently submitted to deprotection reaction with $(C_4H_9)_4NF$ or 5% Pd/C in an atmosphere of H_2 in almost quantitative yield, followed by reduction with $LiAlH_4$ to afford the corresponding tetraol intermediate (**17**) in 87% yield. Finally, **17** was subjected to mesylation, providing the dimesylate which in turn underwent the intramolecular cyclization spontaneously to complete the total synthesis of **1** and **2**. Both spectral data of synthesized **1** and **2** were completely identical with those of the reported synthetic[5] and natural[4] compounds.

In summary, this work constitutes a general and new synthetic opportunity for the total syntheses of diequatorial and axial-equatorial furofuran lignans, such as methyl piperitol and fargesin, through stereoselective manipulation of the mono-terpene lactone and will be widely applicable to the synthesis of other lignan natural products.



Scheme 3. Reagents and conditions: (a) LiHMDS, 3,4-dimethoxybenzaldehyde, THF, -78 °C, 77% (**15a**, 59:41), 95% (**15b**, 47:53); (b) $(C_4H_9)_4NF$, THF (to **15a**), 96% or 5% Pd/C, H_2, $CH_3CO_2C_2H_5$ (to **15b**), 97%; (c) $LiAlH_4$, THF, 87%; (d) MsCl, pyridine, CH_2Cl_2, 38% (**1**), 24% (**2**).

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science.

REFERENCES AND NOTES

1. (a) R. S. Ward, *Nat. Prod. Rep*., 1993, **10**, 1. (b) R. S. Ward, *Nat. Prod. Rep*., 1995, **12**, 183. (c) R. S. Ward, *Nat. Prod. Rep*., 1997, **14**, 43. (d) R. S. Ward, *Nat. Prod. Rep*., 1999, **16**, 75.
2. W. D. MacRae and G. H. N. Towers, *Phytochemistry,* 1984, **23**, 1207. Selected examples of biological activity; (a) antitumor promotion: M. Takasaki, T. Konoshima, I. Yasuda, T. Hamano, and H. Tokuda, *Biol. Pharm. Bull*., 1997, **20**, 776. (b) Ca^{2+} antagonist activity: C. C. Chen, Y. L. Huang, H. T. Chen, Y. P. Chen, and H. Y. Hsu, *Planta Med*., 1988, 438. (c) antihypertensive activity: C. J. Sih, P. R. Ravikumar, F.-C. Huang, C. Buckner, and H. Whitlock, *J. Am. Chem. Soc*., 1976, **98**, 5412. (d) anti-allergic activity: K. Hashimoto, T. Yanagisawa, Y. Okui, Y. Ikeya, M. Maruno, and T. Fujita, *Planta Med*., 1994, **60**, 124. (e) PAF antagonist activity: K. Y. Jung, D. S. Kim, S. R. Oh, S.-H. Park, I. S. Lee, J. J. Lee, D.-H. Shin, and H.-K. Lee, *J. Nat. Prod*., 1998, **61**, 808; J. X. Pan, O. D. Hensens, D. L. Zink, M. N. Chang, and S.-B. Hwang, *Phytochemistry*, 1987, **26**, 1377. (f) insecticidal activity: M. Miyazawa, Y. Ishikawa, H. Kasahara, J. Yamanaka, and H. Kameoka, *Phytochemistry,* 1994, **35**, 611; E. Taniguchi and Y. Oshima, *Tetrahedron Lett*., 1972, 653.
3. For a review covering some of the synthetic routes of lignans and neolignans: (a) D. A. Whiting, *Nat. Prod. Rep*., 1990, **7**, 349. (b) R. S. Ward, *Chem. Soc. Rev*., 1982, **11**, 75. (c) R. S. Ward, *Tetrahedron*, 1990, **46**, 5029. (d) R. C. D. Brown and N. A. Swain, *Synthesis,* 2004, 811. Recent examples: (e) D. J. Aldous, A. J. Dalencon, and P. G. Steel, *J. Org. Chem*., 2003, **68**, 9159. (f) R. C. D. Brown, C. J. Bataille, C. J. R. Bataille, G. Bruton, J. D. Hinks, and N. A. Swain, *J. Org. Chem*., 2001, **66**, 6719. (g) S.-I. Yoshida, T. Ogiku, H. Ohmizu, and T. Iwasaki, *J. Org. Chem*., 1997, **62**, 1310.
4. Methyl piperitol: M. Höke and R. Hänsel, *Arch. Pharm*., 1972, **305**, 33. Fargesin: H. Kakisawa,Y. P. Chen, and H. Y. Hsü, *Phytochemistry,* 1972, **11**, 2289.
5. Methyl piperitol: A. Pelter, R. S. Ward, P. Collins, R. Venkateswarlu, and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1,* 1985, 587. Methyl piperitol and fargesin: T. Ogiku, S. Yoshida, H. Ohmizu, and T. Iwasaki, *J. Org. Chem*., 1995, **60**, 1148 and references cited therein. Fargesin: S. Yoshida, T. Yamanaka, T. Miyake, Y. Moritani, H. Ohmizu, and T. Iwasaki, *Tetrahedron Lett*., 1995, **36**, 7271.
6. (a) H. Yoda, S. Naito, K. Takabe, N. Tanaka, and K. Hosoya, *Tetrahedron Lett*., 1990, **31**, 7623. (b) H. Yoda, H. Kitayama, T. Katagiri, and K. Takabe, *Tetrahedron,* 1992, **48**, 3313. (c) H. Yoda, K. Kimura, and K. Takabe, *Synlett,* 2001, 400. (d) H. Yoda, M. Mizutani, and K. Takabe, *Tetrahedron Lett*., 1999, **40**, 4701.
7. H. Yoda, M. Mizutani, and K. Takabe, *Synlett,* 1998, 855.
8. In order to carry out the total synthesis of both diequatorial and axial-equatorial types of natural products (**1**) and (**2**), these coupling reactions were performed purposely with the use of LiHMDS instead of KHMDS, since *erythro*-selective aldol reaction at the benzyl position was recently reported employing KHMDS during our synthetic studies of these substances; S. Yamauchi and M. Yamaguchi, *Biosci. Biotechnol. Biochem*., 2003, **67**, 838.
9. The *trans*-structure was ascertained after completion of the syntheses of **1** and **2**, whose spectral data were completely identical with those of the reported values, respectively.