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Short Communication

Radical annulation route to the synthesis of lignans: An account†

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Abstract

Due to the widespread occurrence in nature and broad range of biological activities, lignans have attracted considerable interest over the years. Although several elegant synthetic methods have been developed for their synthesis, the radical annulation route remained unexplored until 1989. In this account, the synthesis of different types of natural lignans using radical cyclization reaction with various radical sources has been presented. Most of the cyclizations are highly regio- and stereoselective.

Keywords: Lignans, radical cyclization, regioselective, stereoselective, tributyltin hydride, epoxide, transition metal.

1. Introduction

Due to the widespread occurrence in nature[1–3] and broad range of biological activities,[4] lignans have attracted considerable interest over the years. Some lignans are known to exhibit antitumour activity, while others function as growth inhibitors and antifungal agents. Recent isolation of lignans from animals led to a suggestion that such compounds may be examples of a new type of hormone-controlling cell growth.[5–6] The many varied types of structures that lignans can possess have presented a considerable challenge to organic chemists over the years and indeed many elegant syntheses have been reported[7–14] depending upon a limited number of key reactions to construct the basic 18-carbon skeleton. Two major subgroups of lignans comprise substituted tri- or tetrasubstituted tetrahydrofurans and substituted 3,7-dioxabicyclo [3.3.0] octanes, whose members show a variety of biological activities and their synthesis poses interesting and often unsolved problems of stereocontrol. Although interesting syntheses have been achieved providing these natural products, the tin hydride-mediated intramolecular radical cyclization strategy towards lignans was unexplored. The radical cyclization reaction witnessed a renaissance recently[15–19] leading to the synthesis of complex natural products. This is an account of tin hydride-mediated radical cyclization towards naturally occurring lignans which include mainly the work done in our laboratory along with the works reported by others.

2. Synthesis of furano lignans

In 1989, Belletire and Mahmood utilized the radical cyclization reaction[20] in the total synthesis of deoxypodorhizon (**1**) (Scheme 1). In continuation of our study in radical reactions using tin hydride as the radical source, we could successfully achieve the stereoselective total synthesis of bioactive furano lignan, (±)-dihydrosesamin in good overall yield. Dihydrosesamin is one of the

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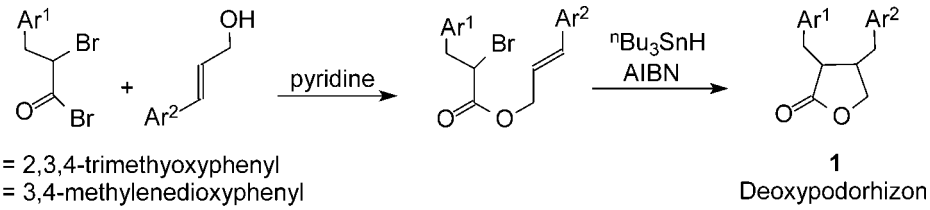
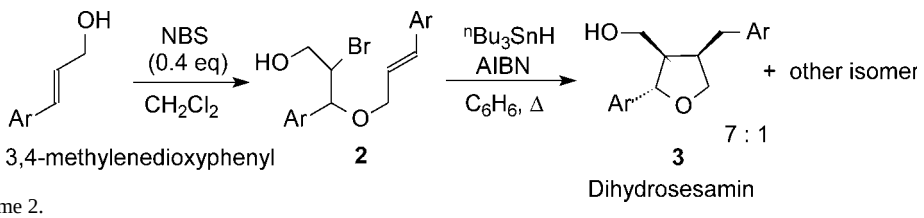
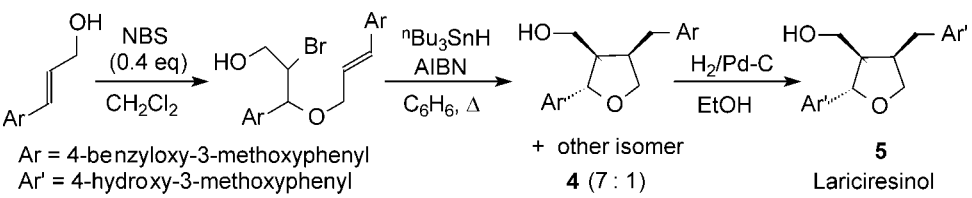


Scheme 1.

representative biologically active furano lignans which was isolated from *Daphne tangutica* Maxim and has been used in the treatment of rheumatism and toothache.[21] Thus radical cyclization of the bromohydrin **2** in the presence of Bu_3SnH afforded dihydrosesamin **3** (60%) along with another compound (could not be separated in pure form) in a ratio of 7:1 (Scheme 2). In a similar sequence, total synthesis of (±)-lariciresinol (**5**) was achieved as shown in Scheme 3. Lariciresinol was isolated from *Dirca occidentalis* and *Wikstroemia elliptica* and is significantly active against the P-388 lymphocytic leukaemia.[22] Lariciresinol (**5**) was obtained by hydrogenolysis of the cyclized product **4**.[23–24]



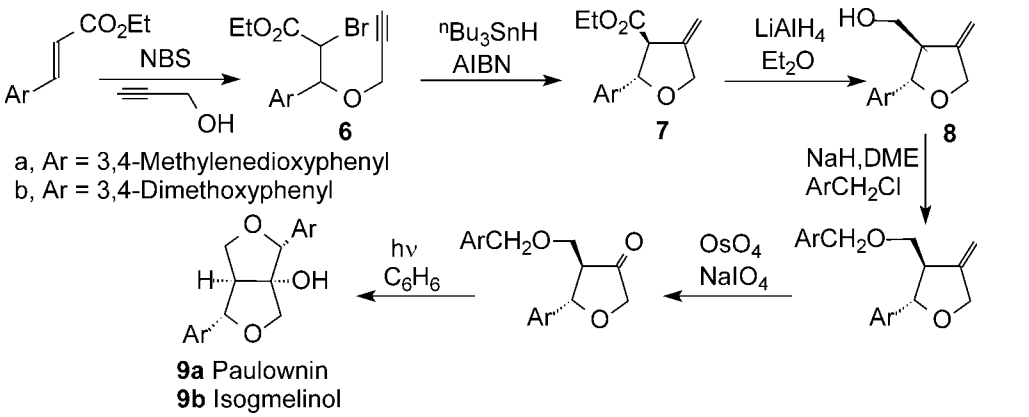
Scheme 2.



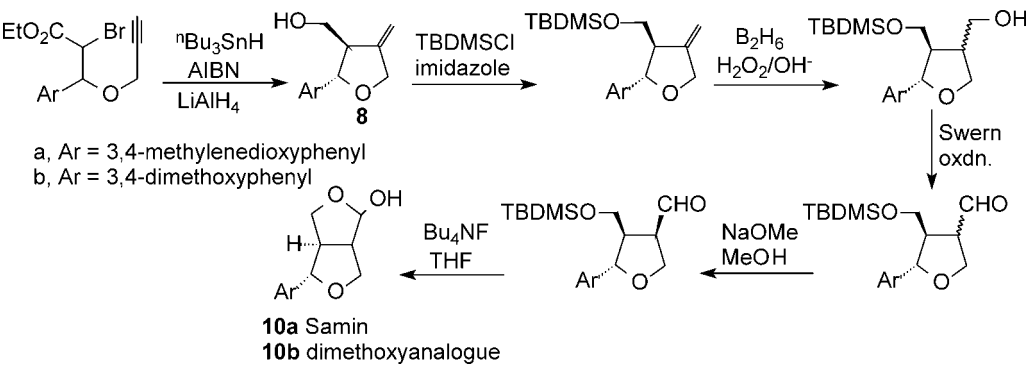
Scheme 3.

3. Synthesis of furofuran lignans

We have successfully demonstrated in our laboratory the total synthesis of a few furofurano lignans using radical cyclization reaction as the key step. We have reported[25–26] the total synthesis of two naturally occurring furofuran lignans, paulownin and isogmelinol (Scheme 4). Tin hydride-mediated radical cyclization of the bromoether **6** afforded the tetrahydrofuran **7** from which the synthesis of paulownin (**9a**) and isogmelinol (**9b**) could be achieved in a stereoselective manner. We have also successfully demonstrated[27–28] the stereoselective synthesis of samin **10a** and the dimethoxy analogue **10b** using the radical cyclization strategy in good overall yield (Scheme 5). Samin, being a natural lignan, has been shown[29] to be a suitable precursor for both symmetrical and unsymmetrical types of lignans such as acuminatolide, sesamolin, sesamin, etc.; the dimethoxy analogue could also be a versatile precursor for Eudesmin, methyl piperitol and many other



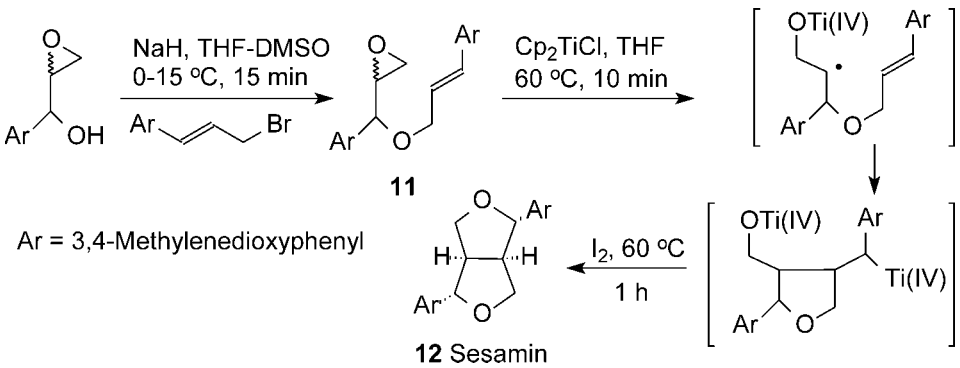
Scheme 4.



Scheme 5.

furofuran lignans. Thus, using the alcohol **8** as the precursor, we could synthesize these compounds by routine experiments.

Although we could achieve various lignans through tin hydride-mediated radical cyclization reaction, the separation of tin compounds from the products is very laborious. Moreover, tin compounds are toxic and the choice of radical precursor is limited. We were exploring for a better method to avoid tin compounds and isolate pure products easily. We found that RajanBabu and Nugent developed[30] a method of preparing radical from epoxides using Ti(III) species as the radical source. This methodology was applied in our laboratory to synthesize a furofuran lignan, sesamin (**12**). Sesamin[31–32] is one of the representative biologically active furofuran lignans which was isolated from hydrocotyle plants. Total synthesis of sesamin has been achieved[33] in a very short and stereoselective route by radical cyclization of the epoxide **11** using a Ti(III) species as the radical source (Scheme 6). The reagent Cp_2TiCl was generated *in situ* from commercially available titanocene dichloride and zinc dust in THF. Applying this radical methodology, the synthesis of various lignans is in progress in our laboratory and will be reported elsewhere.



Scheme 6.

4. Conclusion

Considering the mild reaction condition and its stereoselective nature, intramolecular radical cyclization reaction has appeared to be a valuable tool to synthetic organic chemists for the preparation of natural compounds. This unique methodology has been successfully utilized towards the total synthesis of various active natural lignans and related compounds. Most of the cyclizations were highly stereo- and regioselective. A few syntheses have been done in very short routes. Moreover, the novel method of generating radicals from epoxides has added a tremendous boost to this field which will provide the organic chemists a new tool toward the synthesis of various natural products.

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References

1. Rao, C. B. S. (ed.) — *Chemistry of lignans*, Andhra University Press, Waltair, 1978.
2. Whiting, D. A. — Lignans and neolignans, *Nat. Prod. Rep.*, 1985, **2**, 191; 1987, **4**, 499; 1990, **7**, 349.
3. Ward, R. S. — Lignans, neolignans and related compounds, *Nat. Prod. Rep.*, 1993, **10**, 1; 1995, **12**, 183; 1997, **14**, 43.
4. Gottlieb, O. R. — *New natural products and plant drugs with pharmacological, biological or therapeutical activity*, Springer-Verlag, 1987, pp. 227–248.
5. Stitch, S. R. *et al*. — Excretion, isolation and structure of a new phenolic constituent of female urine, *Nature*, 1980, **287**, 738.
6. Setchell, K. D. R. *et al.* — Lignans in man and in animal species, *Nature*, 1980, **287**, 740.
7. Ward, R. S. — The synthesis of lignans and neolignans, *Chem. Soc. Rev.*, 1982, 75.
8. Kraus, G. A., and Li Chen — A total synthesis of racemic paulownin using a type II photocyclization reaction, *J. Am. Chem. Soc.*, 1990, **112**, 3464.

9. JANSEN, J. F. C. A. AND FERINGA, B. L. — Asymmetric 1,4-addition to γ-methyloxybutenolides. (Part III). Enantioselective synthesis of (-)-eudesmine, *Tetrahedron Lett.*, 1991, **32**, 3239.

10. STEVENS, D. R. AND WHITING, D. A. — Synthesis of the lignan (±)-dihydrosesamin: Problems of stereocontrol in the formation of 2,3,4-trisubstituted tetrahydrofurans and tetrahydrofuranones, *J. Chem. Soc., Perkin Trans. 1,* 1990, 425.

11. STEVENS, D. R. AND WHITING, D. A. — Stereospecific synthesis of the 2,3-*trans*-3,4-*cis*-trisubstituted tetrahydrofuran lignan (±)-dihydrosesamin, *J. Chem. Soc., Perkin Trans. 1,* 1992, 633.

12. MITRA, J. AND MITRA, A. K. — Simple synthesis of furanoid and dioxabicyclo[3.3.0]octane lignans, *J. Chem. Soc., Perkin Trans. 1,* 1992, 1285.

13. OGIKU, T. *et al*. — A new stereocontrolled synthesis of diequatorial furofuran lignans having two different aryl groups: A synthesis of methyl piperitol, *Tetrahedron Lett.*, 1992, **33**, 4473.

14. OGIKU, T. *et al*. — A new stereocontrolled synthesis of axial-equatorial furofuran lignans having two different aryl groups: A synthesis of fargesin, *Tetrahedron Lett.*, 1992, **33**, 4477.

15. GIESE, B. — *Radicals in organic synthesis, formation of carbon–carbon bonds*, Pergamon Press, 1986.

16. RAMAIAH, M. — Radical reactions in organic synthesis, *Tetrahedron*, 1987, 3541.

17. SRIKRISHNA, A. — Radical cyclizations in the synthesis of natural products, *Curr. Sci.*, 1987, **56**, 392.

18. CURRAN, D. P. — The design and application of free radical chain reactions in organic synthesis. Part 1, *Synthesis*, 1988, 417.

19. CURRAN, D. P. — The design and application of free radical chain reactions in organic synthesis. Part 2, *Synthesis*, 1988, 489.

20. BELLETIRE, J. L. AND MAHMOODI, N. O. — Direct butyrolactone production using tin hydride, *Tetrahedron Lett.*, 1989, **30**, 4363.

21. LIN-ZEN, Z., SELIGMANN, O., LOTTER, H. AND WAGNER, H. — (-)- Dihydrosesamin, a lignan from *Daphne tangutica*, *Phytochemistry*, 1983, **22**, 265.

22. DUH, C. Y., PHOEBE, C. H. JR. PEZZUTO, J. M., KINGHORN, A. D. AND FARNSWORTH, N. R. — Plant anticancer agents XLII. Cytotoxic constituents from *Wikstroemia elliptica*, *J. Nat. Prod.*, 1986, **49**, 706.

23. MAITI, G., ADHIKARI, S. AND ROY, S. C. — Short and stereoselective synthesis of (±)-dihydrosesamin by a radical cyclisation reaction, *Tetrahedron Lett.*, 1994, **35**, 3985.

24. MAITI, G., ADHIKARI, S. AND ROY, S. C. — Radical cyclisation route to furanolignans. Short and stereoselective synthesis of (±)-dihydrosesamin and (±)-lariciresinol, *J. Chem. Soc., Perkin Trans. 1*, 1995, 927.

25. ADHIKARI, S. AND ROY, S. C. — Stereoselective radical annulation route to the synthesis of (±)-paulownin and (±) isogmelinol, *Tetrahedron Lett.*, 1992, **33**, 6025.

26. ROY, S. C. AND ADHIKARI, S. — Stereoselective total synthesis of (±)- paulownin and (±)-isogmelinol through radical annulation route, *Tetrahedron*, 1993, **49**, 8415.

27. MAITI, G., ADHIKARI, S. AND ROY, S. C. — Stereoselective total synthesis of (±)-samin, the general furofuran lignan precursor, *Tetrahedron Lett.*, 1994, **35**, 6731.

28. MAITI, G., ADHIKARI, S. AND ROY, S. C. — Stereoselective total synthesis of (±)-samin and the dimethoxy analogue, the general furofuran lignan precursors, *Tetrahedron*, 1995, **51**, 8389.

29. TAKANO, S., OHKAWA, T., TAMORI, S., SATOH, S. AND OGASAWARA, K. — Enantio-controlled route to the furofuran lignans: the total synthesis of (-)-sesamolin, (-)-sesamin and (-)-acuminatolide, *J. Chem. Soc., Chem. Commun.*, 1988, 189.

30. RAJANBABU, T. V. AND NUGENT, W. A. — Selective generation of free radicals from epoxides using a transition-metal radical. A powerful new tool for organic synthesis, *J. Am.Chem. Soc.*, 1994, **116**, 986.

31. BECKER, E. D. AND BEROZA, M. — Proton magnetic resonance studies relating to the stereochemistry of sesamin, asarinin and epiasarinin, *Tetrahedron Lett.*, 1962, 157.

32. SUGINOME, H. *et al*. — Photoinduced molecular transformations 157. A new stereo- and regioselective synthesis of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans involving a β-scission of alkoxyl radicals as the key step. New total syntheses of (±)-sesamin, (±)-eudesmin and (±)-yangabin, *J. Org. Chem.*, 1995, **60**, 3052.

33. RANA, K. K., GUIN, C. AND ROY, S. C. — A short and stereoselective total synthesis of (±)-sesamin by radical cyclisation of an epoxide using a transition-metal radical source, *Tetrahedron Lett.*, 2000, **41**, 9337.