A Concise Diastereoselective Route to Racemic Samin, the General Furofuran Lignan Precursor

Seiichi Takano,* Kiyohiro Samizu and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Exposure of the dihydro-1,3-dioxepine **5** to diisobutylaluminum hydride induces concurrent diastereoselective ring-contraction and reduction to lead to the trisubstituted tetrahydrofuran, oxidative cleavage of which gives (±)-samin **1**, the general furofuran lignan precursor.

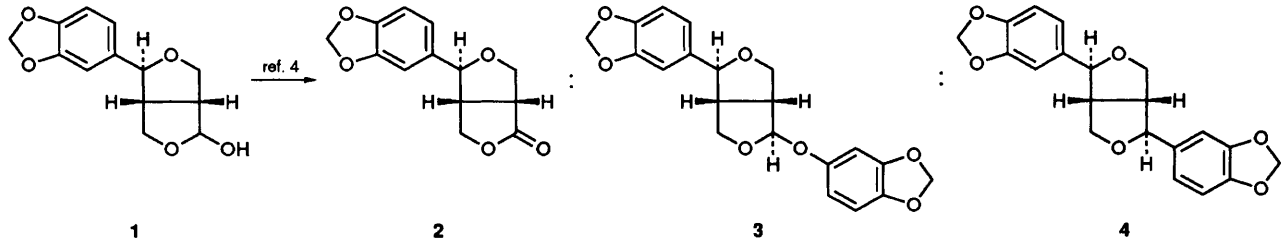
Although a number of interesting synthetic methods[1–3] including enantiocontrolled synthesis[3–5] have been developed for the construction of the furofuran lignans, a general method capable of steric control and at the same time exhibiting synthetic efficiency seemed yet to be reported to date. We report here a concise diastereoselective route to a racemic form of samin[1d,1f,4,6] **1** which has been shown[4] to be a suitable precursor for both symmetrical and unsymmetrical types of the furofuran lignans, such as acuminatolide **2**, sesamolin **3**, and sesamin **4**.

The present synthesis consists of just three steps starting from the readily accessible 2-aryl-4,7-dihydro-1,3-dioxepine[7]† **5** without employing any difficult procedure. Thus, the Heck reaction[8] between **5** and (*E*)-1-iodohept-1-ene[9] afforded the 5-alkenyl-2-aryl-4,5-dihydro-1,3-dioxepine **6** as an unstable diastereoisomeric mixture. Immediate treatment of a crude **6** with diisobutylaluminum hydride in dichloromethane[10] at −78 °C brought about an unexpected but facile reductive rearrangement to give the trisubstituted tetrahydrofuran **9** diastereoselectively in 56% overall yield from **5** in one step. Oxidative cleavage[1d,4,11] of the alkene double bond of **9** led to (±)-samin **1** in 70% yield *via* the transient aldehyde **10**.

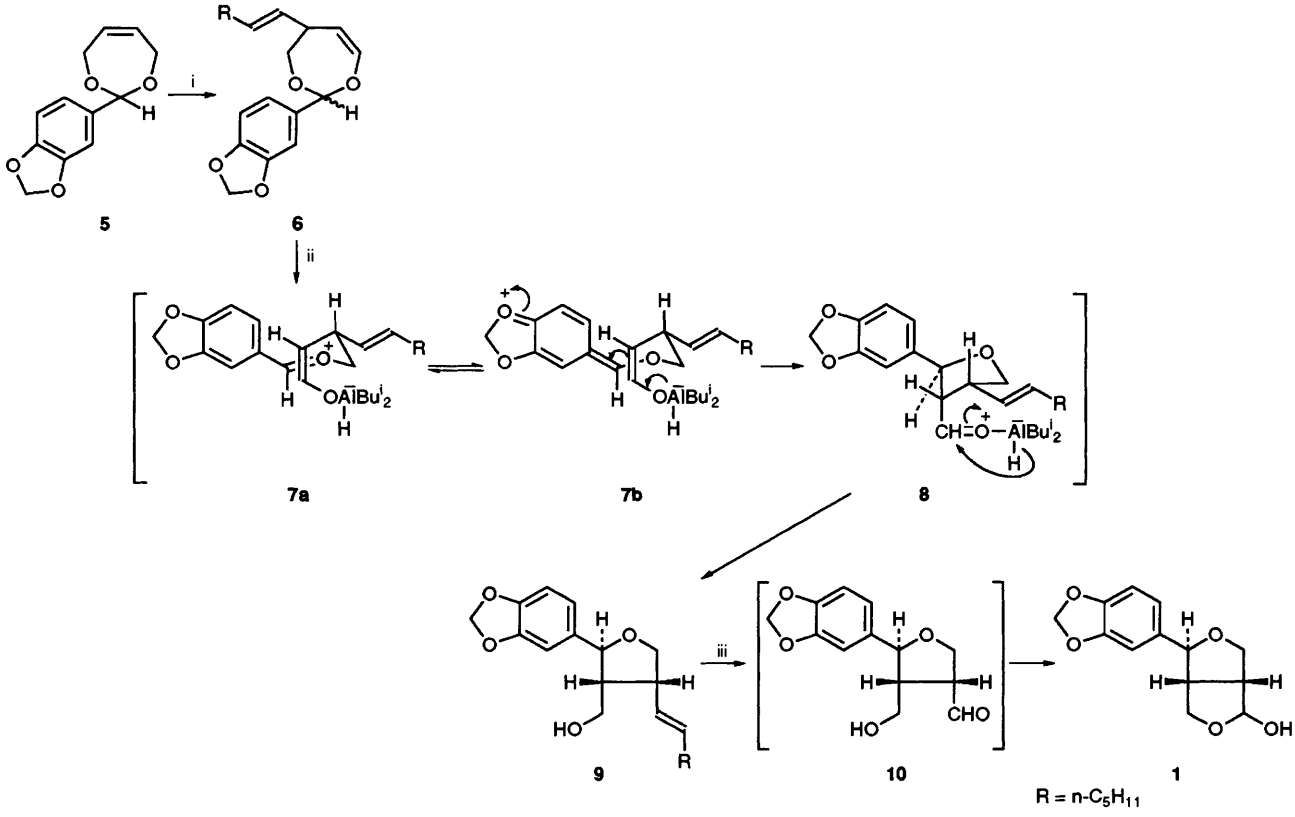
The remarkable one-step transformation of the dihydroxepine **6** into the tetrahydrofuran **9** under the reducing conditions may be due to the nature of diisobutylaluminium hydride. Namely, it reacts initially as a Lewis acid to cleave the seven-membered ring to generate the active enolate intermediate **7a** which, probably, is in the most stable conformation. Then spontaneous cyclization takes place through a 5-*exo*-trigonal process[12] *via* **7b** to generate the penultimate five-membered intermediate[13] **8** which, in turn, is reduced to furnish the product **9**. It is worth noting when **6** was treated with boron trifluoride ethereate, followed by diisobutylaluminium hydride, a diastereoisomeric mixture (*ca.* 1:1) of alcohols (**9** and its epimer) was obtained even though the reaction was carried out at low temperature (−78 °C) (Scheme 2).

The present procedure based on a fortuitous finding can be

† Satisfactory spectral (IR, ^{1}H NMR, mass spectroscopic) and analytical (combustion and/or high resolution mass) data were obtained for new compounds.



Scheme 1



Scheme 2. *Reagents and conditions*: i, (*E*)-1-iodohept-1-ene (2.0 equiv.), $Pd(OAc)_2$ (8 mol%), Pr^i_2NEt (5.0 equiv.), dimethylformamide (DMF), 70 °C, 12 h; ii, Bu^i_2AlH (4.0 equiv.), CH_2Cl_2, −78 °C, 1 h; iii, OsO_4 (10 mol%), *N*-methylmorpholine oxide (NMO) (1.8 equiv.), aq. tetrahydrofuran (THF) (70%), 0 °C to room temp., 2 h, then $NaIO_4$ (2.0 equiv.), 0 °C to room temp., 1.5 h

generally used to prepare a variety of the furofuran lignans bearing aryl group(s) other than methylenedioxyphenyl group both in symmetrical and unsymmetrical forms. Furthermore, the incorporation of chirality into the sequence seems to be promising, since a highly efficient asymmetric induction during the Heck reaction has recently been established in the related system.[14]

Received, 15th March 1993; Com. 3/01480K

References

1 For some recent examples, see (*a*) A. Pelter, R. S. Ward, P. Collins, R. Venkateswalin and I. T. Kay, *J. Chem. Soc., Perkin Trans. 1*, 1985, 587; (*b*) D. R. Stevens and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1990, 425; (*c*) G. A. Kraus and L. Chen, *J. Am. Chem. Soc.*, 1990, **112**, 3464; (*d*) H. M. Bradley and D. W. Knight, *J. Chem. Soc., Chem. Commun.*, 1991, 1641; (*e*) K. Orito, K. Yorita and H. Suginome, *Tetrahedron Lett.*, 1991, **32**, 5999; (*f*) H. M. Bradley, P. G. Jones and D. W. Knight, *Synlett*, 1992, **479**; 1990, **7**, 349.

2 For reviews of lignan chemistry, see D. A. Whiting, *Nat. Prod. Rep.*, 1985, **2**, 191; 1987, **4**, 499; 1990, **7**, 349; R. S. Ward, *Nat. Prod. Rep.*, 1993, **10**, 1.

3 For a pertinent monograph of lignans, see D. C. Ayres and J. D. Loike, *Lignans Chemical, Biological and Clinical Properties*, Cambridge University Press, Cambridge, 1990.

4 S. Takano, T. Ohkawa, S. Tamori, S. Satoh and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, 189.

5 For pertinent reviews, see R. S. Ward, Tetrahedron, 1990, **46**, 5029; B. L. Feriaga, B. deLange, J. F. G. A. Jarsen, J. C. deJong, M. Lubben, W. Faber and E. P. Schudde, *Pure Appl. Chem.*, 1992, **64**, 1865.

6 E. Haslam and R. D. Haworth, *J. Chem. Soc.*, 1955, 827; Y. Fukuda, M. Isobe, M. Nagata, T. Osawa and M. Namiki, *Heterocycles*, 1986, **24**, 923.

7 *cf.* S. Takano, M. Akiyama, S. Sato and K. Ogasawara, *Chem. Lett.*, 1983, 1593.

8 *cf.* R. F. Heck, *Org. React.*, 1982, **27**, 345.

9 *cf.* G. Zweifel and J. A. Miller, *Org. React.*, 1984, **32**, 375.

10 Cleavage of acetal bond by diisobutylaluminium hydride, see ref. 7; S. Takano, M. Akiyama and K. Ogasawara, *Chem. Pharm. Bull.*, 1984, **32**, 791; S. Takano, A. Kurotaki, Y. Sekiguchi, S. Satoh, M. Hirama and K. Ogasawara, *Synthesis*, 1986, 811.

11 *cf.* V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973.

12 J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 1976, 736.

13 Lewis acid promoted ring contraction of the dihydro-1,3-dioxepine derivatives, see H. Suzuki, H. Yashima, T. Hirose, M. Takahashi, Y. Moro-oka and T. Ikawa, *Tetrahedron Lett.*, 1980, **21**, 4927; H. Frauenrath, *Synthesis*, 1989, 721 and references cited therein.

14 For example, see F. Ozawa, A. Kubo and T. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 1417.