Diastereodivergent Chiral Synthesis of the Furofuran Lignans (+)-Sesamin and (–)-Asarinin

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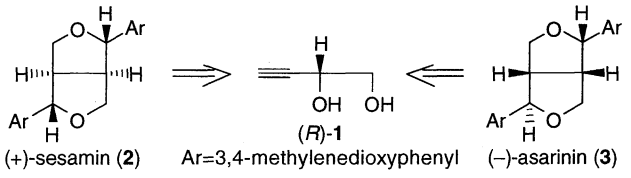
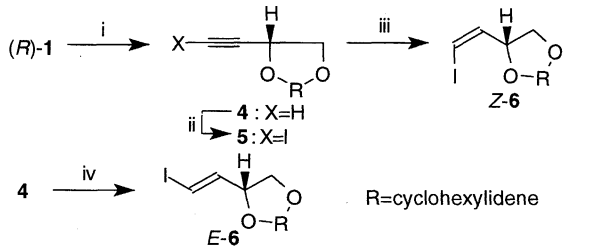
Two diastereomeric lignans (+)-sesamin and (–)-asarinin have been prepared diastereodivergently *via* the common intermediate generated by the chirotopical Heck reaction.

Quite recently, we have developed an efficient route to both enantiomeric 1,2-butynediol (**1**) from *meso*-3,4-epoxy-2,5-dihydrofuran.[1] To exploit **1** as a chiral building block, we used (*R*)-**1** for the diastereodivergent construction of two typical diastereomeric furofuran lignans, (+)-sesamin[2,3] (**2**) and (–)-asarinin[2,3] (**3**) based on the racemic approach we have established[4] (Scheme 1).



Scheme 1.



Scheme 2. *Reagent and conditions*: i) cyclohexanone, *p*-TsOH (cat.) (98%). ii) *n*-BuLi, I_2, THF, –78 °C (99%). iii) $(NCO_2K)_2$, AcOH, MeOH, rt (76%). iv) 1) *n*-Bu_3SnH, xylene (37%), 2) I_2, CH_2Cl_2, –78 °C (73%).

We first transformed[5] (*R*)-**1** (>99% ee) into the *Z*-iodoolefin *Z*-**6**, $[\alpha]_D^{26}$ +17.1° (*c* 0.73, $CHCl_3$), by sequential ketalization, iodination and the diimide reduction[5] *via* **4**, $[\alpha]_D^{31}$ –43.5° (*c* 1.13, $CHCl_3$), and **5**, $[\alpha]_D^{30}$ –37.5° (*c* 1.08, $CHCl_3$). On the other hand, (*R*)-**1** was transformed into the *E*-iodoolefin *E*-**6**, $[\alpha]_D^{27}$ –38.3° (*c* 0.99, $CHCl_3$) on sequential treatment of **4** with tri-*n*-butyltin hydride and iodine[6] (Scheme 2).

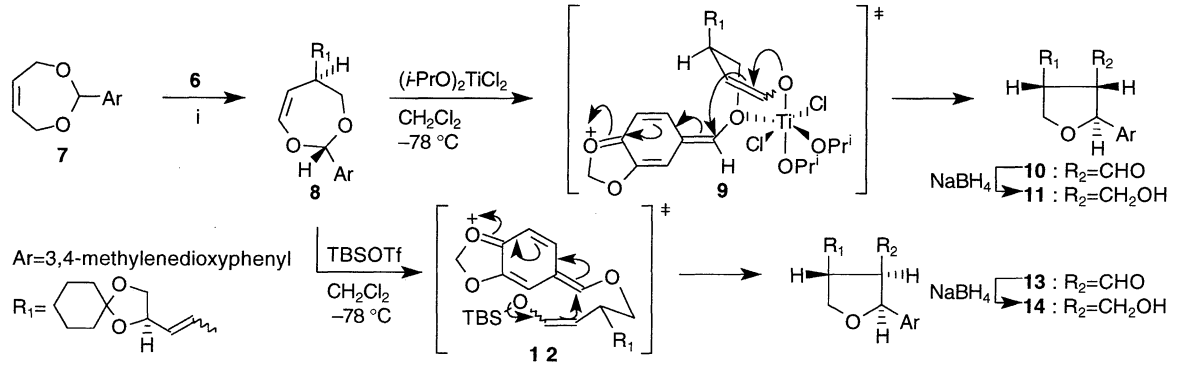
The Heck reaction[4] between *Z*-**6** and the dioxepin **7** was next carried out to give **8** as an inseparable mixture consisted of a pair of the *E*-olefinic and a pair of the *Z*-olefinic diastereomers in ~4:1 ratio both having 2,5-*trans* configuration.[7] ^1H NMR revealed the former to be ~4:1 and the latter to be ~1:1 mixtures of the diastereomers.[7] The mixture was then treated with $Ti(OPr^i)_2Cl_2$[4] followed by sodium borohydride (NBH) to give the diastereomeric *E*-olefinic **11***E* (~4:1)[7] and the diastereomeric *Z*-olefinic **11***Z* (~1:1)[7] mixtures of the 2,3-*trans*:3,4-*cis*-tetrahydrofurans[8] in yields of 51 and 12%, *via* **10**, both preserving the original *E*/*Z*- and diastereomeric ratios.

When the same product was exposed to TBSOTf[4] followed by NBH, the *E*-olefinic **14***E* (~4:1)[7] and the *Z*-olefinic **14***Z* (~1:1)[7] mixture were obtained in yields of 35 and 9%, *via* **13**, both preserving the original *E*/*Z*- and diastereomeric ratios.

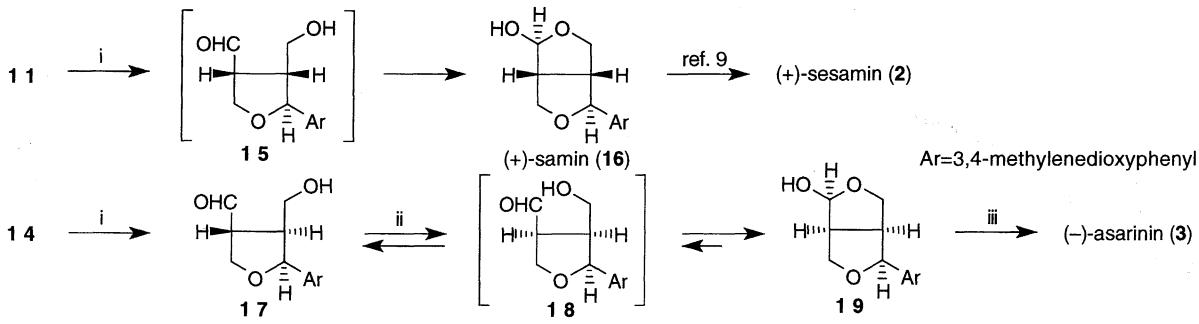
On the other hand, the Heck reaction between *E*-**6** and **7** afforded a complex mixture consisted mostly of the *E*-olefinic 2,5-*trans*/*cis*-mixture (1:1) accompanied by the separable *Z*-olefinic products[7] (*E*/*Z*=12:1). The *E*-mixture furnished either the 2,3-*trans*:3,4-*cis*-**11***E* by $Ti(OPr^i)_2Cl_2$-NBH or the 2,3-*cis*:3,4-*trans*-**14***E* by TBSOTf-NBH as above in comparable yields, but both as 1:1 diastereomeric mixtures.

The diastereoselective formation of the trisubstituted tetrahydrofurans **10** and **13** from the common oxepin **8** depending on the acid catalysts may be rationalized in terms of an intervention of the metal chelating complex **9** in the former and the non-chelating complex **12** in the latter[4] (Scheme 3).

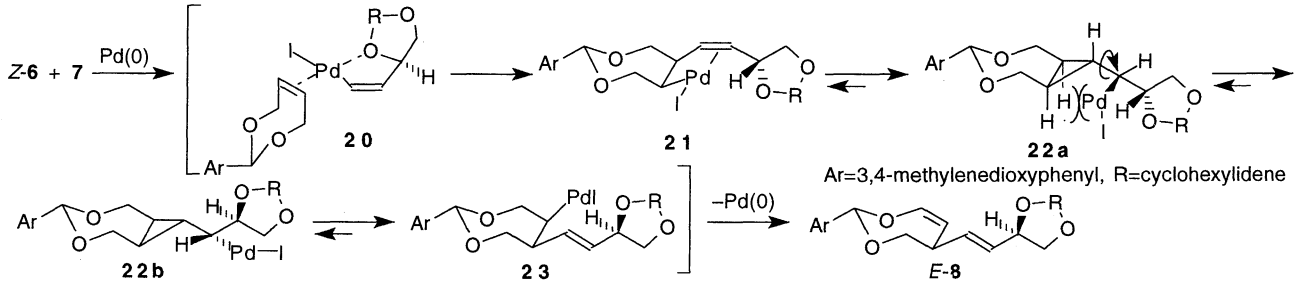
We next transformed **11** and **14** into the natural lignans sesamin (**2**) and asarinin (**3**), respectively. Very surprisingly, only the *E*-isomers generated from *Z*-**6** furnished the optically active products. Thus, **11***E* furnished (+)-samin[9,10] [(+)-**16**], $[\alpha]_D^{27}$ +57.1° (*c* 0.37, $CHCl_3$) (lit.[9]: $[\alpha]_D^{24}$ –88.18° (*c* 1.1, $CHCl_3$) for *ent*-**16**),[11] in 62% ee in 75% yield, *via* **15** on sequential dihydroxylation and periodate cleavage, while **11***Z* gave the optically inactive **16**. Since optically pure (–)-samin



Scheme 3. *Reagents and conditions*: i) $Pd_2(dba)_3$·$CHCl_3$ (cat.), *o*-tol_3P (cat.), K_2CO_3 (2 equiv.), DMF, 40 °C, 1 h then 65 °C, 10 h.



Scheme 4. *Reagents and conditions*: i) OsO_4 (cat.), NMO, aq. THF, 45 °C, then $NaIO_4$, aq. THF, rt (**16**, 75%). ii) MeONa, MeOH, rt (**19**, 64%, 2 steps). iii) 1) TBS-Cl , imidazole, DMF, rt, 16h, 2) TMS-Br, CH_2Cl_2, –78 °C, then ArMgBr (66%, 2 steps).



Scheme 5.

[(–)-**16**] has been transformed into (–)-sesamin (*ent*-**2**) without loss of the original chiral integrity,[9] the present synthesis constitutes a formal acquisition of (+)-sesamin (**2**) in 62% ee.

Similarly, only **14***E* from *Z*-**6** furnished optically active (–)-**19**,[10] $[\alpha]_D^{26}$ –74.9° (*c* 0.19, $CHCl_3$), in 61% ee in 64% yield *via* **17** and **18** on sequential dihydroxylation, periodate cleavage, and base-induced isomerization.[4b] By following the racemic synthesis, (–)-**19** was transformed to (–)-asarinin (**3**), $[\alpha]_D^{26}$ –71.9° (*c* 0.19, $CHCl_3$) (lit.[12]: $[\alpha]_D$ +124° ($CHCl_3$ for *ent*-**3**[11])) (61% ee), in 66% yield (Scheme 4). The optical purities obtained corresponded to the diastereomeric ratio (~4:1) of the starting **11***E* generated from *Z*-**6**. It should be also noted that **11***E* generated from *E*-**6** also furnished **16** and **19**, on the same treatments, which, however, did not have optical activities.

The chirality transfer exerted only by *Z*-**6** may be due to the intervention of the chelation complex **20** having the palladadihydrofuran moiety.[13] This collapsed to *Z*-**21** which in turn isomerized to *E*-**23** through **22a** and its less congested conformer **22b** to leave the optically active **8***E* by β-elimination.[13] A similar reaction involving the palladadihydropyran may also occur competitively leading to a diastereomeric product (enantiomeric at the oxepin ring of **8**) which offset total optical transfer rate. The low chirality transfer in the *Z*-olefin product may be due to the competitive direct β-elimination in **21** and in the palladadihydropyran to give a 1:1 diastereomeric mixture incidentally. Since *E*-**6** was unable to form a palladacyclic complex, no chiral induction occurred under the same conditions (Scheme 5).

References and Notes

1 O. Yamada and K. Ogasawara, *Synlett*, **1995**, 427.
2 For reviews of lignan chemistry: D. A. Whiting, *Nat. Prod. Rep.*, **12**, 183 (1995) and the earlier reviews.
3 For a monograph of lignans: D. C. Ayres and J. D. Loike, '*Lignans Chemical Biological and Clinical Properties*,' Cambridge University Press, Cambridge (1990).
4 a) S. Takano, K. Samizu, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1993**, 1032. b) S. Takano, K. Samizu, and K. Ogasawara, *Synlett*, **1993**, 785.
5 D. J. Pasto and R. T. Taylor, *Org. React.*, **40**, 92 (1991).
6 G. A. Tolstikov, M. S. Miftakhov, N. A. Danilova, and Y. L. Vel'der, *Synthesis*, **1986**, 496.
7 Determined by ^1H NMR (500 MHz) analysis (NOE).
8 Each compound contained ca. 4% of a diastereomer.
9 S. Takano, T. Ohkawa, S. Tamori, S. Satoh, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1988**, 189.
10 Existed in a single isomer as shown in Scheme 4.[7]
11 Both enantiomers are naturally occurring.
12 K. Freudenberg and G. Sidhu, *Chem. Ber.*, **94**, 851 (1961).
13 Torii, H. Okumoto, H. Ozaki, S. Nakayasu, T. Tadokoro, and T. Kotani, *Tetrahedron Lett.*, **33**, 3499 (1992).