Tetrahedron: Asymmetry Vol. 2, No. 5, pp. 357-358, 1991
Printed in Great Britain

0957-4166/91 \$3.00+.00
Pergamon Press plc

First Asymmetric Synthesis of (-)-Sugiresinol Dimethyl Ether

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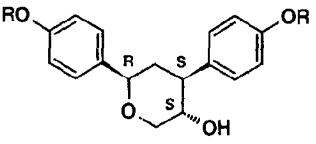
(*Received* 9 *April* 1991)

Abstract: Efficient enantioselective synthesis of (-)-sugiresinol dimethyl ether was accomplished based upon two asymmetric induction processes: asymmetric β-alkylation of α,β-unsaturated aldimines and enantioselective dihydroxylation of olefins.

(-)-Sugiresinol (**1a**)[1] is a constituent in the wood of *Cryptomeria japonica*, *Agathis australis*, *Sequoia sempervirens*, and *Athrotaxis selaginoides*, and has been claimed to have potent vinyl polymerization-inhibitory activity.[2] Several synthetic approaches,[3] to its dimethyl ether (**1b**) and analogs, including our two independent routes have been described. Although its absolute configuration was determined as shown in **1a** on the basis of degradation studies,[4] no asymmetric synthesis has been reported.



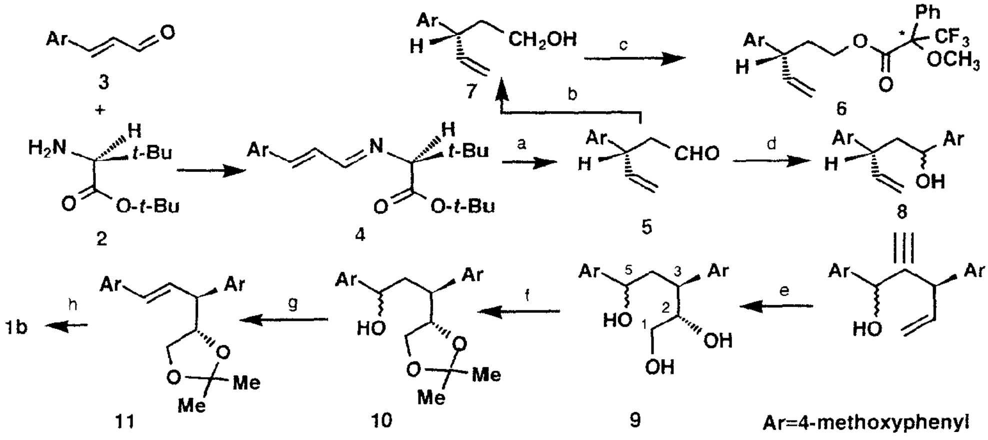
1a: R=H
1b: R=Me

Sharpless and co-workers[5] have recently developed an excellent enantioselective dihydroxylation[6] of olefins by employing optically active alkaloids as chiral ligands. On the other hand, Koga and co-workers[7] established an effective asymmetric β-alkylation of chiral α,β-unsaturated aldimines. Application of these tactics to the synthesis of **1b** enabled us to complete the first asymmetric synthesis of (-)-sugiresinol dimethyl ether ((-)-**1b**) in high optical yields.

Treatment of L-(+)-*t*-butylleucine *t*-butyl ester (**2**) with 4-methoxycinnamaldehyde (**3**)[8] gave an imine (**4**) quantitatively. The Grignard addition of vinylmagnesium bromide to **4** and subsequent careful hydrolysis with dilute hydrochloric acid gave a β-vinyl aldehyde, (-)-3-(4-methoxyphenyl)pent-4-enal (**5**),[9] in 82% yield.

The enantiomeric excess of the product was determined to be >95% on examination of the 500 MHz ^{1}H-nmr spectrum of the corresponding Mosher's ester (**6**), which was readily derived by treatment of the alcohol (**7**) with Mosher's acid chloride.[10] Another Grignard addition of 4-methoxyphenylmagnesium bromide to the aldehyde (**5**) in tetrahydrofuran yielded a diastereomeric mixture of a γ-vinyl alcohol, 1,3-bis(4-methoxyphenyl)pent-4-en-1-ol (**8**), in 86% yield.

The diastereoselective dihydroxylation of **8** was well effected according to the Sharpless's modified method.[5b] Slow addition of **8** to a mixture of osmic acid, dihydroquinine 4-chlorobenzoate (DHQCB), and *N*-methylmorpholine *N*-oxide gave a triol, 3,5-bis(4-methoxyphenyl)pentane-1,2,5-triol (**9**), in 76% yield. The diastereomeric excess of the product was estimated to be >95% by comparison of the 500 MHz ^{1}H-nmr spectrum of the crude product with that of the diastereomeric mixture obtained in the run lacking DHQCB, the latter displaying four separate multiplets, in a region between δ 4.20 and δ 4.60, due to the C_5 protons in four possible diastereomers.



a) CH_2=CHMgBr/Cu_2I_2/THF-ether b) $NaBH_4$/MeOH c) Mosher's acid chloride/py d) 4-MeOPhMgBr/THF
e) OsO_4/*N*-methylmorpholine *N*-oxide/DHQCB f) isopropenyl methyl ether/PPTS/$CHCl_3$ g) MsCl/Py,Δ h) H^+/MeOH

Treatment of the triol (**9**) with isopropenyl methyl ether in the presence of pyridinium *p*-toluenesulfonate afforded an acetonide, 3,5-bis(4-methoxyphenyl)pentane-1,2,5-triol 1,2-acetonide (**10**). Mesylation of **10** and subsequent elimination of the mesyloxyl at 115°C gave an olefin, 3,5-bis(4-methoxyphenyl)pent-4-ene-1,2-diol acetonide (**11**), in 52 % overall yield from **9**. Treatment of **11** with concentrated hydrochloric acid in methanol gave directly the desired **1b**. Single recrystallization from hexane gave optically pure (-)-**1b** in 87% yield. The physical and spectral properties including specific rotation were completely in accordance with those reported.[4]

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9. Bp. 95-98°C/0.01 mmHg: $[\alpha]^{17}_{D}$ -18° (c=1.0, $CHCl_3$); IR ($CHCl_3$) cm^{-1}; 1724, 1637; ^1H-Nmr ($CDCl_3$) δ; 2.78 (1H, ddd. *J*=16.5, 7.0, 2.0), 2.83 (1H, ddd, *J*=16.5, 7.0, 2.0), 3.78 (3H, s), 3.90 (1H, q-like, *J*=7.0), 5.04 (1H, td, *J*=17.5, 1.5), 5.09 (1H, td, *J*=10.5, 1.5), 5.97 (1H, ddd, *J*=17.5, 10.5, 7.0), 6.85 (2H, td, *J*=8.5, 2.0), 7.13 (2H, td, *J*=8.5, 2.0), 9.71 (1H, t, *J*=2.0); MS *m/z* (%); 190 (M^+, 62), 147 (100).
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