Pergamon

Tetrahedron Letters 41 (2000) 2491–2494

TETRAHEDRON LETTERS

A new approach for the synthesis of naturally occurring dihydrobenzo[*b*]furan-type neolignans of potential biological activity†

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Received 9 December 1999; revised 12 January 2000; accepted 25 January 2000

Abstract

A new synthesis of racemic naturally occurring neolignan **1** possessing a PGI_2 inducing effect was achieved via the 2,3-dihydrobenzo[*b*]furan derivative **2**, starting from the commercially available materials *o*-vanillin and acetovanillone.

Neolignans possessing the 2,3-dihydrobenzo[*b*]furan skeleton are a class of naturally occurring heterocyclic compounds with hepatoprotective,[1] hormone blocking,[2,3] antibacterial,[4] antifungal,[5] plant growth regulator[6] and antioxidant[7] activity. The basic ring system of these compounds can be biosynthetically deduced by dimerization of *p*-propenylphenols, such as isoeugenol, coniferyl or sinapyl alcohol. Until now the practical synthetic routes to this structure were based on this biomimetic process involving a neutral phenoxy radical[8–10] or phenoxonium ion[11] intermediate.

In continuation of our investigations of this type of biologically active natural neolignan[10–13] we now report a new simple approach for the synthesis of the neolignan **1** isolated from *Zyziphus jujuba* Mill[14] which shows a significant PGI_2 inducing effect. Although our previous approach[12] based on the oxidative coupling of methyl ferulate led to this natural product (**1**) in a straightforward fashion, it still appeared reasonable to examine a new method permitting the synthesis of analogues differing in the side chain at C-5.

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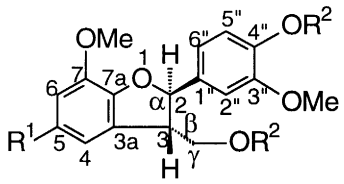
† This paper is dedicated with respect and admiration to Professor Hildebert Wagner on the occasion of his 70th birthday.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00187-8



	R^1	R^2
1	-(*E*)-CH=CH-CO_2CH_3	H
2	H	H
3	H	Ac
4	Br	Ac

The strategy of our synthesis was based on the well-documented[15] synthetic availability of racemic **2** from the commercially available starting materials *o*-vanillin and acetovanillone. Thus, on the basis of quantum chemical calculations [Mullikan charges[16] (q) and superdelocalizations[17] (sd) are given in Table 1], we assumed that bromination of the acetyl derivative (**3**) of **2** would take place at C-5 and this functional group offers opportunity to introduce various side chains to the 2,3-dihydrobenzo[*b*]furan skeleton.

Table 1
Quantum chemical data of **3**

	q	sd
C-6	-0.182	-0.497
C-5	**-0.192**	**-0.489**
C-4	-0.160	-0.494
C-2”	-0.153	-0.513
C-5”	-0.180	-0.510
C-6”	-0.179	-0.512

Indeed, the 5-bromo-2,3-dihydrobenzo[*b*]furan derivative **4** could be obtained from **3** by a simple bromination in acetic acid at room temperature in good yield (80%), although such a high selectivity in this reaction could not be expected only on the basis of our quantum chemical calculations. The structure of **4** was also independently proved by its synthesis from 5-bromo-2-benzyloxy-3-methoxybenzaldehyde prepared from *o*-vanillin according to the literature[18,19] by the same sequence as described for the synthesis of **2**.[15]

Starting from the 5-bromo-2,3-dihydrobenzo[*b*]furan derivative **4**, the synthesis of neolignan **1** was accomplished by two routes (Fig. 1). First, **4** was allowed to react with methyl acrylate under the conditions of the Heck reaction[20] to result in **5** in a moderate yield (30%). Saponification of **5** with sodium methoxide in methanol at room temperature gave our target molecule (**1**).

In the other route, the acetyl protecting groups of **4** were exchanged for methoxymethyl ethers (**4**→**6**→**7**), followed by replacement of the bromine substituent in **7** with an aldehyde group (**7**→**8**) using *n*-butyllithium as the metallation reagent and DMF as the formyl source, in good overall yield (21%).

The *E*-olefinic side chain of **1** was stereoselectively introduced by a Wittig reaction of **8** with carboxymethyltriphenylphosphorane in benzene at 60°C to give **9** in 44% yield. Then cleavage of the methoxymethyl groups of **9** under mild acidic conditions also resulted in **1** in high yield (80%).[21]

In conclusion, we have achieved a simple synthesis of 2,3-dihydrobenzo[*b*]furan derivative **4**, being a suitable intermediate in the synthesis of neolignan **1**. It is our belief that **4** will be a versatile building block for the synthesis of a variety of natural products having the 2,3-dihydrobenzo[*b*]furan skeleton.

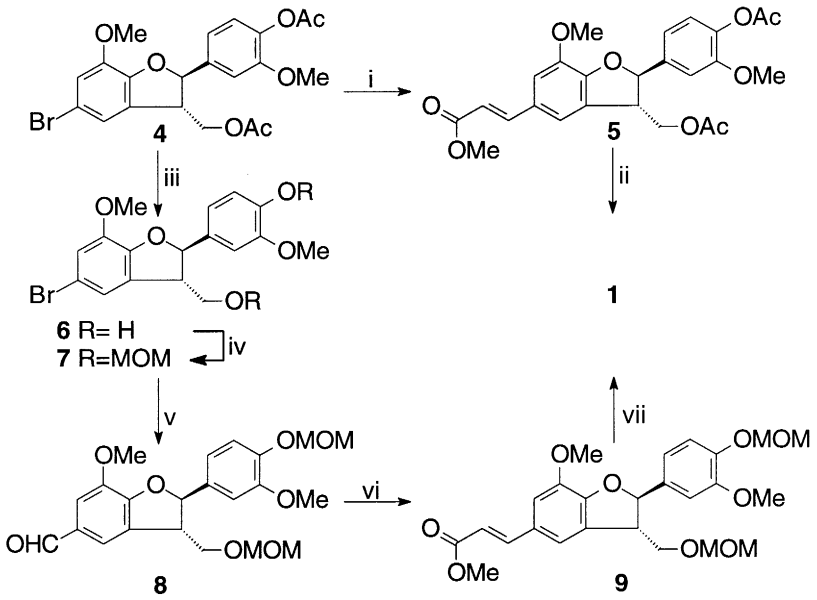


Fig. 1. (i) methylacrylate, $Pd(OAc)_2$, PhP_3/Et_3N, 100°C (30%); (ii) and (iii) NaOMe/MeOH, rt (73% and 86%); (iv) MOMCl, $i Pr_2EtN/CH_2Cl_2$, rt (62%); (v) BuLi, dry DHF/dry THF, −78°–25°C (41%); (vi) $Ph_3P{=}CHCOOCH_3$/dry benzene, 60°C (44%); (vii) 5% HCl/MeOH, rt (71%)

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21. Selected spectroscopic and physicochemical properties: *rac*-**1**, colorless needles of mp 174–176°C, identified with authentic sample[12] by mixed mp and spectroscopic methods. Compound **3**, colorless oil, ^{1}H NMR: δ 2.05 and 2.29 (6H, s, OAc); 3.78 (3H, s, OMe); 3.80 (1H, m, H_β); 3.88 (3H, s, OMe); 4.30 (1H, dd, J=5.2, J=10.5, Hγ); 4.45 (1H, dd, J=5.2, J=10.5, Hγ·); 5.52 (1H, d, J=6.71, H_α). Compound **4**, colorless oil, ^{1}H NMR: δ 2.07 and 2.32 (6H, s, OAc); 3.80 (3H, s, OMe); 3.80 (1H, m, H_β); 3.89 (3H, s, OMe); 4.30 (1H, dd, J=5.21, J=10.5, Hγ); 4.41 (1H, dd, J=5.21, J=10.5, Hγ·); 5.52 (1H, d, J=6.72, H_α); 6.88–7.05 (5H, m, ArH); HRMS *m/z* 448.0518 (calcd for $C_{21}H_{21}O_6Br$: 448.0518). Compound **5**, colorless

oil, ^{1}H NMR: δ 3.82 (3H, s, COOMe); 6.32 (1H, d, J=15.9, $H_{\beta'}$); 7.62 (1H, d, J=15.9, H_{α}); HRMS *m/z* 472.1730 (calcd for $C_{25}H_{28}O_9$: 472.1725). Compound **6**, colorless oil, ^{1}H NMR: δ 3.65 (1H, m, H_{β}); 3.88 and 3.89 (6H, s, OMe); 3.92 (2H, m, H_{γ}); 5.55 (1H, d, J=6.71 H_{α}); 6.85–7.26 (5H, m, ArH); HRMS *m/z* 381.0337 (calcd for $C_{17}H_{18}O_5Br$: 381.0342). Compound **7**, colorless oil, ^{1}H NMR: δ 3.36, 3.50, 3.82 and 3.83 (12H, s, OMe); 4.68 and 5.22 (4H, s, OCH_2O); HRMS *m/z* 470.0944 (calcd for $C_{21}H_{27}O_7Br$: 470.0932). Compound **8**, colorless oil, ^{1}H NMR: δ 9.85 (1H, s, CHO); ^{13}C NMR: δ 178.93 (CHO); HRMS *m/z* 402.1673 (calcd for $C_{22}H_{26}O_7$: 402.1678). Compound **9**, colorless oil, ^{1}H NMR: δ 3.85 (3H, s, COOMe); 5.59 (1H, d, J=6.71, H_{α}); 6.30 (1H, d, J=15.1, $H_{\beta'}$); 7.62 (1H, d, J=15.1, $H_{\alpha'}$); HRMS *m/z* 476.2046 (calcd for $C_{25}H_{32}O_9$: 476.2037).