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Asymmetric Endoselective [4+2] Heterocycloadditions of Styrene Dienophiles with Chiral Benzylidenepyruvic Esters. Total Synthesis of (-)-*O*-Dimethylsugiresinol

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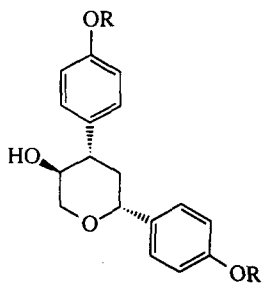
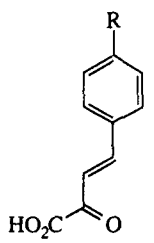
Abstract : Eu(fod)3 catalyzed [4+2] heterocycloadditions of *para*-methoxystyrene **7** with esters **8a-f** of benzylidenepyruvic acids (deriving from various chiral alcohols) furnished *endo* adducts **9a-f** with variable diastereoselective ratios (from 58/42 to 86/14). Interestingly, the benzylidenepyruvic esters **8g** and **8h**, deriving from a new chiral vector, the α-*O*-silyl ether **6** of (D)-(-)-erythronolactone **5**, gave the corresponding *endo* adducts **9g** and **9h** with a high diastereoselective ratio (dr ≥ 95/5). The adduct **9h** was used as a precursor in a five-step synthesis of "natural" (-)-dimethylsugiresinol (**1b**).

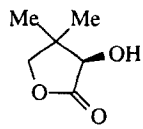
Heterocyclic Diels-Alder reactions involving α,β-ethylenic carbonyl compounds (as electron-deficient heterodienes) and electron-rich dienophiles such as vinyl ethers are well documented.[1] However, there are still relatively few known examples of inverse type heterocycloadditions of 1-oxabutadienes with styrenic compounds of lower dienophilicity.[2] Despite the synthetic potential of this approach (in the C-aryl glycoside chemistry for instance), only two cases of such heterocycloadditions are reported in the asymmetric series. Thus, high pressure cycloaddition of a chiral β-acyloxy-α-phenylthio-α-enone with 3,4-dimethoxystyrene was described, leading to the corresponding *endo* adduct in 81% yield with a diastereofacial ratio 3/1.[3] Very recently, it was found that (S)-(+)-3-*p*-tolylsulfinylbut-3-en-2-one reacted with styrenes and furnished cycloadducts having de's>90%.[4] In 1994, we described high yield endoselective racemic heterocycloadditions involving benzylidenepyruvic esters as the heterodiene and an alkoxystyrene as the dienophile, using Eu(fod)3 as a catalyst.[2] As part of a program pertaining to the asymmetric total synthesis of lignans of the sugiresinol (**1a**) series, we investigated an asymmetric version of the above synthetic strategy.



1a R = H Sugiresinol
1b R = Me



2 R = H
3 R = OMe



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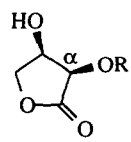


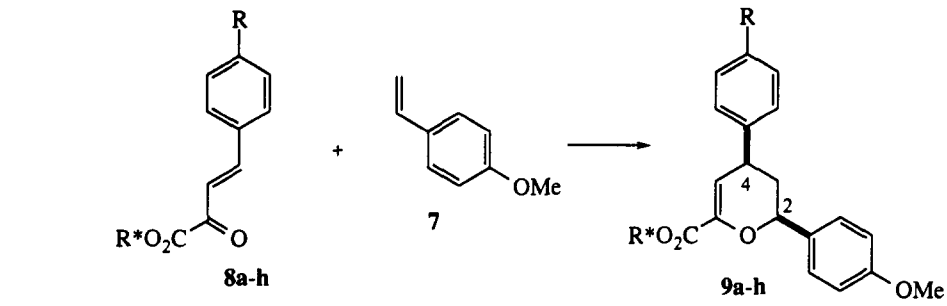
5 R = H
6 R = $SiPh_2Bu_t$

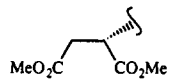
Thus, esterification of the benzylidenepyruvic acids **2** and **3**[2] with (-)-menthol in toluene and in the presence of TsOH, with azeotropic distillation of the water formed, afforded good yields of the corresponding chiral esters **8a,b**[5] (Scheme 1). This method failed in the case of the 8-phenylmenthyl analogue **8c**.[5] However this heterodiene was satisfactorily prepared by a known transesterification method[6] starting from the methyl ester of benzylidenepyruvic acid **2**. Using DCC as a dehydrating agent, in the presence of DMAP and in CH_2Cl_2 at 0°C, the acid **3** was esterified with either dimethyl (S)-malate or (R)-pantolactone **4**, thus giving the corresponding esters **8d,e**.[5] The ester **8f**[5] was similarly obtained from the acid **3** and (R)-pantolactone **4**.

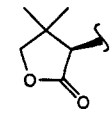
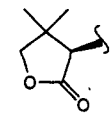
The chiral heterodienes **8a-f** were next treated with 1.2-2.2 equ. of the styrene **7** and in the presence of the catalyst Eu(fod)3, and thus led to the corresponding cycloadducts **9a-f**[5] (see Table). The Table shows that the *endo/exo* selectivity of the cycloaddition is generally excellent (> 94/6 in most cases). With regards to the diastereofacial selectivity of the reaction in the case of the major *endo* diastereomers, the best results so far were obtained when using (-)-8-phenylmenthol (entry 3) and (R)-pantolactone **4** (entries 5 and 6) as chiral inducers. The highest diastereofacial excess (72%, dr = 86/14) was observed for the adduct **9e** (95% yield) deriving from (R)-pantolactone **4**. Incidentally, the Table shows that the heterodiene **8** is less reactive towards cycloaddition with the styrene **7** when it is *para*-substituted with a methoxy group (entries 2 and 6).

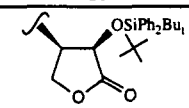
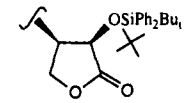
At this stage, we looked for another chiral and rigid inducer, similar to pantolactone **4** but bearing a second stereogenic centre liable to interact efficiently with the heterodiene moiety during cycloaddition. We thus contemplated using a derivative of (D)-(-)-erythronolactone **5**. Indeed, the latter is readily available in one step and on a multigram scale from commercially cheap (D)-(-)-isoascorbic acid.[7] *O*-Silylation of (-)-erythronolactone **5** in standard conditions (1.1 equ. t-$BuPh_2SiCl$/1.1 equ. imidazole/DMF/RT/48h) gave a mixture of three *O*-silyl products, from which the major α-*O*-substituted derivative **6**[5] was crystallized in 68% yield, upon dilution of the reaction medium with ether followed by petrol ether. Esterification of the acids **2** and **3** with the alcohol **6** (1.5 equ. DCC/DMAP/CH_2Cl_2/5h at 0°C, then 10h at RT) gave high yields of the chiral heterodienes **8g** and **8h**.[5] Reaction of the latter with *p*-methoxystyrene **7** (3 equ.) in the presence of 10% molar equ. of Eu(fod)3, as shown in the Table, gave the *endo* adducts **9g** and **9h**[5] in good yields after chromatography, with high *endo/exo* selectivity (>97/3) and diastereofacial selectivity (96/4 and 95/5, respectively). The absolute (2R, 4R) configuration of the major cycloadduct **9h** was determined by its further transformation into (-)-*O*-dimethylsugiresinol (-)-**1b**[8] in the following manner (Scheme 2).

Transesterification of the adduct **9h** with methanol (in the presence of LiOH) gave the methyl ester (+)-**10** (ee. 93%). Catalytic hydrogenation of the latter over 10% Pd-C almost quantitatively afforded the tetrahydropyran (+)-**11** as a single diastereomer, which was next saponified (NaOH/H_2O/THF) to the free carboxylic acid (+)-**12**. Oxidation by means of *m*-CPBA and DCC according to Shiozaki's procedure,[9] followed by basic β-elimination of *m*-chlorobenzoic acid, degraded the acid (+)-**12** to the requisite dihydropyran (+)-**13** (44% yield of enantiopure product). Finally, standard hydroboration-oxidation of the dihydropyran (+)-**13** gave, as the main isolated product, enantiomerically pure "natural" (-)-(2R,4S,5S)-O-dimethylsugiresinol (-)-**1b**, in 12% overall yield from *p*-methoxybenzylidenepyruvic acid **3**. The synthetic compound (-)-**1b** had mp, $[\alpha]_D$ and spectral data in full agreement with those reported in the literature for the dimethyl ether (-)-**1b** deriving from natural sources.[8]



	R	R*
a	H	menthyl
b	OMe	menthyl
c	H	8-phenyl menthyl
d	H	

	R	R*
e	H	
f	OMe	

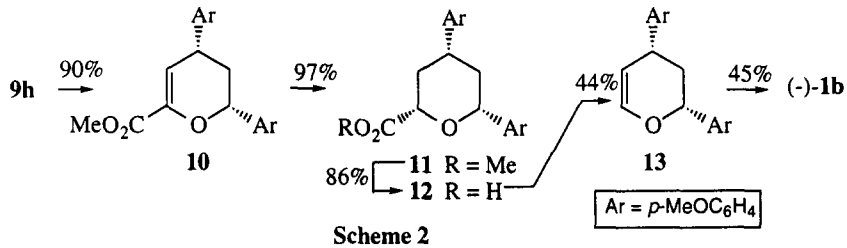
	R	R*
g	H	
h	OMe	

Scheme 1

Entry	Diene **8a-h** a)	Cyclization Conditions b)	Resulting adducts **9a-h** : Yield (%)	*Endo/exo* selectivity	Diastereofacial ratio c)
1	**a**	Hex/60°C/5d	95	> 97/3	65/35
2	**b**	Hex/60°C/5d	88	> 97/3	60/40
3	**c**	Hex/60°C/3d	95	88/12	80/20
4	**d**	Tol/110°C/7d	45	92/8	58/42
5	**e**	Hex/60°C/2d	95	> 97/3	86/14
6	**f**	Hex/60°C/2d	(< 10)		
		+ Tol/110°C/5d	66	94/6	73/27
7	**g**	Hex/60°C/3d			
		+ Tol/60°C/3d	75	> 97/3	96/4
8	**h**	Hex/60°C/3d			
		+ Tol/60°C/3d	76	> 97/3	95/5

a) See Scheme 1. b) Hex, hexane, ; Tol, toluene ; d, days. c) dr's of corresponding pairs of *endo* diastereomers.

Table : Syntheses of adducts **9a-h** by heterocycloaddition of chiral benzylidenepyruvic esters **8a-h** with the styrene **7**, catalyzed by Eu(fod)3.



Scheme 2

Conclusion

We have carried out the asymmetric cycloaddition of *para*-methoxystyrene **7** with benzylidenepyruvic esters **8a-h** deriving from usual chiral alcohols. In most cases the *endo* selectivity was high (*endo/exo* ratio >97/3). The highest diastereofacial selectivities were observed when using 8-phenylmenthol and (R)-pantolactone **4** as chiral alcohols (dr = 80/20 and 86/14, respectively). A much higher diastereofacial selectivity (dr = 96/4) was observed when the chiral alcohol was the α-*O*-silyl ether **6** of (D)-(-)-erythronolactone **5**. The resulting adduct **9h** was successfully used in a five-step synthesis of (-)-dimethylsugiresinol (**1b**). Further studies are in progress in our laboratory in order to determine the scope of the new chiral vector **6**.

References and notes

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5. Physical properties and yields of compounds **6**, white solid, m.p. 168-173°C, $[\alpha]_D$ + 32 (c 1, acetone), *ca.* 70% ; **8a**, yellow solid, m.p. 44°C (ether), $[\alpha]_D$ -57 (c 1, ether), 79% ; **8b**, yellow solid, m.p. 110°C (ether), $[\alpha]_D$ -39.6 (c 1.3, acetone), 80% ; **8c**, see reference 6 ; **8d**, orange oil, $[\alpha]_D$ -13.2 (c 1.4, acetone), 51% ; **8e**, pale yellow crystals, m.p. 98.5°C (ether), $[\alpha]_D$ +30.6 (c 0.8, acetone), 95% ; **8f**, yellow crystals, m.p. 118-121°C, $[\alpha]_D$ + 33 (c 1, acetone), 67%; **8g**, yellow crystals, m.p. 52-55°C, $[\alpha]_D$ - 59 (c 2, acetone), 95% ; **8h**, oil, $[\alpha]_D$ - 69 (c 2, acetone), 95% ; **9a**, m.p. 41-44°C (diastereomeric mixture), 95% ; **9b**, m.p. 124.5-125.5°C (AcOEt/Pet. ether) (diastereomeric mixture), 88% ; **9c**, m.p. 55-58°C (diastereomeric mixture), 95% ; **9d**, orange oil (diastereomeric mixture) 45% ; **9e**, m.p. 142-142.5 °C (AcOEt), $[\alpha]_D$ -62.5 (c 1, acetone), 95% ; **9f**, m.p. 159-160°C (AcOEt) (diastereomeric mixture), 66% ; **9g**, white solid, m.p. 70-74°C (diastereomeric mixture) 75%; **9h**, yellow solid, m.p. 75-80°C, $[\alpha]_D$ + 105 (c 0.8, acetone) (diastereomeric mixture), 76% ; **10**, white solid, m.p. 79-80°C, $[\alpha]_D$ + 134 (c 0.9, acetone) 90%; **11**, oil, $[\alpha]_D$ + 16.6 (c 0.7, acetone), 97%; **12**, white solid, m.p. 140-141°C, $[\alpha]_D$ + 25 (c 0.6, acetone), 86%; **13**, white solid, m.p. 79-80°C, $[\alpha]_D$ + 133 (c 1.0, acetone) , 44%; **1b**, e.e. > 97% [^{1}H NMR at 400 MHz with Eu(hfc)3 as chiral shift reagent], white solid, m.p. 99-100°C, $[\alpha]_D$ -4 (c 1.0, $CHCl_3$), 45%.
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