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ASYMMETRIC SYNTHESES OF SUBSTITUTED DIHYDROPYRANS BY DIELS-ALDER HETEROCYCLOADDITIONS INVOLVING CHIRAL VINYL ETHERS AS DIENOPHILES

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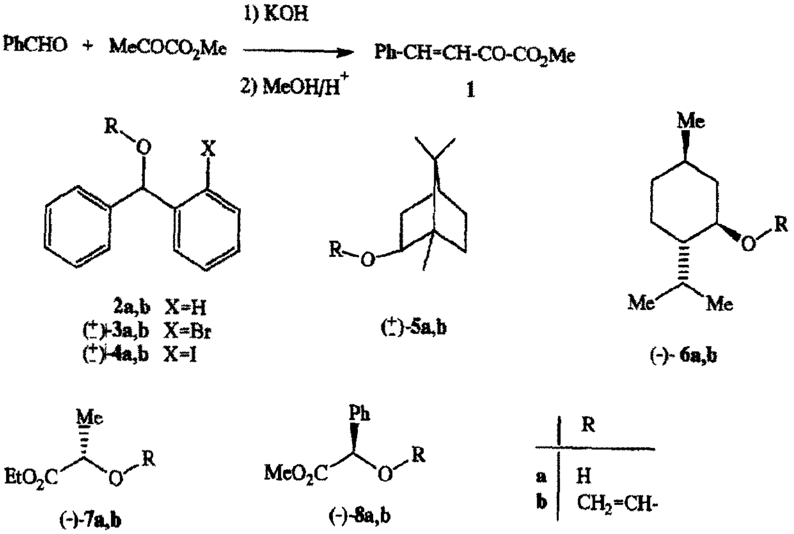
Abstract: The alkyl vinyl ethers **2b-8b** (deriving from the alcohols **2a-8a**) smoothly reacted with methyl E-benzylidenepyruvate **1** in the presence of catalytic amounts of Eu(fod)$_3$, thus leading to the *endo* cycloadducts **9-15** in high yields. The cycloadducts **12-15** were obtained with moderate to good diastereomeric excesses (43-72%). Thus the vinyl ether **8b** deriving from methyl (R)-mandelate gave the *endo* adduct **15** in 83% yield and with 72% diastereomeric excess.

A typical case of "inverse electron demand" heterocyclic Diels-Alder reaction is the [2+4] cycloaddition of an enol ether (electron-rich dienophile) with an α,β-ethylenic carbonyl compound (electron-deficient heterodiene), thus leading to a 2-alkoxy-3,4-dihydro-2*H*-pyran.[1-4] 3,4-Dihydro-2*H*-pyrans are useful intermediates for the syntheses of natural and/or biologically active compounds, such as fused oxygen heterocycles,[5] lignans,[6] and modified carbohydrates.[7-10] A few examples of asymmetric heterocyclic Diels-Alder syntheses of optically active 3,4-dihydro-2*H*-pyrans have been described. In most cases the chirality vector is carried by the heterodiene and not by the dienophile.[10-12] Nevertheless, Tietze and his group have described two examples of asymmetric induction by means of some specific chiral enol ethers.[13,14] But in both examples the stereogenic centre was relatively remote from the dienophile moiety and gave rise to a rather low asymmetric induction. However, chiral enol ethers have been used successfully in asymmetric heterocyclic Diels-Alder reactions involving nitrogen-containing heterodienes.[15,16] In short, no systematic investigation on the cycloaddition of chiral enol ethers with α,β-ethylenic carbonyl compounds seems to have been described. With the aim of synthesizing some natural compounds containing substituted pyran rings, we decided to study the cycloaddition of some chiral vinyl ethers with the α-keto-β,γ-ethylenic ester 1 which has been previously used in non-asymmetric heterocyclic Diels-Alder reactions.[17]

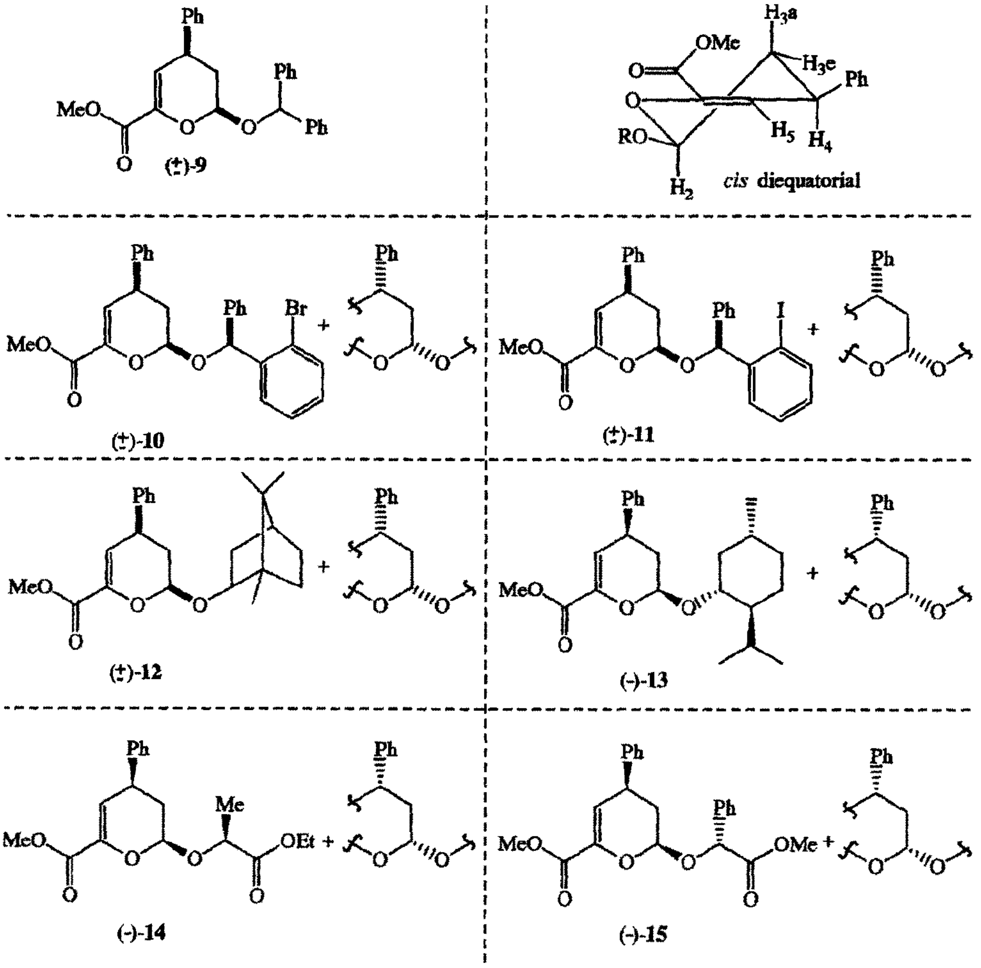


Scheme 1

Methyl E-benzylidenepyruvate **1** was obtained by treatment of methyl pyruvate with benzaldehyde in the presence of methanolic potassium hydroxide, followed by re-esterification with MeOH/HCl.[18,19] The vinyl ethers **2b**-**8b**[19] were prepared from the corresponding alcohols **2a**-**8a**, respectively, by treatment with excess ethyl vinyl ether in the presence of mercuric diacetate under reflux for three days, followed by column chromatography on silica gel (Scheme 1). Compounds **2a,b** are achiral. Compounds **3-5(a,b)** are racemic. Compounds **6-8(a,b)** are levorotary enantiomers.

The cycloaddition of methyl E-benzylidenepyruvate **1** with the achiral benzhydryl vinyl ether **2b** was next studied as a model reaction. We thus found that, in the presence of 5% tris(heptafluorodimethyloctanedionato)europium Eu(fod)$_3$,[20] an equimolecular mixture of **1** and **2b** in refluxing hexane for 72 hours afforded the expected cycloaddition product (±)-**9**[19] in 95% yield after chromatography. Examination of the ^{1}H NMR spectrum (400 MHz) revealed that (±)-**9** was obtained as a single racemic diastereomer, having a relative 2,4-*cis* configuration typical of an *endo* adduct (Scheme 2). Assuming a relative *trans* configuration of the C-2 and C-4 substituents, the most stable conformation would correspond to a pseudo-equatorial configuration of the phenyl group and a pseudo-axial configuration of the alkoxy group. The ketal proton at C-2 being thus pseudo-equatorial, this would imply a low value for both J_{2-3} coupling constants. And indeed, the values we observed, J_{2-3} = 2.4 Hz and 6.5 Hz, respectively, are in agreement with a relative *cis* dipseudo-equatorial arrangement of both substituents at C-2 and C-4. Therefore, this type of lanthanide catalyzed cycloaddition reaction is here totally *endo* selective, which is in agreement with Danishefsky's findings.[20]

This fact being ascertained, the heterodiene **1** was next treated with the chiral vinyl ethers **3b**-**8b** under the experimental conditions we used for the synthesis of (±)-**9**, thus leading to high



Scheme 2

yields of the cycloadducts **10-15**,[19] respectively. These cycloadducts were essentially obtained as a single pair of diastereomers which were not separated. Indeed, the 400 MHz ^1H NMR spectra revealed in each case a high *endo* selectivity (endo/exo ratio = 93/7 for the menthyl derivative (-)-**13** and more than 97/3 in the other five cases), both J_{2-3} coupling constants being in the ranges 1-2.5 Hz for the equatorial-axial coupling and 5.4-7.3 Hz for the axial-axial coupling, respectively. No diastereofacial selectivity was observed in the benzhydryl series (diastereomeric excess = 0% for both the endo adducts **10** and **11**). However, examination of the signals of the vinylic and ketal protons in the 400 MHz ^1H NMR spectra revealed a strong asymmetric induction in the cases of **12** (de. 52%), **13** (de. 43%), **14** (de. 60%) and **15** (de. 72%). The last two results tend to show that the presence of an alkoxycarbonyl group on the chiral carbon atom of the starting vinyl ether (**7b** and **8b**) plays a part in the diastereofacial selectivity of the cycloaddition reaction.

Conclusion

Using mild experimental conditions, we obtained high yields of various 2-alkoxy-4-phenyl-3,4-dihydro-2*H*-pyrans, by means of a regio- and *endo*-selective cycloaddition of methyl E-benzylidenepyruvate **1** with various readily available chiral vinyl ethers. Good asymmetric inductions (de. 60 and 72%) were observed in the cases of the vinyl ethers deriving from ethyl (S)-lactate and methyl (R)-mandelate, respectively. These diastereomeric excesses compare favourably with those of other cycloaddition reactions leading to 4-substituted dihydropyrans.[12-14] Work is in progress in our laboratory in order to improve the enantioselectivity of this reaction and to apply it to other electron-deficient oxygen heterodienes.

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19 - Physical properties and yields of compounds. **1**, yellow crystals, m.p. 73.5°C, 41% ; **2b**, oil, 47% ; **3b**, oil, 57% ; **4b**, oil, 51% ; **5b**, oil, 54% ; (-)-**6b**, oil, $[\alpha]_D$ -76 (2.45, Et_2O), 60% ; (-)-**7b**, oil, $[\alpha]_D$ -99 (1.25, Et_2O), 31% ; (-)-**8b**, oil, $[\alpha]_D$ -106 (1.43, MeOH), 42% ; (±)-**9**, oil, 95% ; (±)-**10**, m.p. 50°C, 95%, diastereomeric ratio (dr.) : 50/50 ; (±)-**11**, m.p. 50-60°C, 91%, dr. 50/50 ; (±)-**12**, oil, 95%, dr. 76/24 ; (-)-**13**, oil, $[\alpha]_D$ -33 (1.25, Et_2O), 91%, dr. 72/28 ; (-)-**14**, oil, $[\alpha]_2$ -22 (2.4, Et_2O), 92%, dr. 80/20 ; (-)-**15**, oil, $[\alpha]_D$ -27 (0.9, MeOH), 83%, dr. 86/14.

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