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Lignans.19. Total Synthesis of (-)-O-Dimethylsugiresinol, involving Asymmetric [4+2] Heterocycloaddition of a Styrene with a Benzylidenepyruvic Ester of an α-O-Silyl Derivative of (D)-Erythronolactone

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Abstract : α-*O*-*t*-Butyldiphenylsilyl-(D)-erythronolactone [(+)-**25**] (a new chiral vector) was esterified with 4-methoxybenzylidene pyruvic acid (**19**). Eu(fod)3 catalyzed [4+2] heterocycloaddition of the latter 1-oxabutadiene with 4-methoxystyrene (as the dienophile), afforded high yields of the *endo* adduct **23c** with 95/5 diastereofacial ratio. Five further steps led to enantiomerically pure natural (-)-*O*-dimethylsugiresinol (-)-**2** in 12% overall yield from the acid **19**. © 1997 Elsevier Science Ltd.

Introduction

The natural norlignans of the sequirin group[1] are typically (2R, 4S, 5S)-2,4-diaryltetrahydropyran-5-ols, as exemplified with sugiresinol **1** which was reported to exhibit various pharmacological properties.[2a] In 1976, Whiting[3] described a total synthesis of racemic *O*-dimethylsugiresinol (±)-**2** in ten steps from 4-methoxyacetophenone and in a very low overall yield (< 1%). At about the same time, Momose and coworkers[4] synthesized the same racemic compound (**2**) in five steps from 4,4'-dimethoxychalcone (15% overall yield). More recently, the latter group carried out the only reported total synthesis of "natural" *O*-dimethylsugiresinol (-)-**2**, [2] using the attainments of both previous racemic syntheses, and incorporating two standard processes of asymmetric induction, namely Koga's conjugate addition to a chiral aldimine and Sharpless' enantioselective alkene dihydroxylation sequence. This efficient synthesis afforded (-)-**2** in seven steps and in 22% overall yield from 4-methoxycinnamaldehyde. It must be emphasized that the above three syntheses are based upon the more or less stereocontrolled construction of an open chain skeleton, with final ring closure involving creation of the stereogenic centre at C-2 position (Scheme 1). Apart from these, the synthesis of racemic *O*-trimethylsequirin E[(±)-**3**], described by Momose and coworkers as early as 1971,[5] involved as a major step the thermal [4+2] heterocycloaddition reaction of 3,4,4'-trimethoxychalcone with butylvinylether. Four subsequent steps afforded the lignan derivative (±)-**3** in 5% overall yield.

We considered synthesizing (-)-*O*-dimethylsugiresinol [(-)-**2**] by asymmetric [4+2] heterocycloaddition of a ring-substituted styrene with a chiral 4-aryl-1-oxabutadiene using Eu(fod)3 as a catalyst, thus controlling the creation of both stereogenic centres at C-2 and C-4 positions of the resulting dihydropyran derivative.

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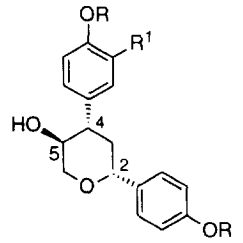
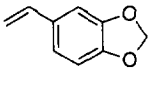
Results and discussion

Studies in the racemic series. We planned to use 4-methoxystyrene (a commercial compound) and 3,4-methylenedioxystyrene (**4**) as dienophiles . The latter was obtained from piperonal and methylene-triphenylphosphorane in 33% yield after purification. The heterodienes we chose are substituted benzylidenepyruvic esters (1-oxabutadienes). Treatment of the benzaldehyde dimethylacetals **6a-c** with methyl 2-(trimethylsiloxy)acrylate **5** in the presence of $BF_3.Et_2O$, followed by methanol elimination, gave high yields of the corresponding benzylidenepyruvic esters, **7a-c** respectively (Scheme 1). Each heterodiene **7a-c** reacted with either 4-methoxystyrene or 3,4-methylenedioxystyrene (**4**) in refluxing hexane or toluene for 2-11 days and in the presence of 5% (molar) of $Eu(fod)_3$ as a catalyst. This gave very good yields of the corresponding adducts **8a-e** in which the *cis*-2,4-disubstituted *endo* diastereomer is largely predominant (> 92% in all cases, and > 97% when the dienophile was 4-methoxystyrene).[6]

Scheme 1



(-)-**1** R = R^1 = H
(-)-**2** R = Me ; R^1 = H
(-)-**3** R = Me ; R^1 = OMe



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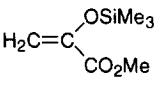
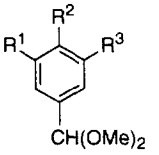


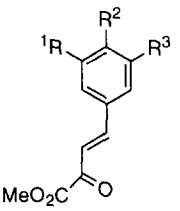
5



6a-c

a R^1 = R^3 = H ; R^2 = OMe
b R^1,R^2 = OCH_2O ; R^3 = H
c R^1 = R^2 = R^3 = OMe

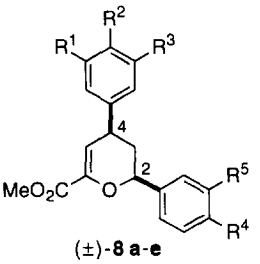
5 + **6a-c** $\xrightarrow[(85\text{-}95\%)]{BF_3\,;\,Et_2O}$



7a-c

a R^1 = R^3 = H ; R^2 = OMe
b R^1,R^2 = OCH_2O ; R^3 = H
c R^1 = R^2 = R^3 = OMe

$\xrightarrow[(77\text{-}97\%)]{\text{subst. styrene}\ Eu(fod)_3}$



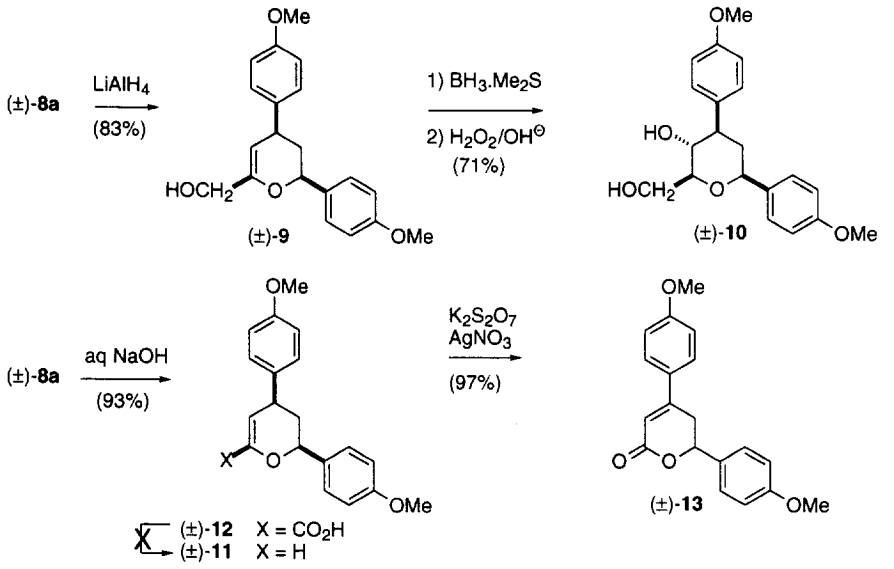
(±)-**8a-e**

a R^1 = R^3 = R^5 = H ; R^2 = R^4 = OMe
b R^1,R^2 = OCH_2O ; R^3 = R^5 = H ; R^4 = OMe
c R^1 = R^3 = H ; R^2 = OMe ; R^4,R^5 = OCH_2O
d R^1,R^2 = R^4,R^5 = OCH_2O ; R^3 = H
e R^1 = R^2 = R^3 = OMe ; R^5,R^6 = OCH_2O

From the now available *endo* adduct **8a** as a precursor, various routes were next investigated in order to get an access to the required (±)-*O*-dimethylsugiresinol [(±)-**2**]. Hydroboration-oxidation of **8a** using standard procedures failed to give the corresponding β-hydroxyester. $LiAlH_4$ reduction of **8a** smoothly

furnished the primary allylic alcohol **9** (Scheme 2). Hydroboration-oxidation of the latter then occurred in a highly stereoselective fashion, and gave good yields of the tetrahydropyran **10** in which the four substituents are equatorial. Selective oxidation of the hydroxymethyl group of **10** (or a derivative) to a carboxy group, followed by decarboxylation, should then lead to the target molecule (±)-**2**. Therefore the diol **10** was subjected to various chemical transformations liable to fulfil this purpose, but none of then proved successful.

Scheme 2

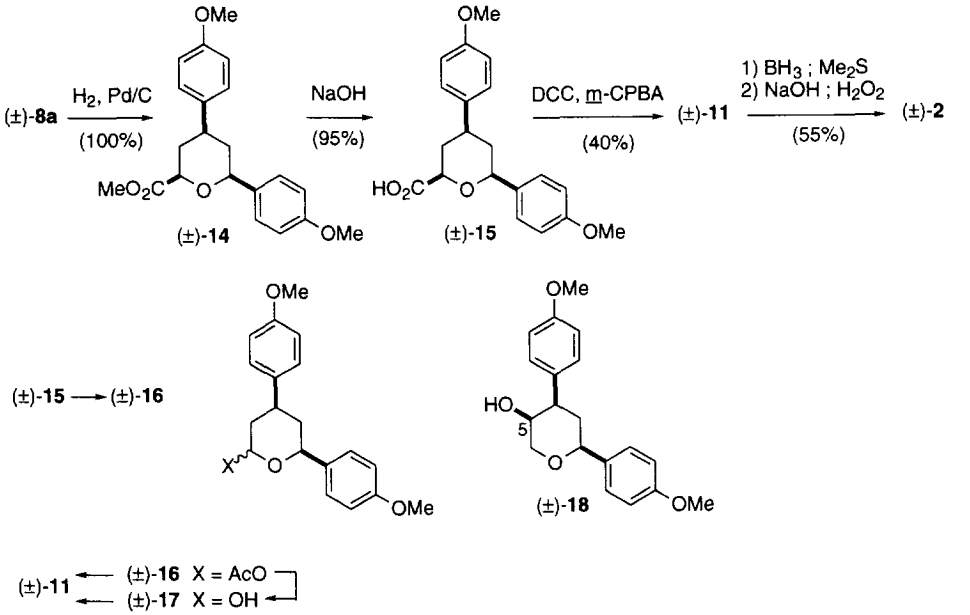


We then synthesized the dihydropyran intermediate **11** since it was expected to yield the required lignan (±)-**2** upon stereoselective hydroboration-oxidation. The methyl ester **8a** gave the oily free acid **12** upon treatment with aqueous sodium hydroxide. The decarboxylation of **12** was attempted, using various methods, which all failed or proved inefficient. On experimenting the radical decarboxylation procedure described by Fristad and coworkers,[7] using silver nitrate and potassium persulfate, the acid **12** almost quantitatively yielded the enelactone **13** which has only one stereogenic centre (at C-6). Much work was next devoted to the selective reduction, into a methylene group, of the carbonyl of the enelactone **13** in order to obtain the corresponding 3,4-dihydropyran, but this again met with poor results.

We were thus led to investigate another approach to the dihydropyran **11**, starting from a suitable tetrahydropyran derivative. Catalytic hydrogenation of the dihydroadduct **8a** quantitatively yielded the corresponding tetrahydropyran **14**, in which the three substituents are equatorial (Scheme 3). The acid **15** (resulting from saponification of the ester **14** with excess sodium hydroxide) was treated with lead tetraacetate in boiling benzene and under UV irradiation, and this gave the acetate **16** in 55% yield, taking into account the recovery of the unreacted starting material **15**. The acetate **16**, on heating in 4-methylpyridine at 160°C gave the dihydropyran **11**, albeit in low yields (*ca.* 26%). Alcoholysis of the acetate **16** using methanol and potassium carbonate, afforded the lactol **17**. Dehydration of the latter, by means of TsOH in benzene (or MsCl/DABCO) furnished the dihydropyran **11** in very low yields (< 10%). The acid **15** was next treated with

NCS/$(AcO)_4Pb$ in order to obtain the intermediate α-chlorotetrahydropyran following Martin's decarboxylation method.[8] β-Elimination of HCl from this crude intermediate using excess DBN at 130°C for 3h gave the dihydropyran **11** in 26% yield only with regards to the starting compound **15** transformed. At last, the acid **15** was treated with *m*-CPBA/DCC in methylene dichloride, according to Shiozaki's degradation procedure,[9] and the resulting crude α-(*m*-chlorobenzoyloxy) tetrahydropyran reacted with 4-methylpyridine at 160°C, thus leading to the requisite dihydropyran **11** in 40% global yield after chromatography.

Scheme 3

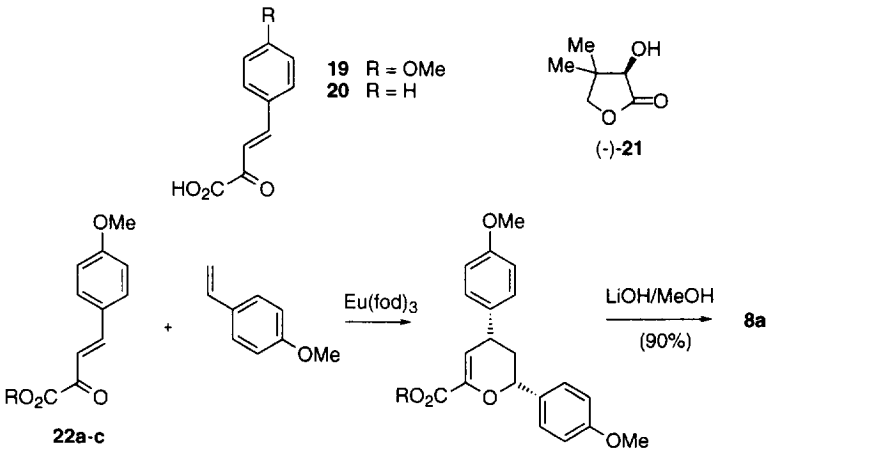


Hydroboration-oxidation in standard conditions gave in good yield a 85/15 mixture of (±)-**2** and its minor 5-epimer **18**. Column chromatography of this mixture followed by crystallization from ether gave pure (±)-*O*-dimethylsugiresinol (±)-**2** in 55% yield. Finally, the best sequence we used to obtain the lignan (±)-**2** proved to be as follows : **7a** --> (±)-**8a** --> (±)-**14** --> (±)-**15** --> (±)-**11** --> (±)-**2**. The overall yield of this five step sequence is 20% starting from the benzylidenepyruvic ester **7a**.

Studies in the optically active series. We planned synthesizing enantiomericaly pure "natural" (-)-*O*-dimethylsugiresinol (-)-**2** using the reaction scheme we developed in the racemic series, the main difference being the use, in the first heterocycloaddition step, of a chiral 1-oxabutadiene resulting from the esterification of 4-methoxybenzylidenepyruvic acid **19** with an appropriate chiral alcohol (Scheme 4). In the course of preliminary studies,[10] benzylidenepyruvic acid **20** was esterified with either (-)-menthol, dimethyl (-)-malate, diethyl (+)-*O*-benzoyltartrate, benzyl (+)-mandelate or (-)-pantolactone (-)-**21**, respectively, and the resulting chiral heterodienes were subjected to Eu(fod)3 catalyzed cycloaddition with 4-methoxystyrene as described above. Poor diastereofacial selectivities were generally observed, except in the cases of (-)-8-phenylmenthol and (-)-pantolactone (-)-**21** which both appeared to be somewhat promising chiral vectors (d.e. up to 72%).

When applied to **22**-type esters, obtained from the requisite 4-methoxybenzylidenepyruvic acid **19**, cyclisation with 4-methoxystyrene led to somewhat disappointing stereochemical results, facial selectivity ranging from 20% for **23a** [R = (-)-menthyl, *endo/exo* ratio : >97/3] to nearly 50% for **23b** [R = (-)-pantolactonyl, *endo/exo* ratio : 94/6]. These results prompted us to search for a new chiral vector which would be more or less closely related to (-)-pantolactone (-)-**21**, while being more efficient. We thus envisaged using an appropriate derivative of (-)-erythronolactone (-)-**24** since the latter is readily available on a multigram scale, and in one step, from relatively cheap isoascorbic acid.[11]

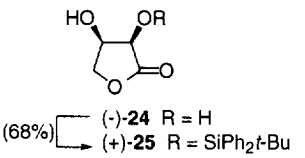
Scheme 4



	ROH
a	(-)-Menthol
b	(-)-**21**
c	(-)-**25**

23	Yield (%)	e.s[a)]	f.s[b)]	Major enantiomer
a	88	97/3	60/40	
b	66	94/6	73/27	(-)-**8a**
c	76	97/3	95/5	(+)-**8a**

a) e.s : endo selectivity
b) f.s : facial selectivity



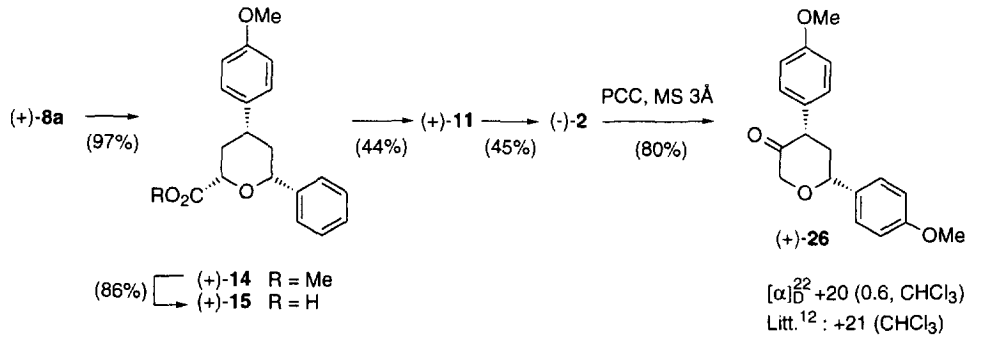
The α,β-dihydroxylactone (-)-**24** reacted with *t*-BuPh2SiCl (1.1 equiv.) in the presence of imidazole using a standard procedure, and this furnished a mixture of *O*-silyl derivatives from which the major α-*O*-silyl compound (+)-**25** was isolated in 68% yield by crystallization. The oily ester **22c** deriving from the acid **19** and the alcohol (+)-**25** was obtained in nearly quantitative yield, using DCC as a dehydrating agent. Reaction of the heterodiene **22c** with 4-methoxystyrene in the usual conditions afforded the corresponding adduct **23c** as an amorphous solid and in 76% yield after chromatography. Again in this case, the *endo/exo* selectivity was high (> 97/3). But more interestingly, *the diastereofacial selectivity ratio was high too* (95/5),

as evidenced from the ^1H NMR spectrum. It was therefore decided to complete the synthesis of the target lignan (-)- **2** starting from the adduct **23c.**

Transesterification of the adduct **23c** (de. 90%) with methanol in the presence of LiOH gave the desired methyl ester (+)-**8a** (ee. 93% determined by ^1H NMR with chiral shift reagent Eu(hfc)3), having the required (4R, 6R) configuration, as established above. On the other hand, the recrystallized adduct **23b** (de. 67%) deriving from (-)-pantolactone (-)-**21** was similarly transesterified with methanol, and yielded a *levorotary* methyl ester (-)-**8a**, with implies that the major enantiomer in this case has the non-natural (4S, 6S) configuration.

Catalytic hydrogenation of the (+)-(4R, 6R) methyl ester (+)-**8a** (ee. 93%) nearly quantitatively afforded the α-methoxycarbonyl tetrahydropyran (+)-**14** which was next saponified to the free acid (+)-**15** (Scheme 5). Following the procedures we developed in the racemic series, the acid (+)-**15** was degraded to the (+)-dihydropyran (+)-**11** (44% yield of crystalline product), and the latter was hydroxylated in the usual fashion, thus leading after chromatographic separation of epimers and recrystallization, to enantiomerically pure (-)-(2R, 4S, 5S)-*O*-dimethylsugiresinol (-)-**2**, in 12% overall yield from 4-methoxybenzylidenepyruvic acid **19**. The 400 MHz proton NMR spectra of (-)-**2** and (±)-**2** were run in the presence of the chiral shift reagent Eu(hfc)3, and revealed that the optically active lignan (-)-**2** was enantiomerically pure, suggesting that enantiomeric enrichment had occurred in the isolation of crystalline (+)-dihydropyran (+)-**11**. The melting point and specific optical rotation of the final product were in agreement with those reported in the literature[12] for the dimethylether (-)-**2** deriving from natural sources ; nevertheless, unambiguous attribution of the absolute configuration was achieved after oxidation of (-)-**2** into (+)-sugiresinone (+)-**26**, whose specific optical rotation, $[\alpha]_D$ +20 (c 0.6, $CHCl_3$), was in agreement with that of **26** obtained from natural sources.[12]

Scheme 5

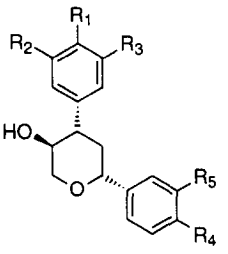


Conclusion

We have observed highly endoselective [4+2] heterocycloadditions of benzylidenepyruvic esters (as 1-oxabutadienes) with styrene dienophiles, with formation of *cis*-2,4-diaryl-3,4-dihydropyrans. This reaction was used as the first stage of a five-step sequence leading to (±)-*O*-dimethylsugiresinol (±)-**2** in 20% overall yield. A similar sequence was applied to the chiral ester **22c** deriving from 4-methoxybenzylidenepyruvic acid

19 and α-O-(*t*-butyl diphenylsilyl) erythronolactone (+)-**25**. Thus, Eu(fod)3 catalyzed cycloaddition of the ester **22c** with 4-methoxystyrenne gave the *endo* adduct **23c** in 76% yield and with a dr = 95/5. The latter gave rise to enantiomerically pure "natural" (-)-*O*-dimethylsugiresinol (-)-**2** in five further steps, and in 12% overall yield from 4-methoxybenzylidenepyruvic acid **19**. Efficient access to dihydropyrans **8b-e** (Scheme 1) we demonstrated earlier makes this strategy practical for the total synthesis of each other member of the sequirin group (e.g. **27-30**) for which, to our knowledge, no asymmetric syntheses were reported (Scheme 6). We are currently investigating the scope of α-O-(*t*-butyl diphenylsilyl) erythronolactone (+)-**25** as a new chiral vector in asymmetric synthesis.

Scheme 6



	Sequirin	R_1	R_2	R_3	R_4	R_5
1	A(Sugiresinol)	OH	H	H	OH	H
27	B	OH	H	H	OH	OH
28	E	OH	OH	H	OH	H
29	F	OH	OH	H	OH	OH
30	G	OH	OH	OH	OH	OH

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Mattson Genesis spectrophotometer. NMR spectra (δ, ppm) were recorded with a Bruker AC 400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Elemental analyses were performed at CNRS-ICSN (Gif-sur-Yvette, France). Compounds were purified by column chromatography over silica gel (Merck Kieselgel 60), using cyclohexane-ethyl acetate mixtures as eluents.

3,4-Methylenedioxystyrene (4). A mixture of methyltriphenylphosphonium bromide (13.5 g, 37.5 mmol), piperonal (4.5 g, 30 mmol) and potassium carbonate (6.2 g, 45 mmol), in diglyme (60 mL) was heated under reflux for 24 h. This, on distillation in vacuo, gave crude styrene **4** which was purified by column chromatography (cyclohexane-AcOEt, 95 : 5) as an oil (1.46 g, 33%), bp 95°C/0.01 mmHg ; R_f 0.62 cyclohexane-AcOEt (6 : 4); IR (film) 1687 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 5.13 (1 H, d, *J* 10.9), 5.58 (1 H, d, *J* 17.3), 5.96 (2 H, s), 6.64 (1 H, dd, *J* 17.3 and 10.9), 7.75 (1 H, d, *J* 8.0), 7.85 (1 H, dd, *J* 8.0 and 1.6) and 6.97 (1 H, d, *J* 1.6). Anal. Calcd for $C_9H_8O_2$: C, 72.96 ; H, 5.44. Found : C, 72.91 ; H, 5.59.

General Procedure for the Preparation of Benzylidenepyruvic esters (7). To a mixture of acetal **6** and methyl 2-(trimethylsiloxy)acrylate **5**[13] in dry dichloromethane under argon at -78°C, boron trifluoride-diethyl ether (1.1eq) was added dropwise. The reaction was warmed to 0°C for over 1 h and stirred at the same temperature for 2 h. Satured aqueous $NaHCO_3$ was added, and the mixture was extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford

crude γ-methoxy-α-oxoesters, which were dissolved in toluene. Silica gel (10-15 g) was then added and the mixture was heated at reflux with vigorous stiring for 12 h. After being cooled to room temperature, the mixture was filtered and the residual solid was washed several times with dichloromethane. The filtrates were combined and concentrated to give the crude esters **7** which were purified by crystallization.

Methyl 2-Oxo-4-(4-methoxyphenyl)but-3-enoate (7a). Methyl 2-(trimethylsiloxy)acrylate **5** (0.73 g, 4.2 mmol) and acetal **6a**[14] (1.15 g, 6.3 mmol) gave compound **7a** (0.78 g, 85%) as yellow needles, mp 109°C [lit.,[15] 106°C] ; IR (film) 1731 (C=O ester), 1687 (C=O) and 1565 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.85 (3 H, s), 3.93 (3 H, s), 6.95 (2 H, d, *J* 8.8), 7.25 (1 H, d, *J* 16.1), 7.60 (2 H, d, *J* 8,8) and 7.88 (1 H, d, *J* 16,1) ; ^{13}C NMR ($CDCl_3$) δ 50.4, 55.5, 114.6, 118.1, 126.8, 131.1, 148.6, 162.7, 162.9 and 182.2.

Methyl 2-Oxo-4-(3,4-methylenedioxyphenyl)but-3-enoate (7b). Methyl 2-(trimethylsiloxy)acrylate **5** (1.92 g, 11.0 mmol) and acetal **6b**[16] (1.96 g, 10.0 mmol) gave compound **7b** (1.99 g, 85%) as yellow needles, mp 141°C (AcOEt) ; R_f 0.52 cyclohexane-AcOEt (6 : 4) ; IR(KBr) 1735 (C=O ester), 1685 (C=O) and 1610 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) 3.95 (3 H, s), 6.10 (2 H, s), 6.85 (1 H, d, *J* 8.3), 7.15 (2 H, m), 7.20 (1 H, d, *J* 15,9) and 7.80 (1 H, d, *J* 15,9); ^{13}C NMR ($CDCl_3$) δ 53.0, 101.9, 106.9, 108.8, 118.4, 126.7, 128.6, 148.5, 148.6, 151.0, 162.7 and 182.1. Anal. Calcd for $C_{21}H_{10}O_5$: C, 61.52 ; H, 4.31. Found : C, 61.84 ; H, 4.81.

Methyl 2-Oxo-4-(3,4,5-trimethoxyphenyl)but-3-enoate (7c). Methyl 2-(trimethylsiloxy)acrylate **5** (1.05 g, 6.03 mmol) and acetal **6c**[16] (1.15 g, 7.24 mmol) gave compound **7c** (1.60 g, 95%) as yellow needles, mp 112°C (AcOEt) ; R_f 0.40 cyclohexane-AcOEt (6 : 4); IR (KBr) 1752 (C=O ester), 1725 (C=O) and 1614 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (9 H, s), 3.95 (3 H, s), 6.85 (2 H, s), 7.30 (1 H, d, *J* 15.9) and 7.80 (1 H, d, *J* 15,9); ^{13}C NMR ($CDCl_3$) δ 53.1, 56.3, 61.0, 106.4, 119.6, 129.4, 141.6, 148.8, 153.5, 162.7 and 182.1. Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.0 ; H, 5.75 ; O, 34.25. Found : C, 59.75 ; H, 5.95 ; O, 34.49.

General Procedure for the Preparation of the Dihydropyran Adducts (8). To a solution of heterodiene **7**, and substituted styrene was added 5% (molar) of Eu(fod)3. After stirring at reflux until complete conversion of **7** (observed by ^1H RMN), and vacuum evaporation of the volatiles, purification of the cycloadduct **8** was performed by flash chromatography (cyclohexane-AcOEt, 95 : 5).

Dihydropyran 8a. Heterodiene **7a** (2.2 g, 10 mmol), 4-methoxystyrene (2.0 g, 15 mmol) and hexane (20 mL), after 3 days, gave pure cycloadduct **8a** (3.43 g, 97%) as white needles, mp 92.5°C (AcOEt/petrol ether) ; R_f 0.62 cyclohexane-AcOEt (6 : 4); IR (nujol) 1735 (C=O) and 1643 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.95 (1 H_{ax}, dt, *J* 13.8, 11.4 and 11.3), 2.32 (1 H_{eq}, ddt, *J* 13.8, 6.4, 1.8 and 1.2), 3.80 (9 H, 3s), 3.85 (1 H_{ax}, m), 5.05 (1 H_{ax}, dd, *J* 11.3 and 1.2), 6.20 (1 H, t, *J* 1.8), 6.88 (2 H, d, *J* 8.7), 6.92 (2 H, d, *J* 8.7), 7.15 (2 H, d, *J* 8.7) and 7.30 (2 H, d, *J* 8.7) : ^{13}C NMR ($CDCl_3$) δ 38.9, 39.5, 52.2, 55.3, 78.7, 113.9, 114.1, 114.7, 127.6, 128.2, 132.5, 135.2, 145.0, 158.5, 159.5 and 163.5. HRMS : Found: $M^{+\cdot}$, 354.1459. $C_{21}H_{22}O_5$ requires *M*, 354.1467. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.16 ; H, 6.26. Found : C, 70.96 ; H, 6.19.

Dihydropyran 8b. Heterodiene **7b** (0.12 g, 0.5 mmol), 4-methoxystyrene (0.08 g, 0.63 mmol) and hexane (5 mL), after 6 days, gave pure cycloadduct **8b** (0.18 g, 96%) as yellow oil; R_f 0.46 cyclohexane-AcOEt (6 : 4) ;

IR (film) 1733 (C=O) and 1643 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (1 H_{ax}, dt, *J* 13.8, 11.4 and 11.4), 2.34 (1 H_{eq}, ddt, *J* 13.8, 6.4, 1.6 and 1.6), 3.82 (1 H_{ax}, ddd, J 11.4, 6.3 and 2.3), 3.90 (3 H, s), 3.91 (3 H, s), 5.01 (1 H_{ax}, dd, *J* 11.4 and 1.6), 5.93 (2 H, s), 6.20 (1 H, dd, *J* 2.3 and 1.6), 6.73 (1 H, dd, *J* 7.9 and 1.8), 6.76 (1 H, d, *J* 1.8), 6.80 (1 H, d, *J* 7.9), 6.92 (2 H, d, *J* 8.7) and 7.37 (2 H, d, *J* 8.7) ; ^{13}C NMR ($CDCl_3$) δ 39.4, 39.5, 52.2, 55.3, 78.6, 101.0, 107.6, 108.4, 113.9, 114.4, 120.2, 127.6, 132.4, 137.0, 145.1, 146.4, 147.9, 159.5 and 163.4. HRMS: Found: $M^{+\cdot}$, 368.1248. $C_{21}H_{20}O_6$ requires *M*, 368.1259 ; Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47 ; H, 5.48 ; O, 26.06. Found : C, 68.63 ; H, 5.54 ; O, 26.31.

Dihydropyran 8c. Heterodiene **7b** (0.11 g, 0.5 mmol), 3,4-methylenedioxystyrene **4** (0.093 g, 0.63 mmol) and hexane (5 mL), after 7 days, gave pure cycloadduct **8c** (0.17 g, 90%) as white needles ; mp 85°C (Et_2O) ; R_f 0.42 cyclohexane-AcOEt (6 : 4) ; IR (film) 1733 (C=O) and 1643 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.90 (1 H_{ax}, dt, *J* 13.8, 11.4 and 11.4), 2.34 (1 H_{eq}, ddt, *J* 13.8, 6.4, 1.7 and 1.7), 3.80 (1 H_{ax}, m), 3.81 (3 H, s), 3.82 (3 H, s), 5.00 (1 H_{ax}, dd, *J* 11.4 and 1.7), 5.93 (2 H, s), 6.20 (1 H, dd, *J* 1.8 and 1.7), 6.30 (1 H, d, *J* 8.0), 6.38 (2 H, d, *J* 8.7), 6.39 (1 H, dd, *J* 8.0 and 1.9), 6.45 (1 H, d, *J* 1.9) and 6.68 (2 H, d, *J* 8.7) ; ^{13}C NMR ($CDCl_3$) δ 38.8, 39.6, 52.2, 55.2, 78.8, 101.1, 106.9, 108.1, 114.1, 114.8, 119.9, 128.1, 134.2, 135.0, 144.8, 147.4, 147.8, 158.5 and 163.4. Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47 ; H, 5.48 ; Found : C, 68.44 ; H, 5.66.

Dihydropyran 8d. Heterodiene **7b** (0.12 g, 0.5 mmol), 3,4-methylenedioxystyrene **4** (0.093 g, 0.63 mmol) and toluene (5 mL), after 6 days, gave pure cycloadduct **8d** (0.18 g, 95%) as yellow oil; R_f 0.43 cyclohexane-AcOEt (6 : 4) ; IR ($CDCl_3$) 1727 (C=O) and 1643 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (1 H_{ax}, dt, *J* 13.8, 11.4 and 11.4), 2.30 (1 H_{eq}, ddt, *J* 13.8, 6.4, 1.8 and 1.8), 3.78 (1 H_{ax}, ddd, *J* 11.4, 6.4 and 2.5), 3.81 (3 H, s), 4.99 (1 H_{ax}, dd, *J* 11.4 and 1.8), 5.87 (2 H, s), 5.88 (2 H, s), 6.16 (1 H, dd, *J* 2.5 and 1.8) and 6.60-6.90 (6 H, m) ; ^{13}C NMR ($CDCl_3$) δ 39.3, 39.6, 52.3, 78.8, 101.1, 106.7, 107.1, 107.6, 108.2, 114.5, 120.0, 120.2, 134.1, 136.9, 145.0, 146.5, 147.5, 147.9 and 163.4. HRMS: Found: $M^{+\cdot}$, 382.1037. $C_{21}H_{18}O_7$ requires *M*, 382.1052.

Dihydropyran 8e. Heterodiene **7c** (0.040 g, 0.14 mmol), 3,4-methylenedioxystyrene **4** (0.025 g, 0.17 mmol) and toluene (2 mL), after 11 days, gave pure cycloadduct **8e** (0.047 g, 77%) as yellow needles, mp 126°C (ether/petrol ether) ; R_f 0.45 cyclohexane-AcOEt (6 : 4) ; IR ($CDCl_3$) δ 1729 (C=O) and 1643 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (1 H_{ax}, dt, *J* 13.8, 11.4 and 11.4), 2.33 (1 H_{eq}, ddt, *J* 13.8, 6.4, 1.7 and 1.7), 3.85 (1 H_{ax}, m), 3.82-3.91 (12 H, 4s), 5.00 (1 H_{ax}, dd, *J* 11.4 and 1.7), 5.96 (2 H, s), 6.20 (1 H, dd, *J* 2.0 and 1.7), 6.43 (2 H, s), 6.79 (1H, d, *J* 8.0), 6.88 (1H, dd, *J* 8.0 and 1.7) and 6.94 (1 H, d, *J* 1.7) ; ^{13}C NMR ($CDCl_3$) δ 39.1, 39.7, 52.0, 55.9, 60.6, 78.5, 100.8, 103.9, 106.6, 107.9, 113.9, 119.6, 133.8, 138.5, 136.6, 144.7, 147.2, 147,6, 153.2 and 163.1. HRMS : Found: $M^{+\cdot}$,428.1471. $C_{23}H_{24}O_8$ requires *M*, 428.1471.

3,4-Dihydro-6-hydroxymethyl-2,4-bis-(4-methoxyphenyl)pyran-2H (9). To a solution of ester **8a** (0.98 g, 2.77 mmol) in dry diethyl ether (10 mL) under argon at 0°C was added portionwise $LiAlH_4$ (0.11 g, 1 eq). After stirring at reflux until complete conversion (observed by TLC), the reaction was hydrolyzed with saturated aqueous Na_2SO_4 (0.35 mL). The mixture was filtered on celite, the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure to afford crude alcohol **9** which was purified by flash chromatography (cyclohexane-AcOEt 9 : 1 to 7 : 3), followed by crystallization from diethyl ether as white

needles (0.75 g, 83%), mp 82-83°C; R_f 0.33 cyclohexane-AcOEt (6 : 4) ; IR (film) 3407 (OH), 1673 (C=C), 1614 and 1511 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.88 (1 H, dt, *J* 13.5, 11.5 and 11.5), 2.05 (1 H, dd, *J* 5.8 and 3.9), 2.23 (1 H, ddd, *J* 13.5, 6.0 and 1.2), 3.69 (1 H, dd, *J* 11.5 and 6.0), 3.76 and 3.77 (6 H, 2s), 4.03 (1 H, dd, *J* 12.9 and 5.8), 4.13 (1 H, dd, *J* 12.9 and 3.9), 4.90 (1 H, s), 4.97 (1 H, dd, *J* 11.5 and 1.2), 6.82 (2 H, d, *J* 8.7), 6.87 (2 H, d, *J* 8.7), 7.15 (2 H, d, *J* 8.7) and 7.30 (2 H, d, *J* 8.7) ; ^{13}C NMR ($CDCl_3$) δ 38.3, 40.3, 55.3, 63.4, 78.1, 101.9, 113.8, 113.9, 127.6, 128.0, 133.2, 136.9, 153.8, 158.2 and 159.4. HRMS: Found: $M^{+\cdot}$, 326.1522. $C_{20}H_{22}O_4$ requires *M*, 326.1518). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60 ; H, 6.79. Found C, 73.36 ; H, 6.82.

5-Hydroxy-6-hydroxymethyl-2,4-bis-(4-methoxyphenyl)tetrahydropyran (10). To a solution of allylic alcohol **9** (0.61 g, 1.87 mmol) in THF (5 mL) was added a 2.0 *M* solution of borane-methyl sulfide complex in THF (2.1 mL, 4.11 mmol) at 0°C. After the reaction mixture had been stirred at 0°C for 1 h, the temperature was raised to 25°C and the mixture was stirred at this temperature for an additional 14 h. The organoborane thus formed was oxidized at 65°C by adding 6 M sodium hydroxide (1.1 mL) followed by dropwise addition of 30% hydrogen peroxide (1.5 mL). After being cooled, brine (25 mL) was added and THF was removed. The aqueous residue was extracted with AcOEt (3 x 10 mL). The organic layers were dried ($MgSO_4$) and concentrated. The compound **10** was purified by flash chromatography (cyclohexane-AcOEt 7 : 3 and 6 : 4) followed by recrystallization from diethyl ether as white needles (0.45 g, 71%), mp 133°C; R_f 0.46 (AcOEt) ; IR (film) 3415 (OH), 1614 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.88 (1 H_{ax}, ddd, *J* 12.5, 12.2 and 11.6), 2.01 (1 H_{eq}, d, *J* 12.5), 2.27 and 2.43 (OH, 2s), 2.80 (1 H, m), 3.51-3.88 (4 H, m), 4.53 (1 H_{ax}, d, *J* 10.9), 6.84 (4 H, 2d, *J* 8.6), 7.16 (2 H, d, *J* 8.6) and 7.26 (2 H, d, *J* 8.6); ^{13}C NMR ($CDCl_3$) δ 40.8, 49.5, 55.3, 63.6, 71.8, 79.0, 81.3, 113.8, 114.3, 127.2, 128.9, 133.3, 136.8, 158.8 and 159.2. Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.74; H, 7.02. Found: C, 69.62; H, 7.07.

6-Carboxy-3,4-dihydro-2,4-bis-(4-methoxyphenyl)pyran-2H (12). To a solution of ester **8a** (1.35 g, 3.81 mmol) in THF (25 mL) and water (25 mL) was added dropwise 3 M sodium hydroxide (7 mL, 21.0 mmol). After stirring the mixture for 24 h at room temperature, the organic solvent was evaporated and the residue was dissolved in satured aqueous Na_2CO_3 (until pH 10). Then, AcOEt (2x30 mL) was added followed by decantation. The aqueous layer was cautiously treated by 3 M hydrochloric acid (until pH 1) and was extracted with methylene chloride. The organic layers were washed with brine, dried ($MgSO_4$), evaporated under reduced pressure and gave acid **12** as an oil (1.20 g, 93%); R_f 0.20 methylene chloride-methanol (95 : 5) ; IR (Nujol) 2925-2543 (COOH), 1697 (C=O), 1644 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.98 (1 H_{ax}, ddd, *J* 13.6, 11.6 and 11.5), 2.33 (1 H_{eq}, dddd, *J* 13.6, 6.2, 1.2 and 1.2), 3.80 (6 H, 2s), 3.80 (1 H_{ax}, m), 5.08 (1 H_{ax}, dd, *J* 11.5 and 1.2), 6.32 (1 H, dd, *J* 1.2 and 1.2), 6.88 (2 H, d, *J* 8.6), 6.91 (2 H, d, *J* 8.6), 7.16 (2 H, d, *J* 8.6) and 7.33 (2 H, d, *J* 8.6) ; ^{13}C NMR ($CDCl_3$) δ 39.4, 40.1, 55.4, 55.5, 79.2, 114.5, 114.8, 115.2, 128.4, 129.0, 133.8, 136.4, 145.8, 159.5, 160.4 and 163.8.

5,6-Dihydro-4,6-bis-(4-methoxyphenyl)-2-oxopyran-2H (13). To a solution of acid **12**(1.20 g, 3.53 mmol) in acetonitrile (25 mL) and water (9 mL) was added silver nitrate (0.014 g, 0.07 mmol). After stirring the mixture for 12 h at 80°C, a solution of potassium persulfate (2.25 g, 8.12 mmol) in water (50 mL) was added dropwise and the mixture was stirred at this temperature for an additional 4 h. After being cooled, the aqueous layer was extracted with methylene chloride (3x100 mL). The organic layer was washed with satured aqueous

$NaHCO_3$, dried over $MgSO_4$ and concentred under reduced pressure to afford crude lactone **13** which was purified by crystallization from AcOEt as white needles (1.06 g, 97%), mp 113°C; R_f 0.33 cyclohexane-AcOEt (6 : 4); IR (Nujol) 1697 (C=O), 1602 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.00 (2 H, dd, *J* 8.0 and 1.2), 3.85 (6 H, 2s), 5.47 (1 H, t, *J* 8.0 and 8.0), 6.40 (1 H, t, *J* 1.2 and 1.2), 6.94 (2 H, d, *J* 9.0), 6.95 (2 H, d, *J* 9.0), 7.40 (2 H, d, *J* 9.0) and 7.55 (2 H, d, *J* 9.0) ; ^{13}C NMR ($CDCl_3$) δ 34.0, 55.4, 55.5, 78.6, 112.8, 114.0, 114.4, 127.7, 128.0, 130.8, 154.0, 159.8, 161.8 and 165.9. HRMS: Found: $M^{+\cdot}$, 310.1191. $(C_{19}H_{18}O_4)^{+\cdot}$ requires *M*, 310.1205). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53 ; H, 5.85 ; O,20.62. Found: C, 73.63 ; H, 5.92 ; O, 20.37.

(±)-6-Methoxycarbonyl-2,4-bis-(4-methoxyphenyl)tetrahydropyran [(±)-14]. A mixture of dihydropyran **8a** (6.27 g, 17.7 mmol), 95% ethanol (120 mL), AcOEt (50 mL) and 10% palladium on activated carbon was stirred at room temperature for 20 h under hydrogen. The mixture was then dried over $MgSO_4$, filtered, evaporated and this gave pure tetrahydropyran **14** (6.30 g, 100%) as colorless oil; R_f 0.43 cyclohexane-AcOEt (6 : 4); IR (film) 1758 (C=O), 1614 and 1511 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.77 (1 H_{ax}, ddd, *J* 13.1, 11.4 and 11.4), 1.79 (1 H_{ax}, ddd, *J* 13.1, 11.4 and 11.4), 2.05 (1 H_{eq}, m), 2.22 (1 H_{eq}, m), 2.99 (1 H_{ax}, dddd, *J* 11.4, 11.4, 3.5 and 3.5), 3.78 (3 H, s),3.81 (6 H, 2s), 4.35 (1 H_{ax}, dd, *J* 11.4 and 2.2), 4.53 (1 H_{ax}, dd, *J* 11.4 and 1.9), 6.85 (2 H, d, *J* 8.7), 6.88 (2 H, d, *J* 8.7), 7.15 (2 H, d, *J* 8.7) and 7.35 (2 H, d, *J* 8.7); ^{13}C NMR ($CDCl_3$) δ 36.8, 41.5, 41.7, 50.7, 56.0, 77.8, 80.4, 114.6, 114.9, 128.2, 128.5, 134.9, 137.5, 159.1, 160.0 and 172.4. HRMS: Found: $M^{+\cdot}$, 356.1622. $C_{21}H_{24}O_5$ requires *M*, 356.1623.

(±)-6-Carboxy-2,4-bis-(4-methoxyphenyl)tetrahydropyran [(±)-15]. To a solution of ester **14** (6.30 g, 17.7 mmol) in THF (40 mL) and water (40mL) was added dropwise 1 M sodium hydroxide. After stirring for 1 h at room temperature, the mixture was basified by addition of saturated aqueous Na_2CO_3 (until pH 10). Then, AcOEt (50 mL) was added followed by decantation. The aqueous layer was treated by 3 M hydrochloric acid (until pH 1) and was extracted with AcOEt (2 x 50 mL). The organic layers were washed with brine, dried ($MgSO_4$), evaporated under reduced pressure and gave a white solid (5.75 g, 95%). This, on recrystallization from AcOEt, gave acid **15** as needles, mp 159°C (AcOEt) ; R_f 0.18 cyclohexane-AcOEt (6 : 4); IR (film) 3500-2900 (COOH), 1747 (C=O), 1610 and 1511 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.76 (1 H_{ax}, ddd, *J* 12.8, 12.4 and 12.1), 1.79 (1 H_{ax}, ddd, *J* 13.1, 12.0 and 11.9), 2.07 (1 H_{eq}, m), 2.38 (1 H_{eq}, m), 3.02 (1 H_{ax}, dddd, *J* 12.1, 11.9, 3.1 and 3.1), 3.80 (3 H, s), 3.81 (3 H, s), 4.35 (1 H_{ax}, dd, *J* 11.9 and 2.3), 4.61 (1 H_{ax}, dd, *J* 11.2 and 1.6), 6.88 (2 H, d, *J* 8.6), 6.91 (2 H, d, *J* 8.6), 7.16 (2 H, d, *J* 8.6) and 7.34 (2 H, d, *J* 8.6); ^{13}C NMR ($CDCl_3$) δ 35.4, 40.3, 40.8, 55.3, 76.1, 80.1, 114.0, 114.1, 127.5, 127.6, 133.2, 136.1, 158.4, 159.5 and 173.0. Anal. Calcd. for $C_{20}H_{20}O_6$: C, 70.16; H, 6.48. Found: C, 69.92; H, 6.53.

6-Acetoxy-2,4-bis-(4-methoxyphenyl)tetrahydropyran (16) (mixture of epimers at C-6). To a solution of acid **15** (1.55 g, 4.52 mmol) in dry benzene (15 mL) was added portionwise lead tetra-acetate (2.20 g, 4.97 mmol). After stirring and irradiation with a 100W UV-visible Hanova lamp for 0.5h at 81°C, diethyl ether (100 mL) was added and the heterogeneous mixture was filtered. Evaporation under reduced pressure of the filtrate left a colorless oil (1.06 g), which, on column chromatography (cyclohexane-AcOEt, 95 : 5), gave compound **16** (0.61 g, 56%) as white needles, mp 102-104°C (AcOEt) ; R_f 0.48 cyclohexane-AcOEt (6 : 4). The filter, containing the mixed $lead^{II}$ salt, was washed with AcOEt (50 mL). The resulting mixture was treated with 3 M hydrochloric acid, followed by decantation. The organic layer was washed with brine, dried

and evaporated to give starting material **15** (0.50 g, 1.46 mmol) as white solid ; IR (film) 1747 (C=O), 1614 and 1513 cm^{-1}. Major isomer (H_{2eq}) : ^1H NMR ($CDCl_3$) δ 1.70-2.10 (4 H, m), 2.16 (3 H, s), 3.28 (1 H_{ax}, dddd, *J* 12.5, 12.5, 3.6 and 3.6), 3.79 (6 H, 2s), 4.98 (1 H_{ax}, dd, *J* 11.6 and 1.9), 6.45 (1 H_{eq}, s), 6.86 (2 H, d, *J* 8.7), 6.87 (2 H, d, *J* 8.7), 7.16 (2 H, d, *J* 8.7) and 7.31 (2 H, d, *J* 8.7); ^{13}C NMR ($CDCl_3$) δ 21.2, 34.9, 35.9, 40.8, 55.2, 73.1, 92.7, 113.7, 113.9, 127.1, 127.5, 133.8, 136.5, 158.2, 159.0 and 169.6; minor isomer : ^1H NMR ($CDCl_3$) δ 1.70-2.10 (4 H, m), 2.16 (3 H, s), 3.02 (1 H_{ax}, dddd, *J* 12.5, 12.5, 3.6 and 3.6), 3.79 (6 H, 2s), 4.65 (1 H_{ax}, dd, *J* 11.2 and 1.8), 5.97 (1 H_{ax}, dd, *J* 10.0 and 2.3), 6.86 (2 H, d, *J* 8.7), 6.87 (2 H, d, *J* 8.7), 7.16 (2 H, d, *J* 8.7) and 7.31 (2 H, d, *J* 8.7) ; ^{13}C NMR ($CDCl_3$) δ21.2, 37.2, 39.5, 40.1, 55.2, 77.9, 94.8, 113.7, 113.9, 127.3, 127.5, 133.1, 136.0, 158.2, 159.1 and 169.3. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found : C, 70.51; H, 6.74.

(±)-3,4-Dihydro-2,4-bis-(4-methoxyphenyl)pyran-2H [(±)-11]. To a solution of acid **15** (0.24 g, 0.7 mmol) in dichloromethane (4 mL) were added m-CPBA (0.19 g, 0.77 mmol) and DCC (0.16 g, 0.77 mmol) at 0°C with stirring. After 10 min the mixture was warmed to room temperature, stirred for 1 h, and chromatographed (cyclohexane-AcOEt 8 : 2). Evaporation of the solvent gave an oil which was dissolved in 4-methylpyridine (2 mL) and heated at 160°C for 5 h. After being cooled, the reaction mixture was chromatographed to give compound **11** (0.08 g, 40%) as an colorles oil which was crystallized from diethyl ether, mp 88-90°C; R_f 0.50 cyclohexane-AcOEt (6 : 4) ; IR (film) 1643 (C=C), 1610 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.93 (1 H_{ax}, ddd, *J* 13.5, 11.7 and 11.5), 2.25 (1 H_{eq}, dd, *J* 13.5 and 6.2), 3.70 (1 H_{ax}, ddd, *J* 11.7, 6.2 and 2.1), 3.80 (6 H, 2s), 4.81 (1 H, d, *J* 6.2), 4.96 (1 H_{ax}, d, *J* 11.5), 6.63 (1 H, dd, *J* 6.2 and 2.1), 6.84 (2 H, d, *J* 8.7), 6.88 (2 H, d, *J* 8.7), 7.19 (2 H, d, *J* 8.7) and 7.30 (2 H, d, *J* 8.7) ; ^{13}C NMR ($CDCl_3$) δ 37.9, 40.6, 55.0, 77.2, 105.0, 113.5, 113.6, 127.7, 127.8, 133.3, 134.1, 144.5, 158.0 and 159.1. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.0 ; H, 6.80. Found: C, 76.83 ; H, 6.82.

(±)-O-Dimethylsugiresinol [(±)-2]. To a solution of dihydropyran **11** (0.14 g, 0.48 mmol) in THF (4 mL) was added dropwise a 2.0 *M* solution of BH_3-Me_2S in tetrahydrofuran (0.53 mL, 1.06 mmol) at 0°C. After the reaction mixture had been stirred at 0°C for 1 h, the temperature was raised to 25°C and the mixture was stirred at this temperature for an additional 12 h. The organoborane thus formed was oxidized at 65°C for 1 h by adding 1 M sodium hydroxide (1.7 mL), followed by dropwise addition of 30% hydrogen peroxide (0.4 mL). After being cooled, brine (10 mL) was added and THF was removed. The aqueous residue was extracted with AcOEt (2 x 10 mL). The organic layers were dried ($MgSO_4$) and concentrated. The compound (+)-**2** was purified by flash chromatography (cyclohexane-AcOEt 6 : 4 and 1 : 9) followed by recrystallization from diethyl ether as white needles (0.08 g, 55%), mp 123-124°C [lit.,[3] 108-110°C (MeOH), lit.,[4] 121-122°C]; R_f 0.79 AcOEt ; IR (film) 3436 (OH), 1610 and 1513 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.92 (1 H_{ax}, ddd, *J* 12.4, 11.3 and 11.0), 2.06 (1 H_{eq}, ddd, *J* 12.4, 3.9 and 2.1), 2.78 (1 H_{ax}, ddd, *J* 11.3, 10.5 and 3.9), 3.48 (1 H_{ax}, dd, *J* 10.5 and 10.5), 3.80 (6 H, 2s), 3.82 (1 H_{ax}, m), 4.29 (1 H_{eq}, dd, *J* 10.5 and 2.1), 4.47 (1 H_{ax}, dd, *J* 11.0 and 2.1), 6.87 (2 H, d, *J* 8.7), 6.90 (2 H, d, *J* 8.7), 7.22 (2 H, d, *J* 8.7), 7.30 (2 H, d, *J* 8.7) ; ^{13}C NMR ($CDCl_3$) δ 40.4, 50.0, 55.3, 70.6, 72.3, 79.6, 113.7, 114.3, 127.1, 128.8, 133.2, 133.8, 158.7 and 159.0. Anal Calcd for $C_{19}H_{22}O_4$: C, 72.59 ; H, 7.05. Found: C, 72.42; H, 6.91.

Chiral Heterodiene (-)-22a. In a round-bottomed flask equipped with a Dean-Stark apparatus, a solution of acid **19**[15] (0.41 g, 2 mmol), (-)-menthol (0.32 g, 2.05 mmol), toluene (10 mL) and TsOH (0.02 g) were heated at 110°C for 2 days. After being cooled, toluene was evaporated and the residue was dissolved in AcOEt (20 mL). The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate and brine and then evaporated to give a yellow oil. Purification by crystallization from ether gave pure ester (-)-**22a** as needles (0.55 g, 80%), mp 110°C (ether) , $[\alpha]_D$ -39.6 (c 1.3, acetone); R_f 0.58 cyclohexane-AcOEt (6 : 4) ; IR (film) 1724 (C=O ester), 1693 (C=O) and 1590 (C=C) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.82 (3 H, d, *J* 7.0), 0.91 (3 H, d, *J* 6.8), 0.93 (3 H, d, *J* 6.8), 0.90-2.09 (10 H, m), 3.86 (3 H, s), 4.89 (1 H, ddd, *J* 10.5, 3.9 and 3.9), 6.94 (2 H, d, *J* 8.8), 7.25 (1 H, d, *J* 16.1), 7.60 (2 H, d, *J* 8,8) and 7.88 (1 H, d, *J* 16,1) ; ^{13} C NMR ($CDCl_3$) δ 15.7, 20.2, 21.5, 22.9, 25.7, 31.0, 33.6, 40.0, 46.3, 76.2, 55.0, 114.1, 118.1, 126.4, 130.5, 147.7, 161.9, 162.1 and 182.9. HRMS: Found: $M^{+\bullet}$, 344.1968. $C_{21}H_{28}O_4$ requires *M*, 344.1987. Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.94; H, 8.17.

Chiral Heterodiene (+)-22b. To a mixture of acid **19**[15] (2.06 g, 10 mmol), D-(-)-pantolactone (-)-**21** (1.17 g, 9 mmol) and DMAP (0.11 g, 0.9 mmol) in dry dichloromethane (13 mL) was added, at room temperature, a solution of DCC (2.6 g, 12.6 mmol) in dry dichloromethane (10 mL). After stirring for 15 h, solvent was removed under reduced pressure and the residue was diluted with diethyl ether (100 mL). The heterogeneous solution was filtered on celite and the filtrate was concentrated to give the ester (+)-**22b** which was purified by recrystallization from AcOEt as yellow needles (1.92 g, 67%), mp 118-121°C, $[\alpha]_D$ +33.0 (c 1, acetone); R_f 0.35 cyclohexane-AcOEt (6 : 4); IR (film) 1789 (C=O lactone), 1741 (C=O ester), 1683 (C=O), 1654 (C=C), 1590 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.22 (3 H, s), 1.28 (3H, s), 3.87 (3 H, s), 4.12 (1 H, d, *J* 14.0), 4.14 (1 H, d, *J* 14.0), 5.51 (1 H, s), 6.94 (2 H, d, *J* 8.8), 7.11 (1 H, d, *J* 16.2), 7.60 (2 H, d, *J* 8,8) and 7.93 (1 H, d, *J* 16,2) ; ^{13}C NMR ($CDCl_3$) δ 20.5, 23.5, 40.9, 77.1, 77.2, 115.3, 119.1, 127.2, 131.9, 150.5, 162.4, 163.5, 172.2 and 182.7. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14 ; H, 5.70. Found: C, 64.17 ; H, 5.76.

(+)-α-O-*t*-Butyldiphenylsilyl Erythronolactone [(+)-25]. To a mixture of D-(-)-erythronolactone (-)-**24**[11] (2.36 g, 20 mmol), imidazole (1.5 g, 22 mmol) in dry DMF (12 mL), was added dropwise *tert*-butyldiphenylsilyl chloride (5.72 mL, 22 mmol) at room temperature. After stirring for 2 days at this temperature, diethyl ether (150 mL) was added and, after standing and slow crystallization within 3 days, the heterogeneous mixture was washed with water and then filtered to give compound (+)-**25** (3.9 g) as a white solid. A second fraction (0.97 g) was isolated after addition of light petroleum (50 mL) to the filtrate, (global yield 68%), mp 168-173°C, $[\alpha]_D$ +32.0 (c 1, acetone) ; IR (KBr) 3569 (OH) and 1793 (C=O lactone) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.11 (9 H, s), 2.83 (1H, s), 4.00-4.10 (2 H, m), 4.28 (1 H, d, *J* 10.5), 4.35 (1 H, d, *J* 4.6) and 7.40-7.85 (10 H, m) ; ^{13}C NMR ($CDCl_3$) δ 18.7, 26.1, 68.0, 70.0, 70.3, 127.3, 127.5, 127.5, 129.8, 129.9, 134.8, 135.3 and 172.9.

Chiral Heterodiene (-)-22c. To a mixture of acid **19**[15] (2.60 g, 12.6 mmol), alcohol (+)-**25** (3.56 g, 10 mmol) and DMAP (0.12 g, 1 mmol) in dry dichloromethane (5 mL) was added at O°C, a solution of DCC (3.1 g, 15 mmol) in dry dichloromethane (15 mL). After stirring at room temperature for 12 h, solvent was removed under reduced pressure and the residue was diluted with diethyl ether (50 mL). The heterogeneous solution was filtered on celite and the filtrate was concentrated to give the ester (-)-**22c** which was purified on column chromatography (cyclohexane-AcOEt 9 : 1) as yellow oil (5.17 g, 95%), $[\alpha]_D$ -69.0 (c 2, acetone); R_f 0.45

cyclohexane-AcOEt (6 : 4) ; HRMS: Found: $M^{+\cdot}$, 545.191. $C_{31}H_{32}O_7Si+H^+$ requires *M*, 545.1996 ; IR (film) 1799 (C=O lactone), 1737 (C=O ester), 1687 (C=O), 1654 (C=C), 1590 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.11 (9 H, s), 3.89 (1H, s), 4.29 (1 H, dd, *J* 11.7 and 3.2), 4.36 (1 H, d, 11.7), 4.51 (1 H, d, *J* 5.2), 5.32 (1 H, dd, *J* 5.2 and 3.2), 6.93 (2 H, d, *J* 8.8), 6.90-7.80 (10 H, m), 7.17 (1 H, d, *J* 16.1), 7.61 (2 H, d, *J* 8.8) and 7.89 (1 H, d, *J* 16.1) ; ^{13}C NMR ($CDCl_3$) δ 19.3, 26.6, 55.5, 68.3, 69.3, 72.3, 114.6, 117.9, 126.6, 127.9, 130.0, 130.3, 131.3, 131.6, 132.3, 135.7, 136.0, 149.1, 161.0, 162.8, 172.4 and 181.0.

General Procedure for the Preparation of the optically Active Dihydropyran Adducts 23. To a mixture of chiral heterodiene **22** and 4-methoxystyrene in hexane or toluene, was added 5% (molar) of Eu(fod)3. After stirring under reflux until complete conversion of **23** (as observed by ^1H NMR), purification of the cycloadduct **23** was performed by flash chromatography, using cyclohexane/AcOEt as an eluent.

Dihydropyran 23a. Heterodiene (-)-**22a** (0.34 g, 0.99 mmol), 4-methoxystyrene (0.16 g, 1.19 mmol) and hexane (10 mL), after 5 days, gave a *ca.* 60 : 40 diastereomeric mixture of cycloadduct **23a** (0.42 g, 88%) as yellow oil, R_f 0.52 cyclohexane-AcOEt (6 : 4) ; IR (film) 1714 (C=O), 1643 (C=C), 1614 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) δ major isomer 0.79 (3 H, d, *J* 6.9), 0.90 (6 H, 2d, *J* 6.8), 0.90-1.70 (8 H, m), 1.90 (1 H_{ax}, m), 2.09 (1 H, m), 2.32 (1 H_{eq}, m), 3.80 (6 H, 2s), 3.83 (1 H_{ax}, m), 4.82 (1 H, m), 5.04 (1 H_{ax}, d, *J* 11.4), 6.12 (1 H, s), 6.88 (4 H, 2d, *J* 8.6), 7.18 (2 H, d, *J* 8.6), 7.36 (2 H, d, *J* 8.6); minor isomer detected by the following characteristic signals : 5.06 (1 H, d, *J* 10.0), 6.14 (1 H, s); ^{13}C NMR ($CDCl_3$) δ major isomer 16.6, 20.7, 22.0, 23.6, 26.4, 31.4, 34.2, 38.9, 39.8, 40.7, 55.3, 75.0, 78.4, 113.8, 113.9, 114.1, 127.4, 128.2, 132.8, 135.6, 145.2, 158.5, 159.3 and 162.4; minor isomer detected by the following characteristic signals : 145.4. HRMS : Found : $M^{+\cdot}$, 478.2723. $C_{30}H_{38}O_5$ requires *M*, 478.2719. Anal. Calcd. for $C_{30}H_{38}O_5$: C, 75.28 ; H, 8.00. Found : C,75.21 ; H, 7.96.

Dihydropyran 23b. Heterodiene (+)-**22b** (0.60 g, 1.89 mmol), 4-methoxystyrene (0.50 g, 3.78 mmol) and toluene (20 mL), after 5 days, gave a *ca.* 69 : 25 : 6 diastereomeric mixture of cycloadduct **23b** (0.57 g, 66%) as needles, mp 159-160°C (AcOEt) (diastereomeric mixture); R_f 0.33 cyclohexane-AcOEt (6 : 4) ; IR (film) 1791 (C=O lactone), 1741 (C=O ester), 1641 (C=C), 1612 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) δ major isomer 1.14 (3 H, s), 1.23 (3 H, s), 1.94 (1 H_{ax}, ddd, *J* 13.8, 11.4 and 11.4), 2.34 (1 H_{eq}, dddd, *J* 13.8, 6.3, 1.2 and 1.2), 3.79 (3 H, s), 3.80 (3 H, s), 3.84 (1 H_{ax}, ddd, *J* 11.4, 6.3 and 2.3), 4.04 (1 H, d, *J* 12.6), 4.06 (1 H, d, *J* 12.6), 5.07 (1 H_{ax}, dd, *J* 11.4 and 1.2), 5.49 (1 H, s), 6.27 (1 H, dd, *J* 2.3 and 1.2), 6.87 (2 H, d, *J* 8.7), 6.88 (2 H, d, *J* 8.7),7.17 (2 H, d, *J* 8.6), 7.33 (2 H, d, *J* 8.6); minor *endo* isomer (25%) detected by the following signals : 5.06 (1 H_{ax}, dd, *J* 11.3 and 1.4), 5.48 (1 H, s), 6.30 (1 H, t, *J* 1.7); *exo* isomer (6%) detected by the following signals : 4.90 (1 H_{ax}, dd, *J* 10.3 and 2.7), 5.51 (1 H, s), 6.35 (1 H, dd, *J* 4.9 and 1.0); ^{13}C NMR ($CDCl_3$) δ major isomer 20.0, 23.1, 39.0, 39.5, 40.4, 55.3, 75.4, 76.2, 78.6, 113.8, 114.2, 116.4, 127.4, 128.3, 132.4, 134.8, 143.9, 158.5, 159.4, 161.5 and 172.1. Anal. Calcd. for $C_{26}H_{28}O_7$: C, 69.01 ; H, 6.24. Found : C, 68.55 ; H, 6.26.

Dihydropyran (+)-23c. Heterodiene (-)-**22c** (5.17 g, 9.5 mmol), 4-methoxystyrene (3.82 g, 28.5 mmol) in toluene (5 mL) and hexane (45 mL), after 3 days at 60°C and 3 days at 110°C, gave a *ca.* 95 : 5 diastereomeric

mixture of cycloadduct (+)-**23c** (4.83 g, 76%) as yellow solid, mp 75-80°C, $[\alpha]_D$ +105 (*c* 0.8, acetone); R_f 0.47 cyclohexane-AcOEt (6 : 4); IR (film) 1791 (C=O lactone), 1735 (C=O ester), 1643 (C=C), 1610 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) δ major isomer 1.10 (9 H, s), 1.97 (1 H_{ax}, ddd, *J* 13.8, 11.4 and 11.4), 2.34 (1 H_{eq}, dddd, *J* 13.8, 6.5, 1.4 and 1.4), 3.80 (3 H, s), 3.81 (3 H, s), 3.82 (1 H_{ax}, m), 4.21 (1 H, dd, *J* 11.4 and 3.3), 4.31 (1 H, d, *J* 11.4), 4.41 (1 H, d, *J* 5.2), 5.04 (1 H_{ax}, dd, *J* 11.4 and 1.4), 5.22 (1 H, dd, *J* 5.2 and 3.3), 6.30 (1 H, s), 6.88 (2 H, d, *J* 8.7), 6.89 (2 H, d, *J* 8.7),7.16 (2 H, d, *J* 8.6), 7.33 (2 H, d, *J* 8.6), 7.30-7.80 (10 H, m); minor isomer detected by the following signals : 4.51 (1 H, d, *J* 5.0), 5.30 (1 H, dd,), 6.35 (1 H, s); ^{13}C NMR ($CDCl_3$) δ major isomer 19.3, 26.6, 39.0, 39.4, 55.3, 68.8, 69.3, 71.1, 78.8, 113.9, 114.2, 116.5, 127.4, 127.8, 127.9, 128.2, 130.2, 130.3, 131.8, 132.3, 134.7, 135.7, 135.9, 144.1, 158.6, 159.4, 161.8 and 172.8. HRMS: Found: $M^{+\cdot}$, 621.1949. $(C_{40}H_{42}O_8Si\text{-}C_4H_9)^{+\cdot}$ requires *M*, 621.1944.

Dihydropyran (+)-8a. To a solution of (+)-**23c** (3.0 g, 4.42 mmol) in dry methanol (10 mL), LiOH (0.11 g, 4.42 mmol) was added portionwise. After stirring at room temperature for 4 h, The solvent was removed under reduced pressure and the residue was partitioned between AcOEt and water. After decantation and concentration of the organic phase, the residue (3.29 g) thus obtained was purified by column chromatography (using cyclohexane/AcOEt 85:15 as eluent), and afforded the pure methyl ester (+)-**8a** (1.40 g, 90%) as white needles, mp 79-80°C, $[\alpha]_D$ +134 (c 0.9, acetone), ee. 93% (^1H NMR with Eu[hfc]$_3$). The spectral data of (+)-**8a** were in full agreement with those given above for the racemic methyl ester **8a**.

α-Methoxycarbonyltetrahydropyran (+)-14. Using the same procedure as in the racemic series, the dihydropyran (+)-**23d** (0.85 g, 2.41 mmol) was hydrogenated over a 10% Pd-charcoal catalyst under 3 bars, and gave the tetrahydropyran (+)-**14** (0.83 g, 97%) as an oil, $[\alpha]_D$ +16.6 (c 0.7, acetone). The spectral data of (+)-**14** were in full agreement with those reported above for the racemic tetrahydropyran (±)-**14**.

α-Carboxytetrahydropyran (+)-15. Using the same procedure as in the racemic series, the α-methoxycarbonyltetrahydropyran (+)-**14** (0.93 g, 2.62 mmol) was converted into the corresponding free acid (+)-**15** (0.80 g, 86%) as needles, mp 140-141°C and $[\alpha]_D$ +25 (c 0.6, acetone). The spectral data of (+)-**15** were in full agreement with those reported above for the racemic acid (±)-**15**.

Dihydropyran (+)-11. Using the same procedure as in the racemic series, the α-carboxytetrahydropyran (+)-**15** (1.08 g, 3.15 mmol) was degraded into the dihydropyran (+)-**11** (0.47 g, 44%), mp 79-80°C (needles) and [α] +133 (c 1, acetone), having the same spectral data as the racemic compound (±)-**11** described above.

(-)-O-Dimethylsugiresinol (-)-2. Using the same procedure as in the racemic series, hydroboration-oxidation of the (+)-dihydropyran (+)-**11** (0.34 g, 1.15 mmol) was converted into "natural" (-)-*O*-dimethylsugiresinol (-)-**2** (0.155 g, 45%), mp 99-100°C (needles) and $[\alpha]_D$ -4.0 (c 0.8, $CHCl_3$). Lit.[2] mp 104-105°C and $[\alpha]_D$ -4.0 (c 1.0, $CHCl_3$). Compound (-)-**2** was enantiomerically pure, as evidenced from the ^1H NMR spectrum run in the presence of Eu(hfc)$_3$. Its spectral data were in full agreement with those reported above for the racemic compound (±)-**2**.

(+)-O-Dimethylsugiresinone (+)-26. To a mixture of (-)-*O*-dimethylsugiresinol (-)-**2** (0,030 g, 0.1 mmol) and 3 Å molecular sieves (50 mg) in CH_2Cl_2 (2 mL) was added portionwise pyridiniumchlorochromate (60 mg, 0.3 mmol). After stirring for 2 h at RT, the reaction mixture was chromatographed

(cyclohexane/AcOEt 90/10) to give an oily mixture (12 mg, 40%) of (+)-**26** and its C-4 epimer [ratio (+)-**26**/epi-**26** : 87/13], R_f 0.37 (cyclohexane/AcOEt 6:4) ; $[\alpha]_D$ +20.0 (c 0.6, $CHCl_3$). Lit.[12] $[\alpha]_D$ +21 ($CHCl_3$). IR ($CDCl_3$) 1725 (C=O), 1614 and 1513 cm^{-1} ; ^1H NMR ($CDCl_3$) (for (+)-**26**) δ 2.63 (2H, dd, *J* 8.1 and 6.7), 3.80 (3H, s), 3.82 (3H, s), 4.03 (1Heq, t, *J* 8.1), 4.21 (1H, AB, *J* 17.0), 4.33 (1H, AB, *J* 17.0), 4.96 (1H, dd), 6.91 (2H, d), 6.92 (2H, d), 7.13 (2H, d), 7.38 (2H, d) ; ^{13}C NMR ($CDCl_3$) (for (+)-**26**) δ 37.0, 49.2, 55.3 (x2), 73.0, 77.2, 114.0, 114.1, 127.1, 129.6, 129.3, 132.7, 158.8, 159.4, 209.6.

References

(1) Whiting, D.A. *Nat. Prod. Reports* **1987**, *4*, 499-525.

(2) a) Muraoka, O. ; Zheng, B.-Z. ; Fujiwara, N. ; Tanabe, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 405-11, and references therein ; b) Muraoka, O. ; Fujiwara, N. ; Tanabe, G. ; Momose, T. *Tetrahedron : Asymmetry* **1991**, *2*, 357-8.

(3) a) Beracierta, A.P. ; Whiting, D.A. *Tetrahedron Lett.* **1976**, *27*, 2367-70 ; b) Beracierta, A.P. ; Whiting, D.A. *J. Chem. Soc., Perkin Trans. I* **1978**, 1257-63.

(4) Horii, Z. ; Iwata, C. ; Tanaka, T. ; Momose, T. *Heterocycles* **1977**, *6*, 697-9.

(5) Horii, Z. ; Go, A. ; Momose, T. ; Iwata, C. *Chem. Pharm. Bull.* **1971**, *19*, 2212-3.

(6) Dujardin, G. ; Maudet, M. ; Brown, E. *Tetrahedron Lett.* **1994**, *45*, 8619-22.

(7) Fristad, W.E. ; Fry, M.A. ; Klang, J.A. *J. Org. Chem.* **1983**, *48*, 3575-7.

(8) Martin, J.D. ; Pérez, C. ; Ravelo, J.L. *J. Amer. Chem. Soc.* **1985**, *107*, 516-8.

(9) Shiozaki, M. *J. Org. Chem.* **1991**, *56*, 528-32.

(10) Dujardin, G. ; Maudet, M. ; Brown, E. *Tetrahedron Lett.* , in press.

(11) Cohen, N. ; Banner, B.L. ; Laurenzano, A.J. ; Carozza, L. *Organic Syntheses* **1985**, *63*, 127-35.

(12) Enzell, C.R. ; Hirose, Y. ; Thomas, B.R. ; *Tetrahedron Lett.* **1966**, 793-6.

(13) Creary, X. ; Inocencio, P.A. ; Underiner, T.L. ; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932-8.

(14) Keays, J.L. *Acta Chem. Scand.* **1954**, *8*, 336-8.

(15) Stecher, E.D. ; Ryder, H.F. *J. Amer. Chem. Soc.* **1952**, *74*, 4392-5.

(16) Powell, E.P. ; Varsel, C.J. *Anal. Chem.* **1963**, *35*, 184-9.

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