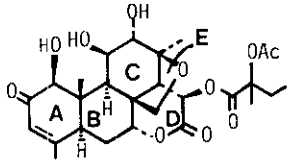
SYNTHETIC STUDIES TOWARDS (-)-QUASSIMARIN: AN INTRAMOLECULAR DIELS-ALDER APPROACH TO THE BCE RING SYSTEM[1]

Kozo Shishido, Kazuyuki Takahashi, Yoshihisa Oshio, and Keiichiro Fukumoto*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Tetsuji Kametani and Toshio Honda
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract—— A novel and a chiral approach to the synthesis of BCE ring system of (-)-quassimarin is described which involves an intramolecular Diels-Alder reaction of the trienic precursor (**18**) as a key step. The key dihydrofuranone (**17**) was prepared from L-(+)-diethyl tartrate via 14 step sequence. The quaternary carbon centre in (**17**) was stereoselectively constructed by magnesium chelation controlled addition of α-lithio-α-methoxyallene to α,β-dialkoxy ketone. Thermolysis of the triene (**18**) and subsequent hydrolysis provided two tricyclic cycloadducts (**19**) and (**20**), both structures were characterized spectroscopically as the corresponding acetates (**21**) and (**22**). Particularly, the major adduct (**21**) was established by the X-ray crystallographic analysis.

The quassinoid quassimarin (**1**) was first isolated from Quassia amara by Kupchan[2] and was found to show significant activity in vivo against the P-388 lymphocytic leukemia in mice and in vitro against cells derived from a human carcinoma, nasopharynx. Although intensive efforts have long been directed towards the total synthesis[3] of the quassinoid having intriguing molecular architecture, to date no total synthesis has yet been accomplished.

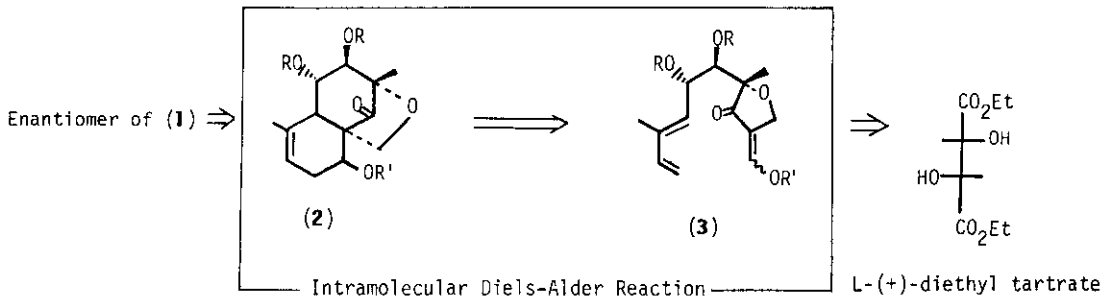


(+)-quassimarin (**1**)

Figure 1.

In connection with our interest[1,3b] in the total synthesis of antitumor quassinoids in an optically pure form, we have undertaken the development of efficient route to a tricyclic chiral synthon (**2**), with the BCE ring system of the enantiomer of (**1**), starting from L-(+)-diethyl tartrate. In this paper, we now report full experimental details of our synthetic efforts for the tricycle.

Scheme 1 summarizes our basic synthetic strategy. We envisaged that the tricyclic synthon (**2**), which contains strategically situated latent functionalities for the elaboration of (-)-quassimarin, might be prepared from the triene (**3**) via an intramolecular Diels-Alder reaction. The triene (**3**) in turn might be assembled via several suitable transformations, such as a diastereoselective introduction of dihydrofuranone ring by methoxyallene annulation[3b,4], from L-(+)-diethyl tartrate.



Scheme 1.

RESULTS and DISCUSSION

According to the procedure of Mukaiyama[5], the monobenzyl ether (**6**) was prepared. Protection of the diol in L-(+)-diethyl tartrate followed by lithium aluminium hydride ($LiAlH_4$) reduction of the resulting acetal (**4**) produced the diol (**5**) which was then partially benzylated with 1 equivalent (eq.) of benzyl bromide and 1 eq. of sodium hydride (NaH) to provide (**6**). To introduce the diene moiety, Swern oxidation[6] of (**6**) afforded the aldehyde (**7**), which was immediately condensed with (α-carbomethoxyethylidene)triphenylphosphorane[7] to provide the unsaturated ester (**8**) as an inseparable isomeric mixture.[8] Reduction of (**8**) with $LiAlH_4$ produced the E-allylic alcohol (**9**) and Z-isomer (**10**) as an easily separable 12:1 mixture in 84 % overall yield from (**6**). Chemoselective hydrogenolytic cleavage[9] of the benzyl ether of the E-allyl alcohol (**9**) was accomplished by treatment of a solution of the corresponding sodium alkoxide in tetrahydrofuran (THF), generated in situ from exposure of (**9**) to 2 eq. of NaH, with 5 eq. of lithium in liquid ammonia in the presence of t-butanol (liq. NH_3: t-BuOH: THF=1.5:0.8:1)† at -78°C to produce 93 % of the diol (**11**). Oxidation of the allyl alcohol moiety in (**11**) with manganese oxide in methylene dichloride and subsequent reaction of the resulting

† The best result could be obtained by using this ratio.

unsaturated aldehyde (**12**) with methylenetriphenylphosphorane in THF provided the diene (**13**) in 69 % yield from (**11**). With diene in hand the stage was set to carry out the key diastereoselective quaternary carbon construction. Initially, the alcohol (**13**) was oxidized with the condition of Swern to provide the aldehyde (**14**), which was then immediately treated with 3 eq. of methyllithium affording the secondary alcohol (**15**) as a mixture of two diastereomers. Then the next three-step conversion of (**15**) to (**17**) was performed without isolation of the products. Thus, Swern oxidation of (**15**) followed by addition of 4 eq. of α-lithio- α-methoxyallene[10], generated in situ by treatment of α-methoxyallene with n-butyllithium, to the resultant methyl ketone (**16**) at -78°C provided the labile adduct which was refluxed with potassium t-butoxide in the presence of 18-crown-6 in t-butanol, then further treated the resulting mixture with the condition of acid hydrolysis (1M aqueous hydrochloric acid) at room temperature to produce the dihydrofuranone[4] (**17**) as an inseparable mixture of two diastereomers in a ratio of 1:1 (from ^{1}H nmr). To achieve the desired diastereoselection in the course of addition reaction[11], it seemed to be necessary to choose the condition forming more tight metal ion chelation[12] in the transition state (via cyclic-Cram diastereoselection) (Figure 2). In fact, addition of α-lithio- α-methoxyallene to the methyl ketone (**16**) in the presence of 6 eq. of magnesium bromide[13] followed by the

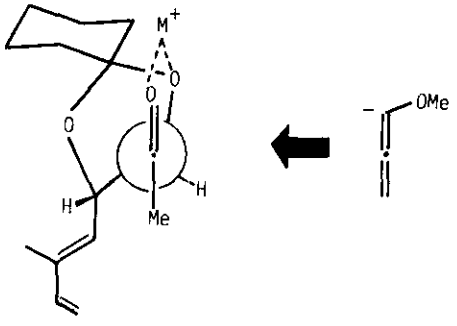
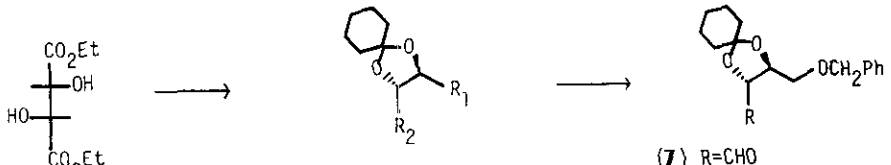
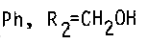


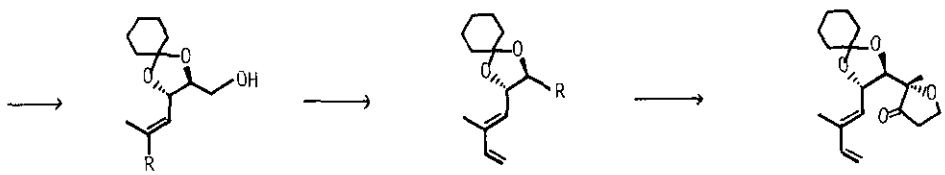
Figure 2.

same treatment as above furnished the desired dihydrofuranone (**17**), which exhibited a single ^{1}H nmr resonance and a single set of ^{13}C nmr signals, in 16 % overall yield from (**15**). At this point, the absolute configuration of the newly formed quaternary centre could not be determined spectroscopically, and it was firmly established as desired S by the eventual conversion of (**17**) to (**21**).



(**4**) R_1=R_2=CO_2Et
(**5**) R_1=R_2=CH_2OH
(**6**) R_1=CH_2OCH_2Ph, R_2=CH_2OH

(**7**) R=CHO
(**8**) R= 
(**9**) R=  (E)
(**10**) R= (Z)



(11) R=CH_2OH
(12) R=CHO
(13) R= $CH=CH_2$

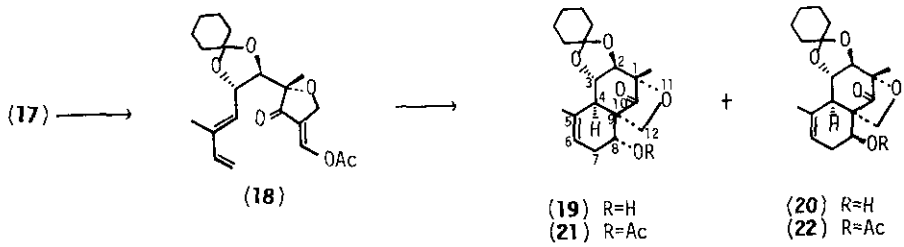
(14) R=CHO
(15) R=CHMeOH
(16) R=COMe

(17)

Scheme 2.

Introduction of dienophile portion to an α-position of carbonyl group in (17) was performed with the procedure described as follows. *Formylation of* (17) was effected with ethyl formate and NaH as a base to yield the labile hydroxymethylene which was *immediately acetylated* with acetyl chloride and triethylamine to provide the triene (18) as a single product. On the basis of the chemical shift (δ_H 8.13)[3b,14] of the olefinic proton at the acetoxy-bearing carbon, E-geometry for the dienophile moiety was assigned.

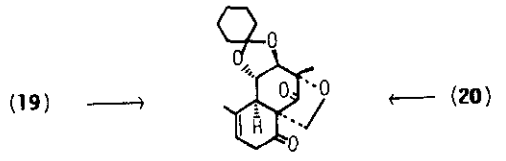
With successful synthesis of the desired triene (18) behind us we were ready to effect the crucial intramolecular Diels-Alder reaction. On heating a solution of (18) in xylene in a sealed tube at 180°C for 53 h[††], the tricyclic adducts were obtained as an inseparable mixture of two diastereomers which was then hydrolized with aqueous lithium hydroxide to give chromatographically separable two isomeric alcohols (19) and (20) in 18 % and 7 % yield *from* (18), respectively.



(18)

(19) R=H
(21) R=Ac

(20) R=H
(22) R=Ac



(23)

Scheme 3.

The structural assignments of (19) and (20) rest on ^1H nmr decoupling experiments at 400 MHz of the corresponding acetates (21) and (22), derived from a standard

†† Although the Lewis acid (e.g. Et_2AlCl, $TiCl_4$, or $BF_3 \cdot OEt_2$) catalyzed cycloaddition was also examined under various conditions, no cycloadducts could be obtained.

acetylation. In the major acetate (21)[$\nu_{max.}$ ($CHCl_3$) 1770 and 1740 cm^{-1}; m/z 376 (M^+)], the methine proton at C-3 was observed at higher field (δ_H 3.02), owing to an anisotropy of the C-10 carbonyl, as a triplet with J 10.7 Hz due to two trans diaxial couplings with 2-H and 4-H indicating that the configurations at C-4 and C-9 should be R and S, respectively. The configuration at C-8 was also deduced as R on the basis of the chemical shift and the coupling pattern of quasi-equatorially oriented 8-H at δ_H 5.13 as a doublet with J 4.0 Hz. On the other hand, the C-3 methine of the minor acetate (22)[$\nu_{max.}$ ($CHCl_3$) 1770 and 1740 cm^{-1}; m/z 376 (M^+)] was also observed at higher field (δ_H 3.07) as a triplet with J 10.7 Hz and the 8-H resonated at δ_H 4.88 as a double doublet with J 10.5 and 6.0 Hz suggesting that both (21) and (22) would be epimeric at C-8. Furthermore, from the fact that independent oxidation of the alcohols (19) and (20) with pyridinium dichromate afforded the same labile diketone[†††](23) [$\nu_{max.}$ ($CHCl_3$) 1760 and 1735 cm^{-1}] as a single product, our presumption could be substantiated. Eventually, the whole structure and the stereochemistry of the major acetate (21) were unambiguously established by a single-crystal X-ray analysis (Figure 3, see Experimental Section).

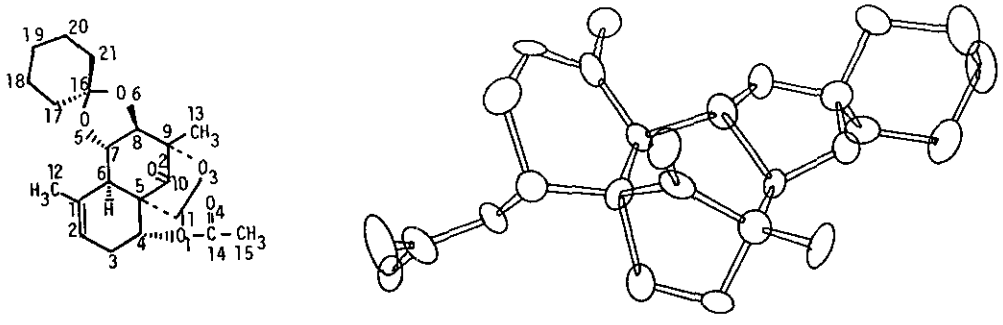


Figure 3. Molecular structure of (21).

Despite the homogeneity of the starting triene (18), the occurrence of an epimerization at C-8 might be explainable by an equilibration via a retro Diels-Alder reaction and re-addition under such considerably harsher thermal conditions[15] (at 180°C for 53 h). From these results, it was found that the intramolecular Diels-Alder reaction of (18) proceeded in a highly endo-selective manner, completely opposite result that of Schlessinger.[3f] Examination of Dreiding molecular models of the two transition states available to (18) reveals that considerable non-bonding interactions develop between the methine at C-3, C-5 methyl, and one of

††† The both products prepared by independent oxidation of (19) and (20) were proved to be completely identical by the behavior on TLC using four different kinds of solvent systems.

Table 1.

Atomic co-ordinates (x 10^4) for compound (21)
with standard deviations in parentheses

Atom	x	y	z
C(1)	3336(10)	6809(0)	10149(13)
C(2)	3302(11)	8605(37)	9382(15)
C(3)	2463(13)	10029(34)	8900(18)
C(4)	1610(12)	8694(33)	8890(12)
C(5)	1690(10)	7461(28)	10120(14)
C(6)	2578(10)	6223(26)	10616(12)
C(7)	2847(10)	6457(34)	12077(14)
C(8)	2036(10)	5973(26)	12582(12)
C(9)	1266(11)	7676(29)	12111(2)
C(10)	1551(10)	9131(23)	11163(14)
C(11)	814(11)	6187(27)	10042(14)
C(12)	4182(11)	5556(40)	10486(17)
C(13)	885(13)	8867(35)	13061(16)
C(14)	1099(11)	7394(34)	6776(15)
C(15)	1015(13)	5467(37)	5925(14)
C(16)	3287(11)	4939(34)	14033(16)
C(17)	4059(11)	6063(42)	15001(16)
C(18)	3923(2)	5936(11)	16396(0)
C(19)	3918(19)	3346(51)	16639(18)
C(20)	3131(15)	2228(36)	15688(19)
C(21)	3260(12)	2452(29)	14342(18)
O(1)	1490(6)	6918(18)	7987(8)
O(2)	1664(8)	11030(20)	11210(10)
O(3)	543(6)	6544(19)	11190(9)
O(4)	848(12)	9177(32)	6421(12)
O(5)	349(8)	5011(21)	12821(9)
O(6)	245(7)	5982(19)	13922(9)

the 12-H in the exo-transition state ($T_1^{\ddagger}$), whereas this type of interactions are absent altogether in the endo-transition state ($T_2^{\ddagger}$). This interaction very well may account for the selectivity realized in the cyclization of (18). The low yield of the cycloaddition process may be attributed to the poor overlapping of π-orbital. (Figure 4)

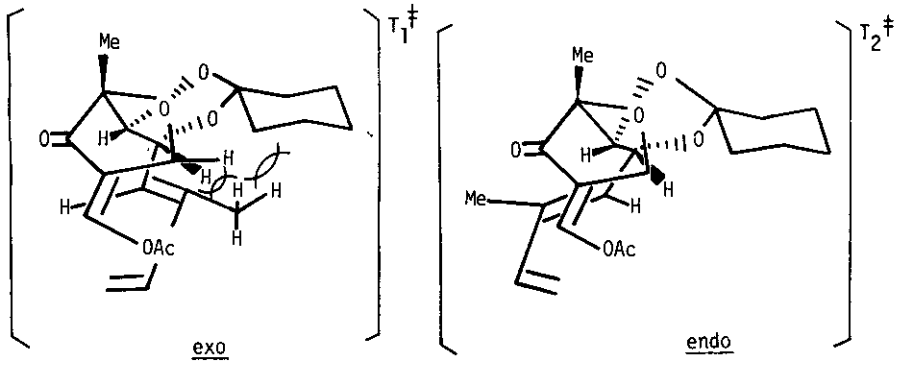


Figure 4. Transition states for thermolysis of (18).

In conclusion, we could establish a methodology for a highly diastereoselective construction of quaternary carbon with accurate configuration in the dihydrofuranone, E ring of quassimarin, from an α,β-dialkoxy ketone precursor and could

also reveal the stereochemical aspect of intramolecular Diels-Alder reaction providing a tricyclic BCE ring system. The two points thus clarified should be considerably helpful for our approach to the total synthesis of the enantiomer of natural quassimarin.

EXPERIMENTAL

General Methods.—— Melting points were determined on a Yanako micro-melting point apparatus and are uncorrected. Ir spectra were measured with Hitachi 260-10 recording spectrophotometer, nmr spectra with JEOL JNM-PMX-60, JEOL PS-100, JEOL FX-100, and JEOL JNM-GX-400 spectrometers. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Mass spectra were taken on a Hitachi M 52-G spectrometer and JEOL-TMS-01SG-2 spectrometer. All optical rotations were measured in chloroform solution on a JASCO DIP-340 and JASCO DIP-360 polarimeter. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue when the organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure. All new compounds described in the Experimental Section were homogeneous on tlc.

(2R,3R)-Dicarbethoxy-1,4-dioxaspiro[4,5]decane (4). A solution of L-(+)-diethyl tartrate (50.6 g, 0.245 mol) in benzene (800 ml) was refluxed for 24 h with cyclohexanone (29.1 g, 0.295 mol) and a catalytic amount of p-toluenesulphonic acid in a Dean-Stark water separator. The reaction mixture was washed successively with water and saturated brine. The residue upon work-up was submitted to vacuum distillation, bp 120-140°C at 1 mmHg, to give the acetal (**4**) (58.6 g, 83 %) as an oil; ir $\nu_{max.}$ (neat) 1760 cm^{-1}; ^1H nmr δ_H (60 MHz; $CDCl_3$) 1.14(6H, t, J=7 Hz, $COCH_2\underline{CH}_3$ x 2), 1.67(10H, br s, $(CH_2)_5C<$), 4.23(4H, t, J=7 Hz, $CO\underline{CH}_2CH_3$ x 2), 5.04(2H, s, $CH_2-\underline{CH}-$ x 2); ms m/z 286 (M^+).

(2S,3S)-2,3-Dihydroxymethyl-1,4-dioxaspiro[4,5]decane (5). To a stirred suspension of lithium aluminium hydride (25.8 g, 0.678 mol) in anhydrous tetrahydrofuran (THF) (700 ml) was added dropwise a solution of the ester (**4**) (77.6 g, 0.271 mol) in anhydrous THF (400 ml) at 0°C. Stirring was continued for 30 min, then the mixture was quenched with ether containing water at 0°C. After filtration through Celite, the filtrate was concentrated to give the residue which was submitted to vacuum distillation, b.p. 130-140°C at 0.05 mmHg, to give the diol (**5**) (40.6 g, 74 %) as an oil; ir $\nu_{max.}$ (neat) 3400 cm^{-1}; ^1H nmr δ_H(60 MHz, $CDCl_3$) 1.60(10H, br s, $(CH_2)_5C<$), 2.68(2H, t, J=8 Hz, OH x 2), 3.66 4.00 (6H, m); ms m/z 202 (M^+).

(+)-(2S,3S)-3-Benzyloxymethyl-2-hydroxymethyl-1,4-dioxaspiro[4,5]decane.[5] (6) To a stirred suspension of sodium hydride (60 % in oil; 2.02 g, 0.0505 mol) in anhydrous dimethylformamide (DMF) (80 ml) was added dropwise a solution of the diol (**5**) (9.60 g, 0.0475 mol) in anhydrous DMF (50 ml) at -20°C. Stirring was continued for 30 min, then a solution of benzyl bromide (8.38 g, 0.049 mol) in anhydrous DMF (20 ml) was added dropwise to the mixture. The mixture was stirred at room temperature for 12 h, after which the solvent was evaporated off, the residue extracted with methylene dichloride, and the organic phase was washed with saturated brine. The residue upon work-up was chromatographed using hexane-ethyl acetate (4:1, v/v) as eluant to afford the alcohol (**6**) (10.50 g, 76 %) as an oil,

$[\alpha]_D^{24}$ +0.90° (c=1.32); ir $\nu_{max.}$ (neat) 3450 cm^{-1}; ^1H nmr δ_H(60 MHz, $CDCl_3$) 1.59(10H, br s, $(CH_2)_5C<$), 4.55(2H, s, $C\underline{H}_2Ph$), 7.28(5H, s, ArH); ms m/z 292 ($\underline{M}^+$).

(2S,3S)-3-Benzyloxymethyl-2-(2-carbomethoxy-1-propenyl)-1,4-dioxaspiro[4,5]decane (8). To a stirred solution of oxalyl chloride (8.13 g, 0.064 mol) in anhydrous methylene dichloride (240 ml) was added dropwise dimethyl sulphoxide (DMSO) (12.94 g, 0.128 mol) at -78°C. To the mixture was added dropwise a solution of the alcohol (6) (17.7 g, 0.058 mol) in anhydrous methylene dichloride (100 ml) and stirring was continued for 15 min. Triethylamine (29.56 g, 0.219 mol) was then added dropwise at the same temperature. The mixture was stirred for 30 min at room temperature, after which it was diluted with water and the aqueous layer was separated and extracted with methylene dichloride. The combined organic phases were washed with saturated brine and the residue upon work-up gave the aldehyde (7) (18.09 g) as an oil; ir $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$) 9.69(1H, br s, CHO). This compound was used in the next reaction without further purification.

A solution of the crude aldehyde (7) (18.09 g) and (α-carbomethoxyethylidene)triphenylphosphorane (20.2 g, 0.058 mol) in anhydrous benzene (400 ml) was stirred for 12 h at 70°C. The mixture was diluted with water and the aqueous phase was extracted with benzene. The combined organic phases were then washed with saturated brine and the residue upon work-up was chromatographed using hexane-ethyl acetate (9:1, v/v) as eluant to afford the ester (8) (20.2 g, 92 %), a mixture of two isomers, as an oil (Found: C, 70.37; H, 7.46. $C_{21}H_{28}O_5$ requires C, 69.97; H, 7.83 %); ir $\nu_{max.}$ ($CHCl_3$) 1710 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$) 1.63(10H, br s, $(CH_2)_5C<$), 1.87(3H, d, J=2 Hz, olefinic CH_3), 3.60(2H, d, J=4 Hz, $C\underline{H}_2OPh$), 3.70(3H, s, $CO_2C\underline{H}_3$), 3.93(1H, dd, J=4 and 8 Hz, CH_2-$C\underline{H}$(O)-), 4.57(2H, s, $C\underline{H}_2Ph$), 4.70(1H, t, J=8 Hz, $C\underline{H}$-C(=O)<), 6.60(1H, dd, J 2 and 8 Hz, olefinic H), 7.30(5H, s, ArH); ms m/z 360 ($\underline{M}^+$).

(-)-(2S,3S)-2-Benzyloxylmethyl-3-[3-hydroxy-2-methyl-1(E)-propenyl]-1,4-dioxaspiro[4,5]decane (9) and (-)-(2S,3S)-Benzyloxymethyl-3-[3-hydroxy-2-methyl-1(Z)-propenyl]-1,4-dioxaspiro[4,5]decane (10) To a solution of lithium aluminium hydride (0.57 g, 0.0151 mol) in anhydrous THF (70 ml) was added dropwise a solution of the ester (8) (5.00 g, 0.0151 mol) in anhydrous THF (30 ml) at 0°C. Stirring was continued for 30 min, then the mixture was quenched with ether containing water. After filtration through Celite, the filtrate upon work-up was chromatographed using hexane-ethyl acetate (4:1, v/v) as eluant to afford the alcohol (10) (0.32 g, 7 %) as an oil; $[\alpha]_D^{25}$-24.4° (c=1.71); ir $\nu_{max.}$($CHCl_3$) 3450 cm^{-1}; ^1H nmr δ_H (100 MHz, $CDCl_3$) 1.50(10H, br s, $(CH_2)_5C<$), 1.74(3H, d, J=1.5 Hz, olefinic CH_3), 3.52(2H, d, J=5.0 Hz, $C\underline{H}_2OBn$), 4.10(2H, br s, $C\underline{H}_2OH$), 4.57(1H, t, J=8.0 Hz, $CH_2C\underline{H}$-O-), 5.43(1H, br d, J=8.0 Hz, olefinic H), 7.25(5H, s, ArH) (Found: $\underline{M}^+$, 332.1987. $C_{20}H_{28}O_4$ requires M, 332.1987). From the later fractions, the alcohol (9) (3.88 g, 84 %) was obtained as an oil (Found: C, 72.62; H, 8.47. $C_{20}H_{28}O_4$ requires C, 72.26; H 8.49 %); $[\alpha]_D^{25}$-25.3° (c=6.28); ir $\nu_{max.}$ ($CHCl_3$) 3400 cm^{-1}; ^1H nmr δ_H (100 MHz, $CDCl_3$) 1.64(10H, br s, $(CH_2)_5C<$), 1.66(3H, s, olefinic CH_3), 3.56(2H, d, J=4.0 Hz, $C\underline{H}_2OBn$), 3.86(1H, dd, J=4.0 and 9.0 Hz, CH_2-$C\underline{H}$(O)-), 4.00(2H, br s, $C\underline{H}_2OH$), 4.57(2H, s, $C\underline{H}_2Ph$), 4.60(1H, t, J 9.0 Hz, CH_2=CHC$\underline{H}$), 5.44(1H, m, olefinic H); ms m/z 332 ($\underline{M}^+$).

(-)-(2S,3S)-2-Hydroxymethyl-3-[3-hydroxy-2-methyl-1(E)-propenyl]-1,4-dioxaspiro[4,5]decane (11) To a suspension of sodium hydride (60 % in oil; 4.6 g, 0.115 mol) in anhydrous THF (130 ml) was added a solution of the alcohol (**9**) (17.28 g, 0.052 mol) in anhydrous THF (70 ml). After being stirred for 1 hr at room temperature, to the mixture was added liq. NH_3 (300 ml) and t-butyl alcohol (160 ml) at -78°C. Stirring was continued for 10 min, then lithium (1.8 g, 0.26 g-atom) was added to the mixture. After being stirred for 10 min at the same temperature, the reaction mixture was treated with an excess ethanol, and the solvent was evaporated off. The residue was diluted with water, and the resulting mixture was extracted with ether. The extract was washed with saturated brine, then the residue upon work-up was chromatographed using methanol-chloroform (5:95, v/v) as eluant to afford the diol (**11**) (11.76 g, 93 %) as an oil; $[\alpha]_D^{23}$ -35.3° (c=1.56); ir $\nu_{max.}$ ($CHCl_3$) 3450 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$), 1.59(10H, br s, $(CH_2)_5C<$), 1.70(3H, s, olefinic CH_3), 2.70(2H, br s, CH_2OH), 5.40(1H, d, J=8 Hz, olefinic H) (Found: M^+, 242.1518. $C_{13}H_{22}O_4$ requires M, 242.1518).

(-)-(2S,3S)-2-Hydroxymethyl-3-[2-methyl-1(E),3-butadienyl]-1,4-dioxaspiro[4,5]-decane (13) To a stirred solution of the alcohol (**11**) (16.81 g, 0.0669 mol) in anhydrous methylene dichloride (450 ml) was added manganese oxide (120 g, 1.38 mol), the mixture was stirred for 7 hr at room temperature. After filtration through Celite, the filtrate was evaporated to give the aldehyde (**12**) (10.01 g) as an oil; ir $\nu_{max.}$ ($CHCl_3$) 3550, 1680 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$), 1.66(10H, br s, $(CH_2)_5C<$), 1.83(3H, s, olefinic CH_3), 4.85(1H, t, J=8 Hz, CH_2-CH-), 6.40(1H, d, J=8 Hz, olefinic H); ms m/z 240 (M^+). This compound was used in the next reaction without further purification.

To a suspension of methyltriphenylphosphonium bromide (43.4 g, 0.125 mol) in anhydrous THF (200 ml) was added dropwise n-butyllithium (1.278 M-hexane solution; 105.7 ml) at room temperature and the mixture was stirred for 1 hr. To the mixture was added a solution of the aldehyde (**12**) (10.01 g) in anhydrous THF (100 ml). The mixture was stirred for 1 hr, and then diluted with saturated aqueous ammonium chloride and most of THF was removed under reduced pressure. The resulting mixture was extracted with ether and the organic phase was washed with saturated brine. The residue upon work-up was chromatographed using hexane-ethyl acetate (4:1, v/v) as eluant to afford the diene (**13**) (6.80 g, 69 %) as an oil (Found: C, 70.38; H, 9.05. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.31 %); ir $\nu_{max.}$($CHCl_3$) 3450 cm^{-1}; ^1H nmr δ_H (60 MHz; $CDCl_3$), 1.63(10H, br s, $(CH_2)_5C<$), 1.83(3H, s, olefinic CH_3), 3.26-4.03(3H, m), 4.53-5.60(4H, m), 6.35(1H, dd, J=11 and 18 Hz, olefinic H); ms m/z 238 (M^+).

(2S,3S)-2-(1-Hydroxyethyl)-3-[2-methyl-1(E),3-butadienyl]-1,4-dioxaspiro[4,5]-decane (15) To a solution of oxalyl chloride (2.60 g, 0.0206 mol) in anhydrous methylene dichloride (60 ml) was added dropwise DMSO (3.21 g, 0.0411 mol) at -78°C. To the mixture was added dropwise a solution of the alcohol (**13**) (4.45 g, 0.0187 mol) in anhydrous methylene dichloride (40 ml) and stirring was continued for 15 min. Triethylamine (8.49 g, 0.0841 mol) was then added dropwise at the same temperature. The mixture was stirred for 1 hr at room temperature after which it was diluted with water and the aqueous phase was separated and extracted with methylene dichloride. The extracts were washed with saturated brine and the

residue upon work-up gave the aldehyde (**14**) (4.50 g) as an oil, which was used in the next reaction without further purification. To a solution of the aldehyde (**14**) (4.50 g) in anhydrous ether (80 ml) was added dropwise a solution of methyllithium (1.21M-ether solution; 41.0ml) at -78°C and the mixture was stirred for 1 hr at the same temperature, and then quenched with saturated aqueous ammonium chloride. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with saturated brine. The residue upon work-up was chromatographed using hexane-ethyl acetate (9:1,v/v) as eluant to afford the alcohol (**15**) (3.87 g, 82 %), an inseparable mixture of two diastereomers, as an oil; ir $\nu_{max.}$ (neat) 3450 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$), 1.01(3H, d, J=6 Hz, $C\underline{H}_3CHOH$), 1.63(10H, br s, $(CH_2)_5C\lessgtr$), 1.90(3H, s, olefinic CH_3), 3.59-4.20(2H, m), 4.66-5.56(4H, m), 6.40(1H, dd, J=10 and 18 Hz, olefinic H). (Found: M^+, 252.1705. $C_{15}H_{24}O_3$ requires M, 252.1680).

(-)-(2R,3S)-[2-Methyl-1(E),3-butadienyl]-2-[2-(2S)-(2-methyl-3-oxo-2,3,4,5-tetrahydro)furyl]-1,4-dioxaspiro[4,5]decane (17) To a solution of oxalyl chloride (78 mg, 0.611 mmol) in anhydrous methylene dichloride (3 ml) was added dropwise DMSO (95 mg, 1.22 mmol) at -78°C. To the mixture was added dropwise a solution of the alcohol (**15**) (140 mg, 0.556 mmol) in anhydrous methylene dichloride (1 ml) and stirring was continued for 15 min at the same temperature. Triethylamine (281 mg, 2.78 mmol) was then added dropwise, and the mixture was stirred for 1 hr at room temperature after which it was diluted with water and the aqueous phase was separated and extracted with methylene dichloride. The extracts were washed with saturated brine and the residue upon work-up gave the ketone (**16**) (150 mg) as an oil; ir $\nu_{max.}$ ($CHCl_3$) 1720 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$), 1.66(10H, br s, $(CH_2)_5C\lessgtr$), 1.82(3H, s, olefinic CH_3), 2.24(3H, s, $COCH_3$), 4.07(1H, d, J=8 Hz, CH_2-C<u>H</u>-O-), 4.66-5.60(4H, m), 6.37(1H, dd, J=10 and 18 Hz, olefinic H) (Found: M^+, 250.1591. $C_{15}H_{22}O_3$ requires M, 250.1569). This compound was used in the next reaction without further purification.

To a solution of n-butyllithium (1.30M-hexane solution; 1.54 ml) in anhydrous THF (2 ml) was added dropwise a solution of α-methoxyallene[10] (140 mg, 2.00 mmol) in anhydrous THF (0.5 ml) at -78°C. After being stirred for 30 min, the mixture was added to anhydrous magnesium bromide (552 mg, 3.00 mmol), generated in situ[13] from 1,2-dibromoethane (564 mg, 3.00 mmol) and magnesium (73 mg, 3.00 mg-atom), by cannulation. After being stirred for 30 min at -78°C, a solution of the ketone (**16**) (150 mg) in anhydrous THF (2 ml) was added dropwise to the mixture. Stirring was continued for 2.5 h at the same temperature, and then the mixture was treated with saturated aqueous ammonium chloride. After removal of the solvent under reduced pressure, the aqueous phase was extracted with ether. The combined organic phases were washed with saturated brine and the residue upon work-up gave the alcohol (203 mg) as an oil; ir $\nu_{max.}$ ($CHCl_3$) 3500 cm^{-1}. This compound was used in the next reaction without further purification.

Potassium t-butoxide (250 mg, 2.25 mmol) and a catalytic amount of 18-crown-6 were added to a solution of the alcohol (203 mg) in anhydrous t-butyl alcohol (4 ml) and the mixture was refluxed for 2 hr. After cooling at 0°C, 1M-aqueous hydrogen chloride (3 ml) was added to the mixture, and stirring was continued for 7 hr at room temperature. The reaction mixture was neutralized with saturated aqueous

sodium hydrogen carbonate, and then most of t-butyl alcohol was removed under reduced pressure. The residue was diluted with ether and the aqueous phase was extracted with ether. The combined extracts were washed with saturated brine and the residue upon work-up was chromatographed using hexane-ethyl acetate (95:5, v/v) as eluant to afford the dihydrofuranone (17) (28 mg, 16 %), which was recrystallised from hexane-ether to give needles, mp 83-85°C (Found: C, 70.56; H, 8.51. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55 %); $[\alpha]_D^{25}$ -66.7° (c=1.29); ir $\nu_{max.}$ ($CHCl_3$) 1755 cm^{-1}; ^1H nmr δ_H (100 MHz, $CDCl_3$), 0.94(3H, s, $-\overset{|}{C}-CH_3$), 1.51(10H, br s, $(CH_2)_5C<$), 1.83(3H, J=1.5 Hz, olefinic CH_3), 2.52(2H, t, J=8.0 Hz, $COCH_2$), 3.74(1H, d, J=8.0 Hz, -CH-O-), 4.22(2H, q, J 8.0 Hz, OCH_2), 4.80-5.44(4H, m), 6.30(1H, dd, J=11 and 15 Hz, olefinic H); ^{13}C nmr δ_C(25 MHz, $CDCl_3$), 12.519(q), 18.837(q), 23.752(t), 23.927(t), 25.097(t), 36.037(t), 36.154(t), 36.622(t), 64.236(t), 72.309(d), 83.834(d), 96.061(s), 109.634(s), 114.080(t), 128.940(d), 139.178(s), 140.523(d), 215.465(s); ms m/z 306 (M^+).

(2S,3R)-2-[(2S)-2-(4-Acetoxymethylene-2-methyl-3-oxo-2,3,4,5-tetrahydro)furyl]-3α-[2-methyl-1(E),3-butadienyl]-1,4-dioxaspiro[4,5]decane (18) To a suspension of sodium hydride (60 % in oil; 105 mg, 2.59 mmol) in anhydrous dimethoxyethane (DME) (2 ml) was added a solution of the dihydrofuranone (17) (198 mg, 0.647 mmol) in anhydrous DME (2 ml) at 0°C and the mixture was stirred for 1 hr at room temperature. To the mixture was added dropwise ethyl formate (192 mg, 2.59 mmol) and, after being stirred for 23 hr at room temperature, the mixture was treated with water. After removal of the solvent, the residue was diluted with ether and water, and the aqueous phase was acidified with 10 % aqueous sulphuric acid at 0°C, and extracted with methylene dichloride. The extract was washed with saturated brine, and the residue upon work-up gave the unstable hydroxymethylene (176 mg) as an oil which was used in the next reaction without further purification. To a stirred solution of the crude hydroxymethylene (176 mg, 0.527 mmol), triethylamine (69 mg, 0.685 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP) was added dropwise acetyl chloride (50 mg, 0.632 mmol) at 0°C and the mixture was stirred at room temperature for 2 h. After removal of the solvent, the residue was chromatographed with hexane-ethyl acetate (4:1, v/v) as eluant to give the acetate (18) (184 mg, 76 %) as an unstable oil; ir $\nu_{max.}$ ($CHCl_3$) 1780, 1740 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$) 1.05(3H, s, $-\overset{|}{C}-CH_3$), 1.53(10H, br s, $(CH_2)_5C<$), 1.90(3H, s, olefinic CH_3), 2.24(3H, s, $COCH_3$), 4.75-5.70(6H, m), 6.38(1H, dd, J=10 and 18 Hz, olefinic H), 8.13(1H, m, =CHOAc) (Found: M^+, 376.1881. $C_{21}H_{28}O_6$ requires M, 376.1884).

Thermolysis of the Acetate (18) A solution of the acetate (18) (184 mg, 0.489 mmol) in degassed anhydrous xylene (20 ml) was heated at 180°C for 53 hr in a sealed tube. After removal of the solvent, the cycloadduct (147 mg) was obtained as a brown oil which was used in the next reaction without further purification.

A solution of the cycloadduct (147 mg) and lithium hydroxide monohydrate (32 mg, 0.783 mmol) in a mixture of methanol (2 ml)-methylene dichloride (0.5 ml)-water (1 ml) was stirred at room temperature for 10 hr. After removal of the solvents, the residue was diluted with water, and extracted with methylene dichloride. The extract was washed with saturated brine and the residue upon work-up was chromato-

graphed with hexane-ethyl acetate (9:1, v/v) as eluant to afford the alcohol (**20**) (11 mg, 7 %) as an oil; $[\alpha]_D^{24}$ -107.5° (c=0.30); ir $\nu_{max.}$ ($CHCl_3$) 3550, 1760 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$) 1.28(3H, s, $-\overset{|}{C}-CH_3$), 1.56(10H, br s, $(CH_2)_5C<$), 1.81(3H, br s, olefinic CH_3), 3.93-4.73(3H, m), 5.36(1H, m, olefinic H) (Found: M^+, 334.1775. $C_{19}H_{26}O_5$ requires 334.1780). From the latter fractions, the alcohol (**19**) (30 mg, 18 %) was obtained as an oil; $[\alpha]_D^{24}$ -150.5° (c=0.60); ir $\nu_{max.}$ ($CHCl_3$) 3350, 1760 cm^{-1}; ^1H nmr δ_H (60 MHz, $CDCl_3$), 1.26(3H, s, $-\overset{|}{C}-CH_3$), 1.55(10H, br s, $(CH_2)_5C<$), 1.87(3H, br s, olefinic CH_3), 3.87-4.57(3H, m), 5.37(1H, m, olefinic H) (Found: M^+, 334.1791. $C_{19}H_{26}O_5$ requires 334.1780).

Acetylation of Alcohol (20) To a solution of the alcohol (**20**) (5.0 mg, 0.015 mmol), pyridine (3.5 mg, 0.045 mmol), and a catalytic amount of DMAP was added acetic anhydride (4.6 mg, 0.045 mmol) at room temperature and the mixture was stirred for 10 hr at the same temperature. After removal of the solvent, the residue was chromatographed with hexane-ethyl acetate (9:1, v/v) as eluant to afford the acetate (**22**) (5.6 mg, 100 %) as an oil; $[\alpha]_D^{24}$ -98.2° (c=0.70); ir $\nu_{max.}$ ($CHCl_3$) 1770, 1740 cm^{-1}; ^1H nmr δ_H (400 MHz, $CDCl_3$), 1.32(3H, s, C_1-CH_3), 1.55(10H, br s, $(CH_2)_5C<$), 1.80(3H, br s, C_5-CH_3), 2.08(3H, s, $COCH_3$), 2.34(1H, ddd, J=6.0, 7.3, and 16.1 Hz, C_7 H), 2.73(1H, br d, J=10.7 Hz, C_4H), 2.98(1H, m, $C_7\beta$ H), 3.07(1H, t, J=10.7 Hz, C_3H), 4.08(1H, d, J=9.5 Hz, $C_{12}H$), 4.14(1H, d, J=10.7 Hz, C_2H), 4.18(1H, d, J=9.5 Hz, $C_{12}H$), 4.88(1H, dd, J=6.0 and 10.5 Hz, C_8H), 5.44(1H, br d, J=7.3 Hz, C_6H) (Found: M^+, 376.1894. $C_{21}H_{28}O_6$ requires M, 376.1886).

Acetylation of Alcohol (19) The alcohol (**19**) (2.0 mg, 0.006 mmol) was acetylated with pyridine (1.4 mg, 0.018 mmol), acetic anhydride (1.8 mg, 0.018 mmol), and a catalytic amount of DMAP as described for (**20**) to afford the acetate (**21**) (2.3 mg, 100 %) which was recrystallised from hexane-ether to give needles, mp 154-156°C (Found: C, 67.18; H, 7.45. $C_{21}H_{28}O_6$ requires C, 66.99; H, 7.50 %); $[\alpha]_D^{24}$ -196.0° (c=0.79): ir $\nu_{max.}$ ($CHCl_3$) 1770, 1740 cm^{-1}; ^1H nmr δ_H (400 MHz, $CDCl_3$), 1.30(3H, s, C_1-CH_3), 1.59(10H, br s, $(CH_2)_5C<$), 1.85(3H, br s, C_5-CH_3), 2.00(3H, s, $COCH_3$), 2.26(1H, dd, J=5.9 and 16.1 Hz, $C_{7\beta}H$), 2.78(1H, d, J=10.7 Hz, C_4H), 2.81(1H, br d, J=16.1 Hz, $C_{7\alpha}$ H), 3.02(1H, t, J=10.7 Hz, C_3H), 4.12(1H, d, J=9.8 Hz, $C_{12}H$), 4.14(1H, d, J=10.7 Hz, C_2H), 4.17(1H, d, J=9.8 Hz, $C_{12}H$), 5.13(1H, d, J=4 Hz, C_8H), 5.37(1H, br d, J=5.9 Hz, C_6H); ms m/z 376 (M^+).

Crystallographic Determination of Compound (21). Compound (**21**) was recrystallised from hexane-ether as monoclinic crystals, mp 154-156°C; $C_{21}H_{28}O_6$, space group $P2_1$, with a=15.335 (11), b=6.123 (13), c=11.003 (8) Å, β=106.16 (5)°, Z=2, Dc=1.26 $g\,mc^{-3}$. Intensity measurements were made with Mo-K_α radiation (λ=0.7107Å; graphite monochromater) on a Rigaku AFC-5FOS diffractometer in the ω-2θ mode within 54°. A total of 1379 unique reflections were measured with $F \geq 2\sigma(F)$. The measured reflections were corrected for Lorentz polarization only. Accurate cell parameters were obtained by least-squares techniques from the diffractometer setting for 24 reflections. The structure was solved using MULTAN[16], and refined by block-diagonal least-squares. Convergence, with anisotropic thermal parameters for all non-hydrogen atoms, was reached at R 0.144 (R_w 0.141) using all the observed reflections. The atomic co-ordinates are given in Table I.

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