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Asymmetric palladium(0)-mediated synthesis of 2-vinylchroman

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Abstract

Optically active 2-vinylchroman was synthesized from the corresponding hydroxy allylic carbonate by palladium-catalyzed cyclization in the presence of various chiral ligands. Enantioselectivity of up to 53% was obtained using NMDPP as the chiral phosphine. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

The 3,4-dihydro-2*H*-1-benzopyran nucleus is present in many biologically active compounds such as α-tochopherol or vitamin E. A useful intermediate in the synthesis of such structures is chromanethanol, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-ethanol.

Racemic chromanethanol has been prepared using a Friedel–Crafts alkylation between trimethylhydroquinone and an appropriate allylic alcohol,[1,2] 3,6-dihydro-4-methyl-2*H*-pyran[3] or 3-methylpentan-1,3,5-triol.[4] Since it was shown that the biological activity was strongly influenced by configuration of the asymmetric center, recent research has focused on the preparation of optically active chromanethanol. Enantiopure (*S*)-chromanethanol has been obtained starting with compounds from the chiral pool such as (*R*)-mevalonolactone[5] or (*S*)-benzylglycidol.[6] The asymmetric Sharpless epoxidation of an intermediate allowed chromanethanol with 78% ee to be obtained.[7] Chemical[8] or enzymatic[9] resolutions of the final product, or of an intermediate, have also been used to obtain optically active chromanethanol.

Following our continuing interest in the formation of C–O bonds via palladium(0) alkylation of allylic substrates by oxygen nucleophiles,[10] we expected that 2-vinylchroman **1**, a precursor of chromanethanol, could be obtained by intramolecular palladium(0) nucleophilic substitution of appropriate hydroxy allylic carbonates **7** or **13**. In this paper we describe our results concerning the synthesis of these two hydroxy allylic carbonates and their asymmetric palladium cyclization.[11]

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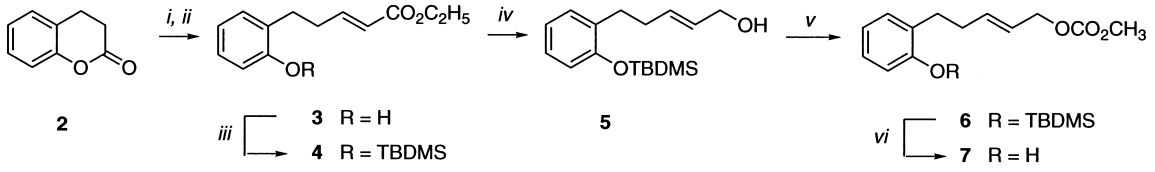
2. Results and discussion

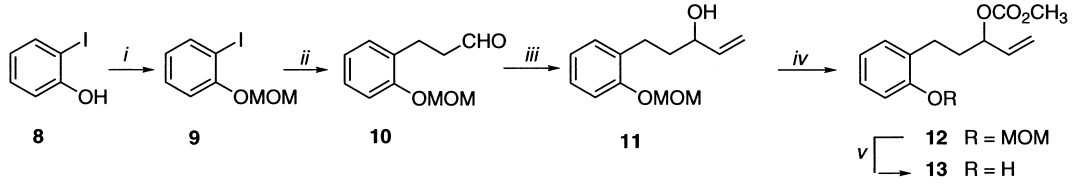
The achiral linear allylic carbonate **7** was prepared as shown in Scheme 1. Reduction of commercial dihydrocoumarin **2** with diisobutylaluminum hydride (dibal) in toluene followed by a Wittig reaction with $Ph_3P{=}CHCO_2C_2H_5$ at room temperature gave hydroxyester **3**.[12] Protection of the phenolic function of **3** was performed with *t*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole. Reduction of the unsaturated ester **4** with dibal at −78°C in toluene afforded (*E*)-allyl alcohol **5**. Esterification of **5** by treatment with methyl chloroformate followed by deprotection of the phenolic function with tetrabutylammonium fluoride $Bu_4NF{\cdot}3H_2O$ led to the linear hydroxy carbonate **7**.



i: Dibal, toluene, -78°C, 2 h, then H_2O, 78%. *ii*: $Ph_3P{=}CHCO_2C_2H_5$, benzene, r.t., 2 h, 100%. *iii* : TBDMSCl, imidazole, DMF, 24 h, 77%. *iv*: Dibal, toluene, -78°C, 2 h, then H_2O, 93%. *v*: $ClCO_2CH_3$, C_5H_5N, DMAP, CH_2Cl_2, r.t. , 2 h, 92%. *iv*: $Bu_4NF.3H_2O$, THF, r.t., 84%.

Scheme 1.

The chiral racemic allylic carbonate **13** was prepared as shown in Scheme 2. Iodophenol **8** was converted to 2-(methoxymethoxy)iodobenzene **9** using chloromethyl methyl ether in the presence of sodium hydride in tetrahydrofuran (THF). Heck reaction of the protected compound **9** with allylic alcohol in the presence of $Pd(OAc)_2$ under Jeffery's conditions,[13] gave aldehyde **10** in 20% yield after column chromatography. Condensation of aldehyde **10** with vinylmagnesium bromide afforded the secondary allylic alcohol **11** which was esterified to the branched carbonate **12** by reaction with methyl chloroformate. Finally, the phenolic function of **12** was deprotected using trimethylsilyl bromide to give the desired chiral racemic hydroxy allylic carbonate **13**.

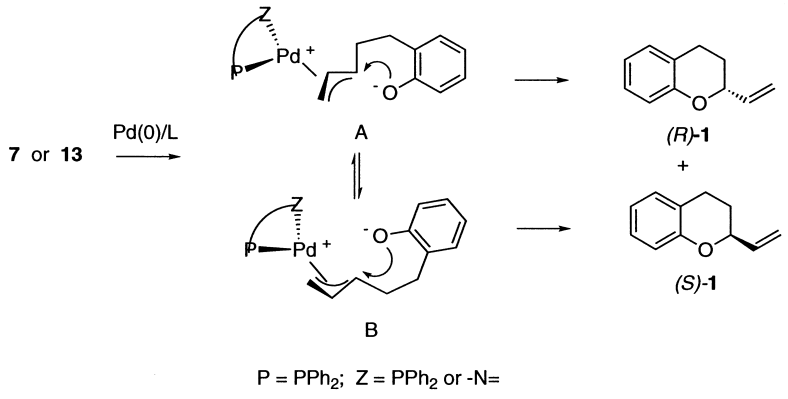


i: NaH, THF, r.t., 30 min, then $ClCH_2OCH_3$, 2 h, reflux, 90%. *ii*: $CH_2{=}CHCH_2OH$, $Pd(OAc)_2$, $NaHCO_3$, Et_3BuNCl, DMF, 50°C, 36 h, 20%. *iii*: $CH_2{=}CHMgBr$, THF, - 30°C to 0°C, then H_2O, 54%. *iv*: $ClCO_2CH_3$, C_5H_5N, DMAP, CH_2Cl_2, 12 h, 74%. *v*: Me_3SiBr, CH_2Cl_2, 0°C, 20 h, then H_2O, 23%.

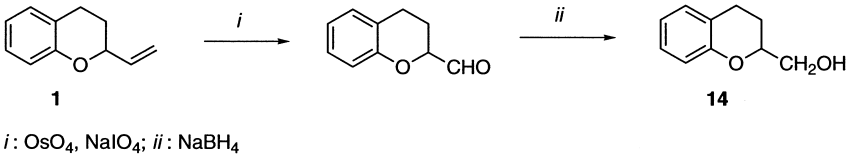
Scheme 2.

Asymmetric cyclization of allyl carbonates **7** and **13** to give chiral 2-vinylchroman **1** (Scheme 3) was carried out in the presence of palladium complexes containing various chiral ligands. The enantiomeric excess of **1** was determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD). Absolute configuration of product **1** was determined after conversion of a sample exhibiting $[\alpha]_D^{20}=-10.3$ (*c* 1.0, CH_2Cl_2) to chromanethanol **14** (Scheme 4) by treatment with a solution of osmium tetroxide and sodium periodate followed by reduction with sodium borohydride, and comparison with the reported sign of rotation $[\alpha]_D^{25}=-113.4$ (*c* 1.1, CH_3OH) for the (*R*)-enantiomer.[14]

Representative results concerning this asymmetric cyclization are shown in Table 1. In the case of BINAP (entry 5) or MeOBIPHEP (entry 7), the product yield in **1**, starting from the achiral linear



Scheme 3.



Scheme 4.

allylic carbonate **7**, was poor (7% and 19%) with ees of up to 4 and 36%, respectively; performing the cyclization at 50°C or in CH_2Cl_2 did not improve these values. In the presence of MeOBIPHEP (entry 8), chiral racemic allylic carbonate **13** gave the cyclized product in higher yield (65%) but with lower ee (12%) (entry 20). Palladium complexes containing Diop (entry 1), Chiraphos (entry 2) or BDPP (entry 3) as the chiral ligand gave high chemical yield in **1**, but low enantioselectivity; in the case of BDPP, performing the reaction at 0°C decreased both the yield and the ee (entry 4). The *P*,*N*-Diop ligand also gave high yield and low ee (entry 11). The result obtained with Trost's ligand are also disappointing from an enantioselectivity point of view (entry 9); however, the same enantioselectivity was obtained starting from carbonates **7** or **13** (entry 19).

The highest ees were obtained using phosphino-oxazoline or NMDPP as the chiral auxiliary. The phosphino-oxazoline ligand gave ees of up to 45% in 67% yield (entry 10). Surprisingly, NMDPP, a chiral monophosphine, gave ees of up to 47% in 92% yield at 25°C (entry 13). Performing the reaction at 0°C or −30°C increased the ees to 50 and 53% (entries 14 and 16), respectively, although a higher reaction temperature (50°C) gave a lower ee (entry 15). Surprisingly, the catalyst generated in situ from $Pd(OAc)_2$ and NMDPP showed a low activity with no induction (entry 18). These results could be rationalized as shown in Scheme 3. Absolute configuration of the product is probably determined by the relative stability of the two intermediates A and B, if the alkylation reaction is slow compared to the equilibrium between these two η^3-allyl complexes, via a $\eta^3 \rightleftharpoons \sigma \rightleftharpoons \eta^3$ mechanism. This is probably the case here, and the nucleophilic addition step determines the asymmetric induction.[15,16]

With Trost's ligand, the substrate could not be well accommodated in the chiral pocket, probably due to steric constraints, and so the enantioselectivity is low. For the phosphino-oxazoline ligand, we assume that the lesser steric constraint positions the nitrogen atom *trans* to the less substituted η^3-allyl terminus, the π-allyl intermediate A being the less stable in this case, due to interaction between the isopropyl group of the phosphino-oxazoline and the two methylene groups of the substrate. The more stable intermediate B will give the (*S*)-enantiomer. For the monophosphine NMDPP, the equilibrium is probably faster, due to easier association and dissociation of the monodentate ligand, and the two

Table 1
Asymmetric palladium(0)-catalyzed cyclization of carbonates **7** and **13**

Entry	Carbonate	Ligand	Solvent	T (°C)	Yield (%)[a]	% ee[b] (Config)
1	**7**	*(S,S)*-Diop	THF	25	74	2 *(S)*
2	**7**	*(S,S)*-Chiraphos	THF	25	93	15 *(R)*
3	**7**	*(S,S)*-BDPP	THF	25	93	16 *(S)*
4	**7**	*(S,S)*-BDPP	THF	0	57	4 *(S)*
5	**7**	*(R)*-BINAP	THF	25	7	4 *(S)*
6	**7**	*(R)*-BINAP	THF	50	38	7 *(R)*
7	**7**	*(S)*-MeOBIPHEP	THF	25	19	36 *(R)*
8	**7**	*(S)*-MeOBIPHEP	CH_2Cl_2	25	10	43 *(R)*
9	**7**	*(R,R)*-Trost	THF	25	88	7 *(S)*
10	**7**	Phosphino-oxazoline	THF	25	67	45 *(S)*
11	**7**	P,N-Diop	THF	25	98	5 *(S)*
12	**7**	Togni	THF	25	97	13 *(R)*
13	**7**	NMDPP	THF	25	92	47 *(R)*[c]
14	**7**	NMDPP	THF	0	92	50 *(R)*
15	**7**	NMDPP	THF	50	75	20 *(R)*
16	**7**	NMDPP	THF	-30	75	53 *(R)*
17	**7**	NMDPP	CH_2Cl_2	25	98	48 *(R)*
18	**7**	NMDPP	THF[d]	25	36	0
19	**13**	*(R,R)*-Trost	THF	25	83	7 *(S)*
20	**13**	*(S)*-MeOBIPHEP	THF	25	65	12 *(R)*

[a] After column chromatography and not optimized

[b] Determined by HPLC analysis with a chiral stationary phase column Chiralpack AD; absolute configuration in brackets

[c] $[\alpha]_D^{25} = -41.9$ (*c* 1, CH_2Cl_2)

[d] $Pd(OAc)_2$ was used as the palladium precursor

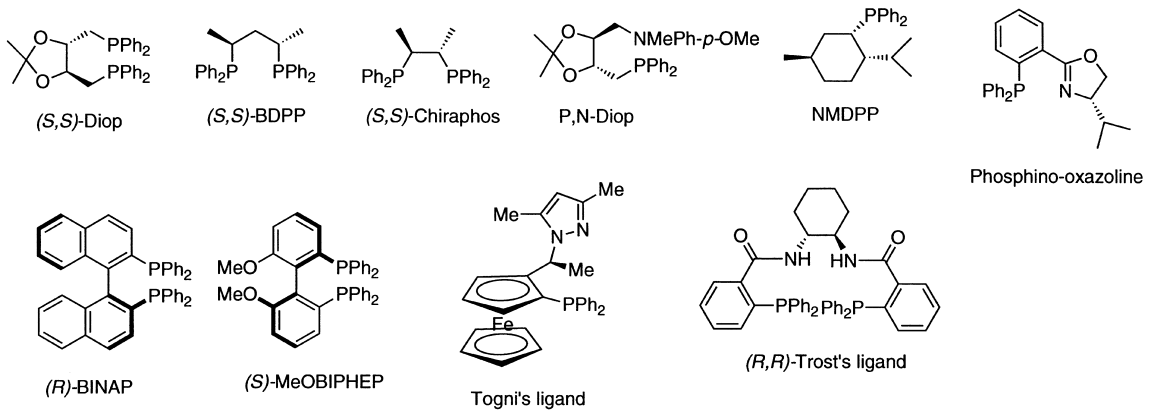


Figure 1. Structures of chiral ligands

chiral ligands are more easily sterically accommodated in the π-allyl intermediate than in the case of the diphosphines.

3. Conclusion

In conclusion, 2-vinylchroman could be obtained in quite good yields and with enantioselectivity of up to 53% by palladium(0)-catalyzed cyclization of the appropriate hydroxy allylic carbonate. The highest enantioselectivities are obtained using the phosphino-oxazoline ligand or the chiral monophosphine NMDPP, although Trost's ligand gives very low enantioselectivities (Fig. 1).

4. Experimental

4.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were measured on a Bruker AM 300 spectrometer. Chemical shifts are reported in δ ppm referring to tetramethylsilane as an internal standard. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Silica gel column chromatography was carried out using Merck silica gel 60 Gerudan (40–63 μm). Analytical HPLC was performed on a Shimadsu instrument and with a UV detector. Reactions involving organometallic catalysis were carried out in Schlenk tubes under an inert atmosphere. Tetrahydrofuran was distilled from sodium–benzophenone. (2*S*,3*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphanyl)butane (Diop), (2*S*,4*S*)-2,4-bis(diphenylphosphanyl) pentane (BDPP), (2*S*,3*S*)-2,3-bis(diphenylphosphanyl)butane (Chiraphos), (*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP), (1*S*,2*S*,5*R*)-5-methyl-1-diphenylphosphanyl)-2-isopropylcyclohexane (NMDPP) were from a commercial source. (*S*)-6,6′-Dimethoxy-2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl (MeOBIPHEP), 1-{(*S*)-1-[(*R*)-3,5-dimethyl-2(diphenylphosphanyl)ferrocenyl]ethyl}-1*H*-pyrazole and (*S*)-2-[2-diphenylphosphanyl)phenyl]-4-isopropyldihydrooxazole were gifts from Dr. Schmid (Hofmann La Roche, Basle, Switzerland), Professor Togni (Zürich, Switzerland) and Professor Pfaltz (Mülheim an der Ruhr, Germany), respectively. (1*R*,2*R*)-1,2-Bis-*N*-[2′-(diphenylphosphanyl)benzoyl]-1,2-

diaminocyclohexane[17] and (2*R*, 3*S*)-*O*-isopropylidene-1-diphenylphosphanyl-4-[(*N*-*p*-methoxyphenyl)-*N*-methylamino]butan-2,3-diol or *P*,*N*-Diop[18] were prepared according to the literature procedure.

4.2. *Ethyl 5-{2-[(*tert-*butyldimethylsilyl)oxy]phenyl}pent-2-enoate* **4**

To a solution of imidazole (30.16 g, 0.44 mol) and *tert*-butyldimethylsilyl chloride (32.05 g, 0.21 mol) in DMF (50 mL) was added ethyl (5-hydroxyphenyl)pent-2-enoate[12] (39.0 g, 0.17 mol) as a mixture of (*E*) and (*Z*) isomers at room temperature. After being stirred for 24 h at room temperature, the solution was hydrolyzed by water (150 mL). The aqueous solution was extracted with CH_2Cl_2 (5×75 mL). The organic phase was washed with a 5% aqueous sodium hydroxide solution (3×100 mL), water (10×50 mL) and then dried with sodium sulfate. Evaporation of the solvent gave a residue which was purified by flash chromatography, using petroleum ether:ethyl acetate (25:1) as the eluent, to give compound **4** (*E:Z* mixture, 90:10) as an oil (45.5 g, 77%). Isomer **4**, *E*: R_f=0.42; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 0.24 (s, 6H, $SiCH_3$), 1.05 (s, 9H, *t*-Bu), 1.29 (t, 3H, *J*=7.1 Hz, CH_3), 2.48 (td, 2H, *J*=7.9, 7.0 Hz, C*H*$_2$CH=), 2.75 (t, 2H, *J*=7.9 Hz, CH_2), 4.18 (q, 2H, *J*=7.1 Hz, C*H*$_2$CH$_3$), 5.85 (d, 1H, *J*=15.8 Hz, =CH–CO), 6.75–7.15 (m, 5H, =CH–, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) −4.1 ($SiCH_3$), 14.3 (CH_3), 18.3 (CMe_3), 25.8 (CMe_3), 29.3 (CH_2), 32.8 (CH_2), 60.2 (OCH_2), 118.4, 121.2, 121.6, 127.3, 130.2, 131.5, 148.6 and 153.6 (–CH=, C_{arom}), 166.7 (CO). Isomer **4**, *Z*: R_f=0.48; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 0.27 (s, 6H, $SiCH_3$), 1.05 (s, 9H, *t*-Bu), 1.30 (t, 3H, *J*=7.2 Hz, CH_3), 2.77 (t, 2H, *J*=7.6 Hz, CH_2), 2.98 (tdd, 2H, *J*=7.6, 7.4, 1.5 Hz, C*H*$_2$CH=), 4.18 (q, 2H, *J*=7.2 Hz, C*H*$_2$CH$_3$), 5.78 (dt, 1H, *J*=11.4, 1.5, Hz, =CH–CO), 6.25 (dt, 1H, *J*=11.4, 7.4 Hz, –CH=), 6.75–7.25 (m, 4H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) −4.1 ($SiCH_3$), 14.4 (CH_3), 18.3 (CMe_3), 25.9 (CMe_3), 29.3 (CH_2), 29.7 (CH_2), 59.8 (OCH_2), 118.4, 121.1, 120.1, 127.1, 130.3, 131.8, 149.6 and 153.6 (–CH=, C_{arom}), 166.4 (CO). Anal. calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04. Found: C, 68.45; H, 8.89.

4.3. *(*E*)-5-{2-[(*tert-*Butyldimethylsilyl)oxy]phenyl}pent-2-en-1-ol* **5**

To a solution of compound **4** (62 g, 0.185 mol) in toluene (600 mL) maintained at −78°C was added slowly a 1.5 M solution of dibal (310 mL) in toluene. After being stirred for 2 h at −78°C, the solution was treated at room temperature with methanol (400 mL), acidified by 1 N hydrochloric acid (500 mL), and filtered on Celite. The aqueous solution was extracted with CH_2Cl_2 (5×75 mL). The organic phase was dried with sodium sulfate, and evaporated in vacuo to give an oil which was purified by flash chromatography, using petroleum ether:ethyl acetate (4:1) as the eluent, to give compound **5** (50.1 g, 93%). Oil; R_f=0.27; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 0.25 (s, 6H, $SiCH_3$), 1.05 (s, 9H, *t*-Bu), 1.48 (s, 1H, OH), 2.34 (dtd, 2H, *J*=9.2, 6.9, 2.1 Hz, C*H*$_2$CH=), 2.68 (td, 2H, *J*=6.9, 2.2 Hz, CH_2), 4.08 (d, 2H, *J*=5.5 Hz, C*H*$_2$OH), 5.56–5.82 (m, 2H, –CH=), 6.78 (dd, 1H, *J*=8.1, 1.1 Hz, H_{arom}), 6.88 (ddd, 1H, *J*=7.3, 7.3, 1.1 Hz, C_{arom}), 7.02–7.16 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) −4.1 ($SiCH_3$), 18.3 (CMe_3), 25.9 (CMe_3), 30.4 (CH_2), 32.7 (CH_2), 63.8 (CH_2OH), 118.4, 121.0, 127.0, 129.4, 130.3, 132.3, 132.9 and 153.6 (–CH=, C_{arom}). Anal. calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65. Found: C, 69.74; H, 9.95.

4.4. *(*E*)-5-{2-[(*tert-*Butyldimethylsilyl)oxy]phenyl}pent-2-enyl methyl carbonate* **6**

To a solution of alcohol **5** (52 g, 0.18 mol), 4-dimethylaminopyridine (4.34 g, 35 mmol) and pyridine (37.3 mL, 0.71 mol) in CH_2Cl_2 (510 mL) maintained at 0°C, was slowly added methyl chloroformate (55 mL, 0.71 mol). After being stirred at room temperature for 24 h, the solution was hydrolyzed by

a saturated aqueous solution of copper sulfate (250 mL), and the aqueous phase was extracted with diethyl ether (4×100 mL). Evaporation of the solvent in vacuo gave a residue which was purified by flash chromatography, using petroleum ether:ethyl acetate (3:1) as the eluent, to give carbonate **6** (57.3 g, 92%). Oil; R_f=0.45; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 0.21 (s, 6H, $SiCH_3$), 1.10 (s, 9H, *t*-Bu), 2.34 (td, 2H, *J*=7.9, 6.6 Hz, C*H*$_2$CH=), 2.67 (t, 2H, *J*=7.9 Hz, CH_2), 3.78 (s, 3H, CH_3), 4.57 (d, 2H, *J*=6.6 Hz, CH_2OCO), 5.62 (dt, 1H, *J*=15.4, 6.6 Hz, –CH=), 5.87 (dt, 1H, *J*=15.4, 6.6 Hz, –CH=), 6.75 (dd, 1H, *J*=6.9, 6.9 Hz, H_{arom}), 6.78 (d, 1H, *J*=8.1 Hz, H_{arom}), 7.10 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) −4.1 ($SiCH_3$), 18.3 (CMe_3), 25.8 (CMe_3), 30.4 (CH_2), 32.7 (CH_2), 54.7 (CH_3), 68.7 (CH_2O), 118.4, 121.0, 123.6, 127.0, 130.3, 132.1, 136.8 and 153.6 (–CH=, C_{arom}), 155.7 (CO). Anal. calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 64.73; H, 8.64.

*4.5. (*E*)-5-(2-Hydroxyphenyl)pent-2-enyl methyl carbonate **7***

A solution of compound **6** (13.1 g, 37 mmol) and tetrabutylammonium fluoride trihydrate (19.6 g, 74 mmol) in THF (200 mL) was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was treated with diethyl ether (100 mL) and water (50 mL). After usual workup, evaporation of the solvent in vacuo gave a residue which was purified by flash chromatography, using petroleum ether:ethyl acetate (8:3) as the eluent, to give hydroxy carbonate **7** (7.4 g, 84%). Oil; R_f=0.49; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 2.38 (td, 2H, *J*=7.4, 6.9 Hz, C*H*$_2$CH=), 2.72 (t, 2H, *J*=7.4 Hz, CH_2), 3.78 (s, 3H, CH_3), 4.57 (d, 2H, *J*=6.7 Hz, CH_2OCO), 5.61 (dt, 1H, *J*=15.4, 6.9 Hz, –CH=), 5.88 (dt, 1H, *J*=15.4, 6.7 Hz, –CH=), 6.74 (d, 1H, *J*=7.8 Hz, H_{arom}), 6.87 (ddd, 1H, *J*=8.3, 8.3, 1.1 Hz, H_{arom}), 7.08 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) 29.5 (CH_2), 32.4 (CH_2), 54.9 (CH_3), 68.7 (CH_2O), 115.4, 120.8, 123.7, 127.3, 127.5, 130.3, 136.7 and 153.6 (–CH=, C_{arom}), 155.9 (CO). Anal. calcd for $C_{13}H_{15}O_4$: C, 66.09; H, 6.83. Found: C, 65.84; H, 6.56.

*4.6. 2-(Methoxymethoxy)iodobenzene **9***

A solution of iodophenol **8** (20.0 g, 91 mmol) in THF (90 mL) was added to a mixture of 60% NaH (4.45 g, 0.11 mol) in THF (60 mL). After 20 min, chloromethyl methyl ether (8.3 g, 0.1 mol) was added slowly at room temperature. The solution was refluxed for 2 h, then hydrolyzed by cold water (900 mL), and extracted with diethyl ether (5×180 mL). Evaporation of the solvent in vacuo gave a residue which was purified by flash chromatography, using petroleum ether:ethyl acetate (50:1) as the eluent, to give compound **9** (21.5 g, 90%). Oil; R_f=0.36; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 3.51 (s, 3H, CH_3), 5.24 (s, 2H, OCH_2O), 6.77 (ddd, 1H, *J*=7.9, 7.4, 1.5 Hz, H_{arom}), 7.08 (dd, 1H, *J*=8.1, 1.5 Hz, H_{arom}), 7.29 (ddd, 1H, *J*=8.1, 7.4, 1.5 Hz, H_{arom}), 7.78 (dd, 1H, *J*=7.9, 1.5 Hz, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) 56.4 (CH_3), 94.9 (CH_2), 87.2, 114.9, 123.6, 129.4, 139.5 and 156.0 (C_{arom}). These spectral data are in agreement with the literature.[19]

*4.7. 3-[2-(Methoxymethoxy)phenyl]propanal **10***

A solution of 2-(methoxymethoxy)iodobenzene **9** (2.5 g, 9.5 mmol) and allylic alcohol (1.37 g, 23.5 mmol) in DMF (40 mL) was added to a stirred solution of $Pd(OAc)_2$ (72.3 mg, 0.32 mmol), $NaHCO_3$ (2.0 g, 23 mmol), and benzyltriethylammonium chloride (2.16 g, 9.5 mmol), in DMF (15 mL). The mixture was heated at 70°C for 36 h, then cooled to 25°C, and hydrolyzed by a saturated aqueous ammonium chloride solution (250 mL). The aqueous phase was extracted with diethyl ether (7×25 mL). The organic phase was washed with saturated aqueous sodium chloride (4×30 mL) and dried with sodium sulfate.

The solvent was removed in vacuo to afford an oil which was purified by flash chromatography, using petroleum ether:ethyl acetate (6:1) as the eluent, to give compound **10** (363 mg, 20%). Oil; R_f=0.54; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 2.75 (dt, 2H, *J*=7.5, 1.4 Hz, C*H*$_2$CHO), 2.95 (t, 2H, *J*=7.5 Hz, CH_2), 3.47 (s, 3H, CH_3), 5.21 (s, 2H, OCH_2O), 6.90–7.20 (m, 4H, H_{arom}), 9.83 (t, 1H, *J*=1.4 Hz, CHO); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) 23.5 (CH_2), 44.0 (*C*H$_2$CHO), 56.1 (CH_3), 94.3 (OCH_2O), 113.9, 121.8, 127.8, 129.3, 130.1 and 155.1 (C_{arom}), 202.3 (CHO); *m/z* (EIMS, 70 eV) 194 (M^+, 2%), 132 (17) and 45 (100).

4.8. 5-[2-(Methoxymethoxy)phenyl]pent-1-en-3-ol ***11***

A 1 M solution of vinylmagnesium bromide in THF (29.4 mL, 30 mmol) was added very slowly to a stirred solution of aldehyde **10** (1.94 g, 10 mmol) in THF (30 mL) and cooled to −30°C. After being stirred at room temperature for 3 h, the solution was hydrolyzed by a saturated aqueous ammonium chloride solution (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (5×25 mL). The organic solution was washed with a saturated solution of sodium chloride (3×80 mL) and dried with sodium sulfate. The solvent was removed in vacuo to afford an oil which was purified by flash chromatography, using petroleum ether:ethyl acetate (4:1) as the eluent, to give compound **11** (1.18 g, 54%). Oil; R_f=0.42; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 1.58 (s, 1H, OH), 1.84 (m, 2H, C*H*$_2$CHOH), 2.76 (t, 2H, *J*=7.7 Hz, CH_2), 3.49 (s, 3H, CH_3), 4.15 (bdt, 1H, *J*=6.3, 6.3 Hz, C*H*OH), 5.13 (ddd, 1H, *J*=10.3, 1.4, 1.4 Hz, =CH_2), 5.22 (s, 2H, OCH_2O), 5.25 (ddd, 1H, *J*=17.1, 1.4, 1.4 Hz, =CH_2), 5.91 (ddd, 1H, *J*=17.1, 10.3, 6.3 Hz, –CH=), 6.95 (ddd, 1H, *J*=7.3, 7.3, 1.1 Hz, H_{arom}), 7.07 (dd, 1H, *J*=9.0, 1.1 Hz, H_{arom}), 7.13–7.21 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) 26.2 (*C*H$_2$CHOH), 37.4 (CH_2), 56.2 (CH_3), 72.3 (CHOH), 94.5 (OCH_2O), 114.0, 114.6, 121.9, 127.3, 130.8, 141.1 and 155.1 (C_{arom}, –CH=, =CH_2). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.04; H, 8.09. Found: C, 70.24; H, 8.16.

4.9. 3-[2-(Methoxymethoxy)phenyl]-1-vinylpropyl methyl carbonate ***12***

A solution of methyl chloroformate (1.7 mL, 25 mmol) in CH_2Cl_2 (5 mL) was added slowly to a solution of alcohol **11** (1.18 g, 5.3 mmol), 4-dimethylaminopyridine (0.13 g, 1.0 mmol), and pyridine (1.2 mL, 20 mmol), in CH_2Cl_2 (10 mL) at 0°C. After being stirred for 24 h, the solution was hydrolyzed by a saturated copper sulfate aqueous solution (10 mL), and extracted with diethyl ether (4×10 mL). The organic phase was washed with water (4×10 mL) and dried with sodium sulfate. Removal of the solvent in vacuo afforded an oil which was purified by flash chromatography, using petroleum ether:ethyl acetate (6:1) as the eluent, to give compound **12** (1.1 g, 74%). Oil; R_f=0.62; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 1.84–2.10 (m, 2H, C*H*$_2$CHOH), 2.71 (t, 2H, *J*=7.0 Hz, CH_2), 3.48 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 5.10 (bdt, 1H, *J*=6.6, 6.6 Hz, CHO), 5.19 (s, 2H, OCH_2O), 5.23 (ddd, 1H, *J*=10.3, 1.3, 1.3 Hz, =CH_2), 5.34 (ddd, 1H, *J*=17.2, 1.3, 1.3 Hz, =CH_2), 5.85 (ddd, 1H, *J*=17.2, 10.3, 6.6 Hz, –CH=), 6.93 (ddd, 1H, *J*=7.3, 7.3, 1.5 Hz, H_{arom}), 7.05 (dd, 1H, *J*=8.1, 1.5 Hz, H_{arom}), 7.10–7.20 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) 26.1 (*C*H$_2$CHO), 34.4 (CH_2), 54.7 (CH_3), 56.1 (CH_3), 78.8 (*C*HOCO), 94.4 (OCH_2O), 113.9, 117.2, 121.7, 127.4, 130.1, 130.2, 136.0 and 155.2 (C_{arom}, –CH=, =CH_2), 155.3 (CO_2). Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.87; H, 7.09.

4.10. 3-(2-Hydroxyphenyl)-1-vinylpropyl methyl carbonate ***13***

To a solution of carbonate **12** (1.10 g, 3.9 mmol) in CH_2Cl_2 (25 mL) at −30°C containing molecular sieves, trimethylsilyl bromide (2.41 g, 15.7 mmol) was added slowly. After being stirred for 20 h at 0°C, the solution was hydrolyzed by a saturated aqueous solution of $NaHCO_3$ (100 mL). The solution was

then stirred in the presence of Amberlyst 15 (20 g) for 20 min. After filtration, the organic layer was separated and washed with a saturated aqueous sodium chloride solution (3×50 mL). The organic phase was dried with sodium sulfate, evaporated to give an oil which was purified by flash chromatography, using petroleum ether:ethyl acetate (5:1) as the eluent, to give compound **13** (154 mg, 17%). Oil; R_f=0.44; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 2.00 (m, 2H, C*H*$_2$CHOH), 2.68 (t, 2H, *J*=7.9 Hz, CH_2), 3.80 (s, 3H, CH_3), 5.10 (m, 1H, CHO), 5.23 (ddd, 1H, *J*=10.5, 1.1, 1.1 Hz, =CH_2), 5.33 (ddd, 1H, *J*=17.3, 1.1, 1.1 Hz, =CH_2), 5.85 (ddd, 1H, *J*=17.3, 10.5, 6.6 Hz, –CH=), 6.75 (d, 1H, *J*=7.5 Hz, H_{arom}), 6.87 (ddd, 1H, *J*=7.5, 7.5, 1.1 Hz, H_{arom}), 7.10 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) 25.8 (*C*H_2CHOCO), 34.2 (CH_2), 54.9 (CH_3), 79.1 (CHOCO), 115.4, 117.8, 120.7, 127.3, 127.5, 130.3, 135.8 and 153.9 (C_{arom}, –CH=, =CH_2), 155.6 (CO_2); *m/z* (EIMS, 70 eV) 160 (M^+−CH_3OH−CO_2, 60%), 145 (75), 131 (40), 107 (75) and 77 (100); *m/z* (CIMS, NH_3) 254 (MH^++NH_3, 30), 161 (MH^+−CH_3CO_2H, 100), 159 (82), 145 (20), 131 (15), 107 (32) and 94 (42).

4.11. General procedure for the cyclization reaction

A solution of tris(dibenzylideneacetone)dipalladium (22.9 mg, 0.025 mmol) and the ligand (0.1 mmol for a bidendante ligand or 0.2 mmol for a monophosphine) in 5 mL of THF was stirred at room temperature for 30 min. To the solution was added the hydroxy carbonate (23.6 mg, 0.1 mmol) dissolved in 4 mL of THF. The mixture was stirred at the desired temperature for 24 h and then the solvent was removed in vacuo. The residue was purified by silica gel chromatography, using petroleum ether:ethyl acetate (10:1) as the eluent, to give 2-vinylchromane **1**. Oil; R_f=0.72; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 1.86 (dddd, 1H, *J*=13.6, 9.9, 9.3, 5.5 Hz, H-3$_{ax}$), 2.08 (dddd, 1H, *J*=13.6, 5.9, 4.4, 2.6 Hz, H-3$_{eq}$), 2.78 (ddd, 1H, *J*=16.5, 5.5, 4.4 Hz, H-4$_{eq}$), 2.88 (ddd, 1H, *J*=16.5, 9.3, 5.9 Hz, H-4$_{ax}$), 4.56 (bddd, 1H, *J*=9.9, 5.5, 2.6 Hz, H-2), 5.24 (ddd, 1H, *J*=10.7, 1.5, 1.5 Hz, =CH_2), 5.39 (ddd, 1H, *J*=17.3, 1.5, 1.5 Hz, =CH_2), 6.00 (ddd, 1H, *J*=17.3, 10.7, 5.5 Hz, –CH=), 6.85 (m, 2H, H_{arom}), 7.09 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz): δ ($CDCl_3$) 24.2 (CH_2), 27.5 (CH_2), 76.2 (CHO), 116.3, 116.9, 120.2, 121.8, 127.3, 129.5, 137.6 and 154.3 (–CH=, =CH_2, C_{arom}). These data are in agreement with the literature.[20]

The enantiomeric excess of 2-vinylchroman **1** was determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD, eluent: *n*-hexane, rate 0.5 mL min^{-1}), the enantiomer (*S*) being eluted first.

4.12. Determination of the configuration of compound *1*

A solution of **1** (100 mg, 0.63 mmol), exhibiting $[\alpha]_D^{20}$=−10.3 (*c* 1.0, CH_2Cl_2), in 7 mL of acetone:water (3:1) and cooled to 0°C was treated by a 2.5% solution of osmium tetroxide (128 mg, 0.013 mmol) in *t*-butanol, then by sodium periodate (403 mg, 1.88 mmol). The mixture was stirred for 6 h at room temperature, then diluted with 40 mL water, and extracted with 3×35 mL ethyl acetate. Evaporation of the solvent in vacuo gave an oil which was diluted in ethanol (10 mL). $NaBH_4$ (170 mg, 4.5 mmol) was added and the solution was stirred at 0°C for 30 min. After hydrolysis with a 10% HCl solution (53 mL), the chromanethanol was extracted with ethyl acetate (4×30 mL). Evaporation of the solvent gave a residue which was purified by flash chromatography, using petroleum ether:ethyl acetate (2:1) as the eluent, to give 75.2 mg of chromanethanol **14** (73%) having $[\alpha]_D^{20}$ −13.6 (*c* 1.2, CH_3OH), and so the (*R*) configuration was assigned.[14]

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