An Approach to Cannabinoids by Radical Cyclisation of 1,7-Dienes Using Diethyl Thiophosphite

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Abstract: Various 1,7-dienes, prepared efficiently in five steps from salicylaldehyde, react with diethyl thiophosphite (in the presence of AIBN) to form substituted chromans, which are potential precursors to cannabinoids. The influence of the substitution of the 1,7-diene on the efficiency of the radical cyclisation is discussed.

Key words: addition reactions, cyclisations, ethers, radical reactions, substituent effects

Cannabinoids are a class of more than 60 compounds isolated from *Cannabis sativa* (the Indian hemp plant).[1] Cannabis is widely used as a recreational drug for its psychotropic effects and it has been shown to have some important medicinal properties, mediated through binding to two receptors, called CB1 and CB2.[2]

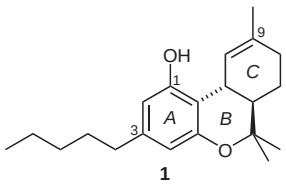

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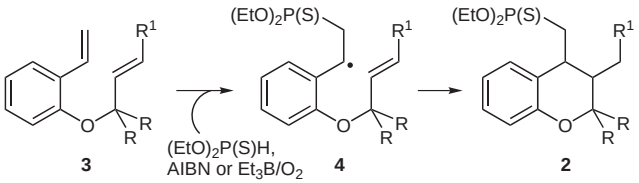
Figure 1

One particularly well-known cannabinoid is Δ^9-THC (Δ^9-tetrahydrocannabinol; **1**), which is the principal psychoactive component of marijuana (Figure 1). Cannabinoids such as Δ^9-THC (**1**) exhibit a wide range of pharmacological effects; this includes analgesic, antiemetic, anti-inflammatory, bronchodilatory and anticonvulsant effects as well as reduction of blood ocular pressure in glaucomic patients and alleviation of neurological disorders in multiple sclerosis and Huntington's chorea. The diverse and extremely important range of biological activities has led to various QSAR (quantitative structure–activity relationship) studies designed to probe the binding of cannabinoid compounds to CB1 and CB2.[2,3] This work has shown the importance of the phenolic hydroxyl group at C1, the C9 position and the C-3 side chain with respect to binding at the CB1 receptor. However, less is known about the SAR (structure–activity relationship) of CB2-active compounds and there is a need to separate CB1 activity from CB2 activity because compounds that bind selectively to the CB2 receptor could act as potential therapeutic agents.[4]

With the aim of developing a new, concise and general synthetic route to bi- and tricyclic cannabinoid analogues, the preparation of chromans of type **2** was developed. As shown in Scheme 1, these compounds, which contain the aromatic ring (called the A ring) and the dimethyltetrahydropyran ring (the B ring) of Δ^9-THC (**1**), were expected to be formed upon radical cyclisation of 1,7-dienes of type **3** using diethyl thiophosphite (*O*,*O*-diethyl phosphonothioate).[5] The intermediate phosphorus-centred radical, $(EtO)_2P(S)\cdot$, was expected to add regioselectively to the styrene C=C bond in **3**, to give benzylic radical **4**, which could then undergo a 6-*exo*-*trig* cyclisation to form the dimethylpyran ring in chroman **2**.[6] Chroman **2** could then be converted into a variety of cannabinoid analogues through manipulation of the phosphonothioate group.



Scheme 1

Initial studies concentrated on the reaction of diene **5** [prepared in 90% yield by O-allylation and then Wittig reaction of salicylaldehyde (**6**) using $Ph_3P{=}CH_2$] with $(EtO)_2P(S)H$ (2 equiv) using Et_3B (2×0.5 equiv) at room temperature in cyclohexane (see Figure 2).[7] Unfortunately, none of the desired cyclic product was isolated. In comparison, when 1,7-octadiene was reacted with $(EtO)_2P(S)H$ and Et_3B under similar reaction conditions, cyclohexane **7** was isolated in up to 62% yield (as an equal mixture of diastereoisomers). Reaction of **5** with alternative phosphorus hydrides, using Et_3B–O_2 or AIBN as initiator, was also unsuccessful. For example, when diene **5** was treated with diphenylphosphine oxide [$Ph_2P(O)H$; 2.15 equiv] and Et_3B at room temperature in cyclohexane for 24 hours, only benzylic alcohol **8** was recovered (in 13% yield) after column chromatography. The formation of **8** is presumably explained by reaction of the intermediate benzylic radical (of type **4**) with O_2, followed by reduction of the resulting hydroperoxide.

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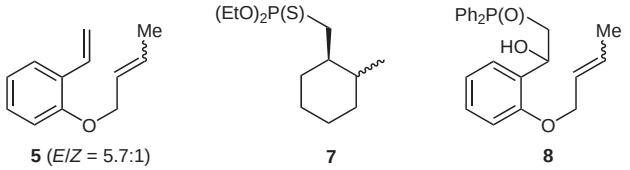


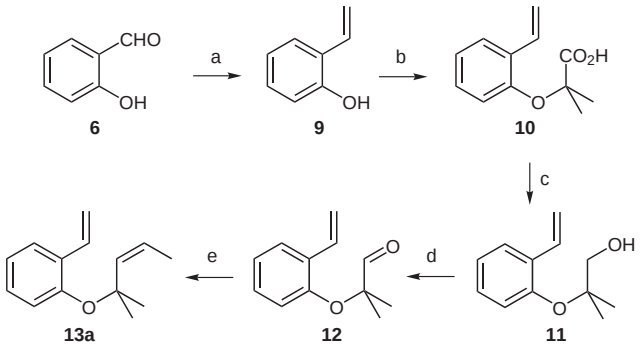
5 (*E*/*Z* = 5.7:1) **7** **8**

Figure 2

The unsuccessful cyclisation of **5** using $(EtO)_2P(S)H$ could be explained by the relatively slow rate of cyclisation of the intermediate benzylic radical, the relatively slow rate of reduction of the secondary radical formed on 6-*exo*-*trig* cyclisation (cf. the successful cyclisation of 1,7-octadiene to form **7**) and/or the intermediate benzylic radical could undergo a competitive 1,5-hydrogen atom abstraction (to form an allylic radical).

Studies then progressed to the synthesis of diene precursors, which on cyclisation would form the dimethyltetrahydropyran ring present in the cannabinoids. It was anticipated that the introduction of a geminal dimethyl group in the allylic ether side-chain (**3**, R = Me) would facilitate the radical cyclisation: not only do the geminal dimethyl groups prevent the intermediate benzylic radical undergoing 1,5-hydrogen transfer, but the rate of 6-*exo* cyclisation should be higher due to the Thorpe–Ingold effect.[8]

A concise and efficient route to diene **13a** from salicylaldehyde (**6**) was developed as shown in Scheme 2. Following a Wittig reaction of **6**, the resulting phenol was treated with chloroform, acetone and hydroxide ion to form carboxylic acid **10**. Subsequent reduction of **10** gave primary alcohol **11**, which was oxidised to **12** using Swern conditions. Finally, a Wittig reaction of **12** with $Ph_3P{=}CHMe$ (prepared in situ) afforded diene **13a** as the *Z*-isomer.[9] It was possible to convert **6** into **13a** in an overall yield of 70% without the need to purify intermediates **9**–**12** by chromatography; the crude products from each reaction were taken on to give crude **13a**, which was purified by column chromatography.

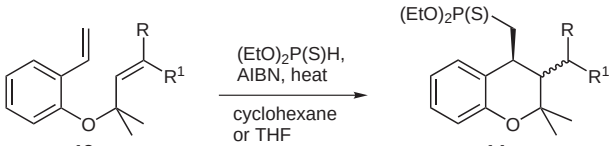


6 **9** **10** **11** **12** **13a**

Scheme 2 *Reagents and conditions*: (a) BuLi (2 equiv), $Ph_3(Me)P^+Br^-$ (1.5 equiv), THF, 0 °C to r.t. (98%); (b) $CHCl_3$ (2 equiv), NaOH (2.7 equiv), acetone, 0 °C to r.t. (87%); (c) $LiAlH_4$ (1.5 equiv), Et_2O, 0 °C to r.t. (88%); (d) $(COCl)_2$, Me_2SO, CH_2Cl_2, –60 °C, then Et_3N, –40 °C, then r.t.; (e) BuLi (2 equiv), $Ph_3(Et)P^+Br^-$ (1.5 equiv), THF, –0 °C to r.t. (93% over two steps).

Reaction of **13a** with diethyl thiophosphite (2 equiv) was then investigated (Table 1). Initial results using Et_3B–O_2 as the initiator were disappointing as no chroman products were isolated. The major product isolated (in up to 11% yield) was a secondary benzylic alcohol derived from addition of $(EtO)_2P(S)\cdot$ to the styrene C=C bond followed by reaction with O_2 (cf. the formation of **8**). Using more than one equivalent of $(EtO)_2P(S)H$ also led to the formation of the 'simple' addition product, derived from addition of $(EtO)_2P(S)H$ to the styrene C=C bond. However, changing the initiator to AIBN (0.8 equiv) and using one equivalent of $(EtO)_2P(S)H$ did lead to the isolation of chroman **14a** in 28% yield as an equal mixture of two diastereoisomers.[10,11]

Table 1 Radical Cyclisation of Dienes **13a–c** Using $(EtO)_2P(S)H$



13a–c **14a–c**

Diene **13**	R	R^1	Chroman **14**	Yield (%)/dr[a]
a	H	Me	**a**	28[b]/1:1
b	COMe	H	**b**	45[c]/1:0
c	CO_2Me	H	**c**	54[d]/1:0

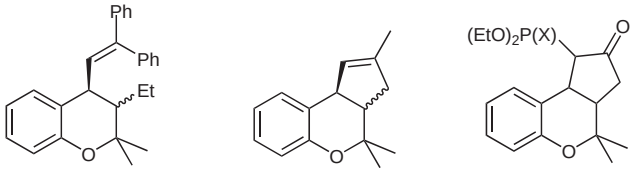
[a] Calculated from the ^1H NMR spectrum.
[b] Using 1 equiv of $(EtO)_2P(S)H$ in cyclohexane.
[c] Using 5 equiv of $(EtO)_2P(S)H$ in cyclohexane.
[d] Using 5 equiv of $(EtO)_2P(S)H$ in THF.

The effect of changing the substitution of the C=C bond in the allylic ether side chain (on the efficiency of the radical cyclisation) was investigated. Reaction of unsaturated ketone **13b** (prepared by reacting **12** with $Ph_3P{=}CHCOMe$; 59% yield over two steps from **11**) with $(EtO)_2P(S)H$ and AIBN gave chroman **14b** in 45% yield as a single diastereoisomer. The stereochemistry of **14b** was tentatively assigned as *trans* on the basis of a NOESY NMR experiment. The higher yield of **14b** compared to **14a** presumably reflects the faster rate of 6-*exo* radical cyclisation on to the electron-deficient C=C bond of **14b** (hence cyclisation occurs even in the presence of five equivalents of the thiophosphite), while the isolation of a single isomer of **14b** could be explained by a reversible radical cyclisation leading to the thermodynamic product.[12]

A similar result was observed on cyclisation of unsaturated ester **13c** (prepared by reacting **12** with $Ph_3P{=}CHCO_2Me$; 48% yield over two steps from **11**) to give chroman **14c** in 54% yield as a single diastereoisomer.[13]

Preliminary studies to demonstrate the use of chromans **14a–c** to prepare various cannabinoid analogues were also investigated. For example, a Horner–Wadsworth–Emmons-type (HWE-type)[5j] reaction of chroman **14a** using *s*-BuLi (2 equiv) and benzophenone (2 equiv) in THF (–

78 °C to r.t.) gave trisubstituted alkene **15**[14] in 56% yield after chromatography (as an inseparable mixture of diastereoisomers in the ratio 6.5:1) (Figure 3). Unfortunately, an attempted intramolecular HWE-type reaction (using NaH in DME) of **14b** only gave the desired cyclopentene **16** in an unoptimised 10% yield (as a 4:1 mixture of isomers). However, tricyclic cannabinoid derivatives, such as **17**, can be prepared in reasonable yield from **14c**. Hence, reaction of **14c** with MCPBA gave the corresponding phosphonate in 47% yield, which on deprotonation with NaH (2 equiv) in refluxing DME[15] underwent cyclisation to form tricycle **17** in 62% yield (of unknown stereochemistry). In comparison, the corresponding phosphonothioate **18**, formed on anionic cyclisation of **14c**, was isolated in a reduced yield of 30%.



15 **16** **17** X = O **18** X = S

Figure 3

In conclusion, we have developed a concise and efficient synthesis of 1,7-dienes of type **13a**–**c** and shown, for the first time, that these compounds react with $(EtO)_2P(S)H$ and AIBN to form chromans **14a**–**c**; the efficiency and diastereoselectivity of the cyclisation being influenced by the structure of the 1,7-diene. Chromans of type **14a**–**c** have the potential to act as useful building blocks for the synthesis of a variety of novel bi- and tricyclic cannabinoid analogues of biological interest. In addition, this work further illustrates the synthetic use of $(EtO)_2P(S)H$ in radical cyclisations of dienes; this method of cyclisation offers an attractive alternative to traditional approaches using Bu_3SnH, which are hampered by the toxicity of the metal hydride.

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References and Notes

(1) (a) Fichera, M.; Cruciani, G.; Bianchi, A.; Musumarra, G. *J. Med. Chem.* **2000**, *43*, 2300. (b) Turner, C. E.; Elsohly, M. A.; Boeren, E. G. *J. Nat. Prod.* **1980**, *43*, 169.

(2) See for example: (a) Keimowitz, A. R.; Martin, B. R.; Razdan, R. K.; Crocker, P. J.; Mascarella, S. W.; Thomas, B. F. *J. Med. Chem.* **2000**, *43*, 59. (b) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Pertwee, R. G. *Pharmacol. Rev.* **2002**, *54*, 161. (c) Salo, O. M. H.; Raitio, K. H.; Savinainen, J. R.; Nevalainen, T.; Lahtela-Kakkonen, M.; Laitinen, J. T.; Järvinen, T.; Poso, A. *J. Med. Chem.* **2005**, *48*, 7166.

(3) For some previous synthetic approaches to cannabinoids, see: (a) Papahatjis, D. P.; Kourouli, T.; Abadji, V.; Goutopoulos, A.; Makriyannis, A. *J. Med. Chem.* **1998**, *41*, 1195. (b) Papahatjis, D. P.; Nikas, S. P.; Kourorli, T.; Chari, R.; Xu, W.; Pertwee, R. G.; Makriyannis, A. *J. Med. Chem.* **2003**, *46*, 3221. (c) Sun, H.; Mahadevan, A.; Razdan, R. K. *Tetrahedron Lett.* **2004**, *45*, 615. (d) Chu, C.; Ramamurthy, A.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.* **2003**, *68*, 55. (e) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. (f) Lesch, B.; Toräng, J.; Nieger, M.; Bräse, S. *Synthesis* **2005**, 1888. (g) Nikas, S. P.; Thakur, G. A.; Parrish, D.; Alapafuja, S. O.; Huestis, M. A.; Makriyannis, A. *Tetrahedron* **2007**, *63*, 8112.

(4) Mahadevan, A.; Siegel, C.; Martin, B. R.; Abood, M. E.; Beletskaya, I.; Razdan, R. K. *J. Med. Chem.* **2000**, *43*, 3778.

(5) For related addition reactions of phosphorus-centred radicals, see: (a) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. J. *Eur. J. Org. Chem.* **2006**, 1547. (b) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* **2003**, *44*, 479. (c) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. J. *Tetrahedron Lett.* **2004**, *45*, 5095. (d) Cho, D. H.; Jang, D. O. *Synlett* **2005**, 59. (e) Hunt, T. A.; Parsons, A. F.; Pratt, R. *J. Org. Chem.* **2006**, *71*, 3656. (f) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388. (g) Leca, D.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Soc. Rev.* **2005**, *34*, 858. (h) Parsons, A. F.; Sharpe, D. J.; Taylor, P. *Synlett* **2005**, 2981. (i) Hunt, T.; Parsons, A. F.; Pratt, R. *Synlett* **2005**, 2978. (j) Healy, M. P.; Parsons, A. F.; Rawlinson, J. G. T. *Org. Lett.* **2005**, *7*, 1597. (k) Carta, P.; Puljic, N.; Robert, C.; Dhimane, A.-L.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2007**, *9*, 1061.

(6) For complementary 6-*exo*-*trig* radical cyclisation approaches to tetrahydropyrans, see: (a) Lee, E. *Pure Appl. Chem.* **2005**, *77*, 2073. (b) Hiramatsu, N.; Takahashi, N.; Noyori, R.; Mori, Y. *Tetrahedron* **2005**, *61*, 8589. (c) Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619. (d) Evans, P. A.; Roseman, J. D. *Tetrahedron Lett.* **1997**, *38*, 5249. (e) Leeuwenburgh, M. A.; Litjens, R. E. J. N.; Codée, J. D. C.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Org. Lett.* **2000**, *2*, 1275. (f) Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335.

(7) All new compounds gave consistent spectral and high resolution mass spectroscopic data.

(8) See for example: (a) Journet, M.; Lacôte, E.; Malacria, M. *J. Chem. Soc., Chem. Commun.* **1994**, 461. (b) Maulide, N.; Markov, I. E. *Chem. Commun.* **2006**, 1200.

(9) **(*Z*)-1-(2-Methylpent-3-en-2-yloxy)-2-vinylbenzene** (**13a**): yellow oil. IR ($CDCl_3$): 3085, 3065, 2958, 2927, 1603, 1487, 1456, 1439, 1377, 1174, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.80–7.70 (m, 4 H, 4 × ArCH), 7.10 (dd, *J* = 17.5, 11.0 Hz, 1 H, C*H*=CH_AH_B), 5.72 (dd, *J* = 17.5 1.5 Hz, 1 H, CH=C*H*$_A$H$_B$), 5.64 (dq, *J* = 12.0, 1.5 Hz, 1 H, C*H*=CHMe), 5.54 (dq, *J* = 12.0, 7.0 Hz, 1 H, CH=C*H*Me), 5.22 (dd, *J* = 11.0, 1.5 Hz, 1 H, CH=CH$_A$*H*$_B$), 1.70 (d, *J* = 7.0 Hz, 3 H, Me), 1.53 (s, 6 H, MeCMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 (Ar*C*O), 135.1, 132.0, 128.4, 127.4, 126.1, 120.7, 118.1 (4 × Ar*C*H, *C*H=CH$_A$H$_B$, *C*H=*C*HMe), 128.6 (Ar*C*CH=C), 113.7 (CH=*C*H$_A$H$_B$), 79.4 (Me*C*Me), 28.8 (*Me*C*Me*), 13.7 (CH=CH*Me*). MS (CI, NH_3): *m*/*z* (%) = 203 (8) [MH^+], 83 (100). HRMS (CI): *m*/*z* calcd for $C_{14}H_{19}O$ [M + H^+]: 203.1436; found: 203.1436.

(10) **Synthesis of *O*,*O*-Diethyl (3-Ethyl-2,2-dimethyl-3,4-dihydro-2*H*-chromen-4-yl)methylphosphonothioate (14a)**: 1,7-Diene **13a** (0.150 g, 0.74 mmol, 1 equiv), diethyl

thiophosphite (0.114 g, 0.74 mmol, 1 equiv) and AIBN (0.097 g, 0.59 mmol, 0.8 equiv, 1 portion) were heated to reflux in degassed cyclohexane (20 mL) overnight. After cooling to r.t., the solvent was evaporated and purification of the crude product by column chromatography (silica, petrol) afforded **14a** (0.073 g, 28%) as a colourless oil, as an inseparable 1:1 mixture of *cis*- and *trans*-diastereoisomers as indicated by the ^{1}H NMR spectrum. IR (CH_2Cl_2): 3055, 2983, 2937, 2904, 2879, 1606, 1581, 1487, 1452, 1387, 1371, 1302, 1261, 1225, 1159, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$; both diastereoisomers): δ = 7.40, 7.29 (2 × d, 2 × *J* = 8.0 Hz, 1 H, ArCH), 7.11, 7.09 (2 × t, 2 × *J* = 8.0 Hz, 1 H, ArCH), 6.98, 6.86 (2 × t, 2 × *J* = 8.0 Hz, 1 H, ArCH), 6.78, 6.74 (2 × d, 2 × *J* = 8.0 Hz, 1 H, ArCH), 3.96–4.28 (m, 4 H, 2 × OC*H*$_2$Me), 3.58, 3.32 (2 × app. ddt, *J* = 19.0, 6.0, 5.0 Hz and *J* = 24.0, 5.5, 5.0 Hz, 1 H, PCH$_A$H$_B$C*H*), 2.40–2.62, 2.27 (m and app. td, *J* = 16.0, 5.0 Hz, 2 H, PC*H*$_A$*H*$_B$), 1.19–1.83 (m, 15 H, MeCMe, C*H*C*H*$_2$Me, 2 × OCH$_2$*Me*), 1.04, 1.02 (2 × t, 2 × *J* = 7.5 Hz, 3 H, CHCH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$; both diastereoisomers): δ = 153.6, 152.9 (Ar*C*O), 127.8, 127.7, 127.5, 2 × 125.7 (2 × d, $^3J_{CP}$ = 10.5, 7.0 Hz, PCH$_A$H$_B$CHAr*C*), 120.5, 120.0, 2 × 117.3 (4 × Ar*C*H), 78.7 (Me*C*Me), 62.7, 62.6, 62.3, 62.2 (4 × d, $^2J_{CP}$ = 4 × 7.0 Hz, 2 × O*C*H$_2$Me), 48.1 (d, $^3J_{CP}$ = 5.5 Hz, PCH$_A$H$_B$CH*C*H), 42.3, 34.6 (2 × d, $^1J_{CP}$ = 109.0, 110.5 Hz, P*C*H$_A$H$_B$), 33.1, 32.0 (2 × d, $^2J_{CP}$ = 2.5, 1.5 Hz, PCH$_A$H$_B$*C*H), 28.7, 27.8, 26.3, 24.3 (*Me*C*Me*), 23.2, 19.5 (CH*C*H$_2$Me), 3 × 16.2, 16.1 (4 × d, $^3J_{CP}$ = 4 × 7.0 Hz, 2 × OCH$_2$*Me*), 14.2, 13.7 (CHCH$_2$*Me*). MS (CI, NH_3): *m*/*z* (%) = 357 (100) [MH$^+$]. HRMS (CI): *m*/*z* calcd for $C_{18}H_{30}O_3PS$ [M + H$^+$]: 357.1653; found: 357.1652.

(11) For other examples of 6-*exo* cyclisations of benzylic radicals, see: (a) Studer, A. *Angew Chem. Int. Ed.* **2000**, 1108. (b) Pattenden, G.; Reddy, L. K.; Walter, A. *Tetrahedron Lett.* **2004**, *45*, 4027. (c) Binot, G.; Quiclet-Sire, B.; Saleh, T.; Zard, S. Z. *Synlett* **2003**, 382.

(12) Resonance-stabilised radicals are known to undergo reversible cyclisations. See for example: (a) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6064. (b) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. (c) Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553.

(13) **Synthesis of Methyl 2-{4-[(Diethoxyphosphorothioyl)methyl]-2,2-dimethyl-3,4-dihydro-2*H*-chromen-3-yl}acetate (14c)**: 1,7-Diene **13c** (0.250 g, 1.02 mmol, 1 equiv), diethyl thiophosphite (0.782 g, 5.08 mmol, 5 equiv) and AIBN (0.042 g, 0.25 mmol, 0.25 equiv, 5 portions, 1 h between additions) were heated to reflux in anhyd degassed THF (20 mL) overnight. After cooling to r.t., the solvent was evaporated and excess diethyl thiophosphite was removed by distillation (75 °C/3 mmHg). Purification of the residue by column chromatography (silica; PE–Et_2O, 9:1) afforded **14c** (0.221 g, 54%) as a yellow oil. IR (CH_2Cl_2): 2982, 2953, 2853, 1735, 1608, 1582, 1488, 1453, 1437, 1388, 1372, 1302, 1249, 1228, 1170, 1138, 1116, 1098, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.5 Hz, 1 H, ArCH), 7.11 (t, *J* = 7.5 Hz, 1 H, ArCH), 6.90 (t, *J* = 7.5 Hz, 1 H, ArCH), 6.76 (d, *J* = 7.5 Hz, 1 H, ArCH), 4.06–4.28 (m, 4 H, 2 × OC*H*$_2$Me), 3.70 (s, 3 H, CO$_2$Me), 3.05–3.18 (m, 1 H, PCH$_2$C*H*), 2.69 (dd, *J* = 16.0, 3.5 Hz, 1 H, C*H*$_A$H$_B$), 2.32–2.55 (m, 4 H, PC*H*$_2$CHC*H*CH$_A$*H*$_B$), 1.35 (s, 3 H, *Me*CMe), 1.34 (t, *J* = 7.0 Hz, 6 H, 2 × OCH$_2$*Me*), 1.21 (s, 3 H, MeC*Me*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (*C*O$_2$Me), 152.6 (Ar*C*O), 129.3, 127.7, 120.7, 117.3 (4 × Ar*C*H), 125.5 (d, $^3J_{CP}$ = 7.5 Hz, PCH$_2$CHAr*C*), 76.8 (Me*C*Me), 62.8, 62.6 (2 × d, $^2J_{CP}$ = 2 × 7.0 Hz, 2 × O*C*H$_2$Me), 51.9 (CO$_2$*Me*), 44.1 (d, $^3J_{CP}$ = 7.0 Hz, PCH$_2$CH*C*H), 41.3 (d, $^1J_{CP}$ = 111.0 Hz, PCH$_2$), 35.6 (*C*H$_2$CO$_2$), 33.6 (d, $^2J_{CP}$ = 1.5 Hz, PCH$_2$*C*H), 27.3, 21.7 (*Me*C*Me*), 16.2, 16.1 (2 × d, $^3J_{CP}$ = 2 × 7.0 Hz, 2 × OCH$_2$*Me*). MS (CI, NH_3): *m*/*z* (%) = 401 (100) [MH$^+$]. HRMS (CI): *m*/*z* calcd for $C_{19}H_{29}O_5PS$ [M + H$^+$]: 401.1552; found: 401.1551.

(14) **4-(2,2-Diphenylvinyl)-3-ethyl-2,2-dimethylchromane (15)**: colourless oil (6.5:1 mixture of diastereoisomers). IR (CH_2Cl_2): 3019, 2958, 2931, 1598, 1581, 1484, 1451, 1386, 1302, 1148, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$; both diastereoisomers): δ = 7.20–7.42 (m, 11 H, 11 × ArCH), 7.11 (t, *J* = 7.0 Hz, 1 H, ArCH), 6.85 (t, *J* = 7.0 Hz, 1 H, ArCH), 6.77 (d, *J* = 7.0 Hz, 1 H, ArCH), 6.29, 5.95 (2 × d, *J* = 2 × 10.5 Hz, 1 H, *cis*-C=CH and *trans*-C=CH), 3.42 (app. t, *J* = 10.5 Hz, 1 H, C*H*CH=C), 1.54 (dt, *J* = 10.5, 4.5 Hz, 1 H, C*H*CH$_2$Me), 0.98, 1.42 (2 × s, 2 × 3 H, MeCMe), 1.20–1.40 (m, 2 H, C*H*$_2$Me), 0.80–0.92 (m, 3 H, CH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$; both diastereoisomers): δ = 153.1 (Ar*C*O), 143.2, 142.3, 139.8 (3 × Ar*C*), 131.1, 2 × 129.6, 2 × 128.4, 2 × 128.2, 127.8, 2 × 127.3, 2 × 127.2, 124.1, 119.7, 117.0 (14 × Ar*C*H, C=CH), 78.0 (Me*C*Me), 48.9 (*C*HCH$_2$Me), 40.1 (*C*HCH=C), 28.3 (*Me*CMe), 23.6 (*C*H$_2$Me), 20.3 (MeC*Me*), 15.2 (CH$_2$*Me*). MS (CI, NH_3): *m*/*z* (%) = 369 (45) [MH$^+$], 357 (100). HRMS (CI): *m*/*z* calcd for $C_{27}H_{28}O$ [M + H$^+$]: 369.2218; found: 369.2217.

(15) For a related cyclisation, see: Samarat, A.; Landais, Y.; Amri, H. *Tetrahedron Lett.* **2004**, *45*, 2049.