Transformation of substituted 2*H*-pyran-5-carboxylates into 3*R**-vinyl-1,2*R**-cyclopropanedicarboxylates†

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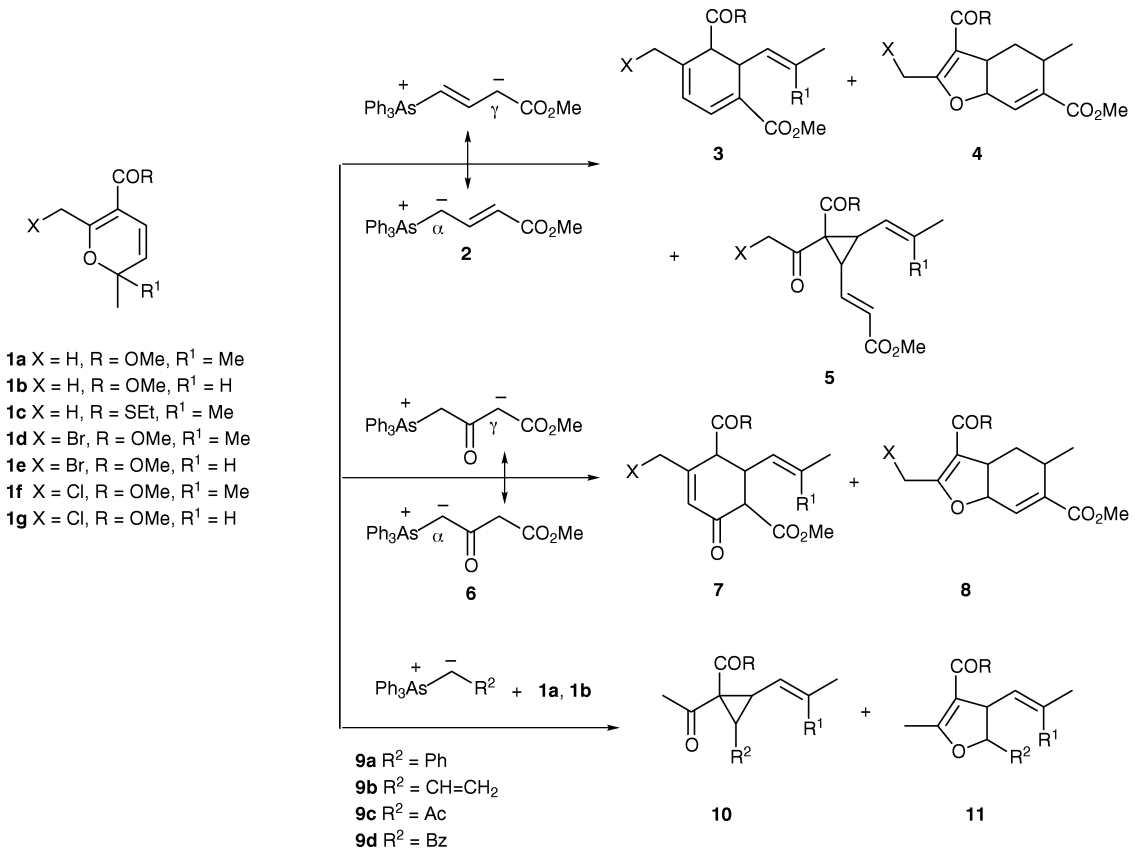
Substituted alkyl 2*H*-pyran-5-carboxylates, **1**, have been condensed with methyl 2-(triphenylarsoranylidene) ethanoate, **14a**, to form substituted 3-vinyl-1,2-cyclopropanedicarboxylates, **15**, and, in a number of cases, 2,3-dihydro-3-vinyl-2,4-furandicarboxylates, **16**. NMR experiments showed that for the majority of cyclopropane products formed, the cyclopropane ring hydrogen atoms have the *trans* configuration. This was validated by molecular orbital calculations. Biological screening tests revealed that these compounds showed some ectoparasiticidal activity.



Scheme 1

2*H*-Pyrans are not very common.[1] As part of a program aimed at developing new synthetic methods for substituted alkyl 2*H*-pyran-5-carboxylates, **1**, we investigated the reaction between these rather unstable heterocycles and arsonium ylides (Scheme 1). For example, we have found that the condensation of 2*H*-pyran-5-carboxylates, **1**, and crotonate arsonium ylide, **2**, gave in some cases a mixture of cyclohexa-3,5-diene-1,3-dicarboxylates, **3**, and tetrahydrobenzofurandicarboxylates, **4**. Both types of products are formed due to Michael additions of the γ-ylide of the arsonium ylide **2**, followed by intramolecular cyclization and elimination of either $Ph_3As{=}O$ or Ph_3As, respectively. However, the main products isolated were divinylcyclopropanes, **5**.[2] In contrast, condensation of acetoacetate arsonium ylide, **6**, with 2*H*-pyran-5-carboxylates, **1**, gave no cyclopropane compounds, but instead, vinylcyclohexenonedicarboxylates, **7**, were identified with minor amounts of tetrahydrobenzofurandicarboxylates, **8**. The products **7** and **8**

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† Non-SI unit employed: 1 kcal ≈ 4.18 kJ.

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resulted from an initial Michael addition of the γ-ylide of the arsonium ylide **6**, followed by intramolecular cyclization and elimination of either $Ph_3As{=}O$ or Ph_3As, respectively.[3] In a recent communication we described our preliminary results on the condensation of 2*H*-pyran-5-carboxylates, **1a** and **1b**, with arsonium ylides **9a**–**d**. In all of these cases a mixture of two substituted vinylcyclopropanecarboxylates, **10**, and in some cases also vinyldihydrofurancarboxylates, **11**, were isolated.[4] Cyclopropanations with phosphonium ylides are known.[5]

In this work we give a detailed account of the condensation of 2*H*-pyran-5-carboxylates **1a**–**f** with arsonium ylides $Ph_3As{=}CHCO_2Me$, **14a** and $Ph_3As{=}CHCN$, **14b**, and the biological activities of the cyclopropanes **15** obtained.

Results and Discussion

We have described the synthesis of substituted 2*H*-pyran-5-carboxylates, **1**, from alkyl 3-oxobutanoates and α,β-unsaturated aldehydes.[6] We have also found that the most distinctive property of this heterocyclic ring system is its ability to undergo reversible electrocyclic ring opening to the *cis*-2,4-dienone tautomer **12**,[7] making these compounds available for Michael attack. Both species **1** and **12** can be observed by NMR. Increasing steric interaction in the system generally favours the 2*H*-pyran form.[8]

In most cases the equilibrium is shifted towards the 2*H*-pyran **1** system and the entire mixture, for example **1a** and **12a**, can be trapped with nitroethylene[9] to give, in a stereoselective manner, the *endo*-Diels–Alder cycloadduct **13**, a dehydro-1,8-cineole derivative[10] (Scheme 2). Few other Diels–Alder reactions of 2*H*-pyrans are known.[11]

Methyl 2-(triphenylarsoranylidene)ethanoate, **14a**, was prepared *in situ* from (methoxycarbonylmethyl)triphenylarsonium bromide[12] and potassium *tert*-butoxide in THF and reacted with 2*H*-pyran-5-carboxylates **1a** to **1f** at room or elevated temperatures to form highly functionalised *trans*-3-vinyl-1,2-cyclopropanedicarboxylates, **15**.[13] In most cases substituted 3-vinyl-2,3-dihdro-2,4-furandicarboxylates, **16**,[14] were isolated in trace or minor amounts (Table 1).

It has been reported that the reaction of conjugated carbonyl compounds and arsonium ylides gives cyclopropanes.[15] The preparation of vinylcyclopropanes using arsonium ylides and conjugated carbonyl compounds is less common.[16] Cyclopropanedicarboxylates are useful reagents in synthesis,[17] while the production of dihydrofurans from arsonium ylide and conjugated carbonyl compounds is rather rare[18] and may be useful in synthesis.[19] We have not been able to manipulate successfully the exclusive formation of **16**.

To explain the mechanism, as discussed before, at room temperature 2*H*-pyran-5-carboxylate **1** is in equilibrium with the conjugated ketodiene **12**. A C^{α}–C^3 Michael attack of the arsonium ylide **14** to **12**, followed by ring closure and expulsion of triphenylarsine gives **15**.[20] Alternatively, an intramolecular attack of the enolate oxygen of the C^{α}–C^3 Michael adduct on C^{α} gives **16**[21] (Scheme 3). Thus, methyl 2,2,6-trimethyl-2*H*-pyran-5-carboxylate, **1a**, reacted with **14a** in THF at 0 °C to give a mixture of cyclopropanes **15a**(i) and **15a**(ii) in a ratio of 62 : 38 in a combined yield of 79%. Furthermore, J_{HH} coupling constants of the cyclopropane ring protons showed that the cyclopropanes **15** have a *trans* configuration. Only a trace amount of dihydrofuran **16a** was isolated. Changing the solvent or temperature had little effect on the ratio and yield of products (Table 1, entries 1–5). Michael addition of the arsonium ylide **14** to the dienone **12** is expected to take place such that the large groups are positioned in the lowest energy conformation (Scheme 3).[15] Therefore, elimination of triphenylarsine in pathway *a* gives the preferred C^2,C^3 (*trans*) vinyl-1,2-cyclopropanedicarboxylates **15**(i) and **15**(ii) or 2,3-dihydro-3-vinyl-2,4-furandicarboxylates **16** (pathway *b*). The configuration of the intermediate complex whereby the large Ph_3As— and the acetyl(methoxycarbonyl) groups are still opposite, but the two protons positioned in a *syn* configuration, pathway *c*, seems not to have taken place. With the arsonium ylide $Ph_3As{=}CHCN$, **14b**, however, some *cis* isomer **18** had formed (entry 14, Table 1). In the precursor of product **18**, that is the *cis* isomer of **15g**, the acetyl group was unhindered and therefore ready for a Wittig condensation to furnish **18**. All other *trans* cyclopropanes, **15a**–**f**, showed no desire for a further Wittig condensation of the acetyl group; although we have not investigated such condensations under prolonged conditions or elevated temperatures.

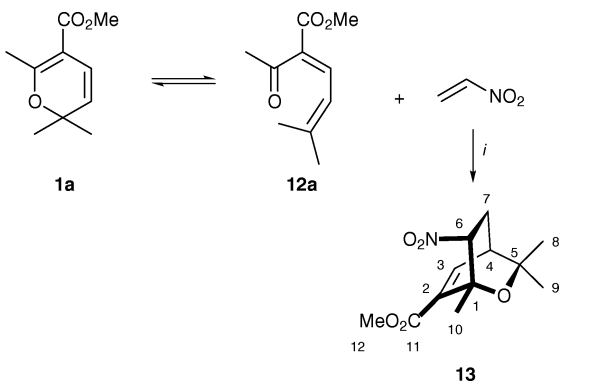
The molecular orbital calculations showed that the two postulated structures of the intermediate in Scheme 3 have different energies due to steric interaction between the esters in one case, and the ester and enol in the other. The intermediate postulated to follow path *a* was 6.44 kcal mol^{-1} more stable than the intermediate postulated to follow the *c* pathway. This energy difference is consistent with the proposed mechanism. The results of other condensations of **1** and **14a** or **14b** are summarized in Table 1.

As expected, *trans*-cyclopropane ring protons H^4 and H^5 of **15** showed large vicinal coupling constants ($J_{H^4H^5}$). In general, both *cis*- and *trans*-cyclopropane ring protons with a number of strong electron-withdrawing groups on the ring seem to have particularly large vicinal coupling constants, with those of the *cis*-cyclopropane ring protons being even larger than for the *trans* isomer.[21] For example, both *trans* isomers of **15a** had a *trans* vicinal coupling constant of $J_{H^4H^5} = 7.1$ Hz, while **15b**, **15c** and **15f** (two isomers) had $J_{vic(trans)}$ in the range 6.8–7.6 Hz. The vicinal coupling constant between the cyclopropane ring protons and the vinyl substituent protons is also large ($J_{H^4H^6} = 8.3$ to 8.6 Hz) and suggests a *trans* conformation.[22i] 2*H*-Pyran **1d** gave minor amounts of the cyclopropane **15f**. Instead, the main product isolated was the very labile cross-conjugated 2*H*-pyran-5-carboxylate **17**. Nucleophilic salt coupling of **1d** had taken place, followed by base-induced elimination of triphenylarsine to give **17** (Scheme 4).

^{13}C-NMR[22,23] and ^{1}H-NMR[22,24] data of all compounds are outlined in Tables 2 and 3, respectively. NOESY NMR correlations of **15c** and **19**[2] are shown in Scheme 5. The absence and the presence of an nOe effect between the *trans* and *cis* ring protons H^a and H^b in the former and the latter is indicative of the configuration of **15c** and **19**.

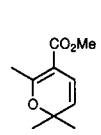
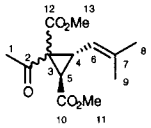
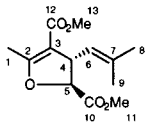
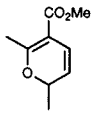
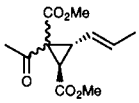
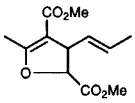
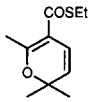
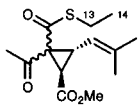
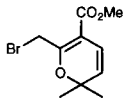
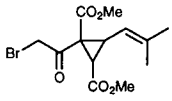
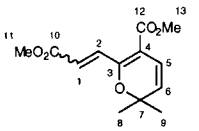
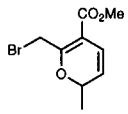
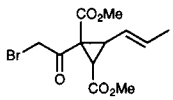
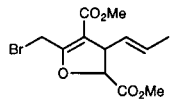
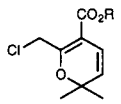
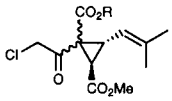
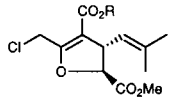
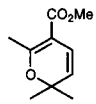
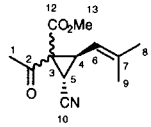
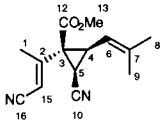
Biological screening tests revealed that of the 2*H*-pyran-5-carboxylates **1** submitted, only **1b**, **1c**, **1g** and **1h** (Table 1 and Scheme 6) showed some ectoparasiticidal activity while **1h** also showed some endoparasiticidal activity. Compounds **1a**, **1d**, **1e**, **1f** and **1i** did not show any activity against parasites.

Of the vinylcyclopropane-1,2-dicarboxylates **15** submitted, **15a**, **15b**, **15c** and **15g** (Table 1) showed some ectoparasiticidal activity. However, **15e** and **18** did not show any activity against parasites.[25] Other vinylcyclopropanes recently prepared by us[2,4] also showed some ectoparasiticidal activity. For example, compounds **5a**, **5b**, **5c**, **5f** and **20**[26] and also **10a**,

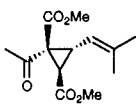
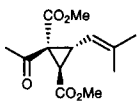


Scheme 2 Reactions and conditions: *i* toluene, 20 °C, 48 h, 86%

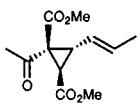
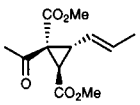
Table 1

Entry	2*H*-pyran, **1**	Reaction conditions	Yield of products: Ph_3As	**1**	Cyclopropane, **15**[a]	Other products
1		0 °C, 15 min 45 °C, 16 h in THF				
	1a		70%	[b]	**15a**, 79% 62 : 38[c]	**16a**[b]
2	**1a**	THF, r.t., 15 h	[b]	[b]	**15a**, 82% 66 : 34[c]	**16a**, ≈1%
3	**1a**	THF, 60 °C, 8 h	[b]	[b]	**15a**, 59% 70 : 30[c]	**16a**, 2%
4	**1a**	CH_2Cl_2, r.t., 15 h	[b]	[b]	**15a**, 73% 62 : 38[c]	**16a**, 2%
5	**1a**	DMSO, r.t., 15 h	[b]	[b]	**15a**, 59% 60 : 40[c]	**16a**, 5%
6		0 °C, 10 min 20 °C, 1 h				
	1b		74%	2%	**15b**, 73% 6 : 4	**16b**[b]
7	**1b**	THF, r.t., 15 h	[b]	[b]	**15b**, 69% 79 : 21[c]	**16b**, 2%
8		0 °C, 10 min 45 °C, 1 h				Trace of unidentified product
	1c		75%	[b]	**15c**, 90%	<3%
9		0 °C, 15 min 20 °C, 6 h				
	1d		53%	48%	**15d**, trace single isomer	*trans*-**17**, 30%, *cis*-**17**, 24%
10		60 °C, 30 min				
	1e		48%	9%	**15e**, 14%	**16e**, 6%
11		0 °C, 10 min 20 °C, 1 h 45 °C, 1 h				
	1f (R = Me)		61%	22%	**15f** (R = Me), trace	**16f** (R = Me), 44%
12	**1f** (R = Me)	20 °C, 14 h	73%	[b]	**15f** (R = Me), 49%	**16f** (R = Me), trace
13	**1f** (R = Et)	20 °C, 14 h	[b]	[b]	**15f** (R = Et),[c] 50%	**16f** (R = Et), trace
14		0 °C, 15 min 20 °C, 6 h				
	1a		55%	[b]	**15g**, 22%	**18**, 15%

[a] The configuration and the ratio of cyclopropanes **15** and **16f** were determined by ^{1}H-NMR experiments. [b] The yield either not anlaysed or too low for determination. [c] Ratios of:

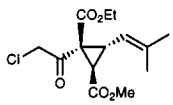
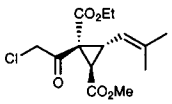



3 : 2
15a(i) : **15a**(ii)

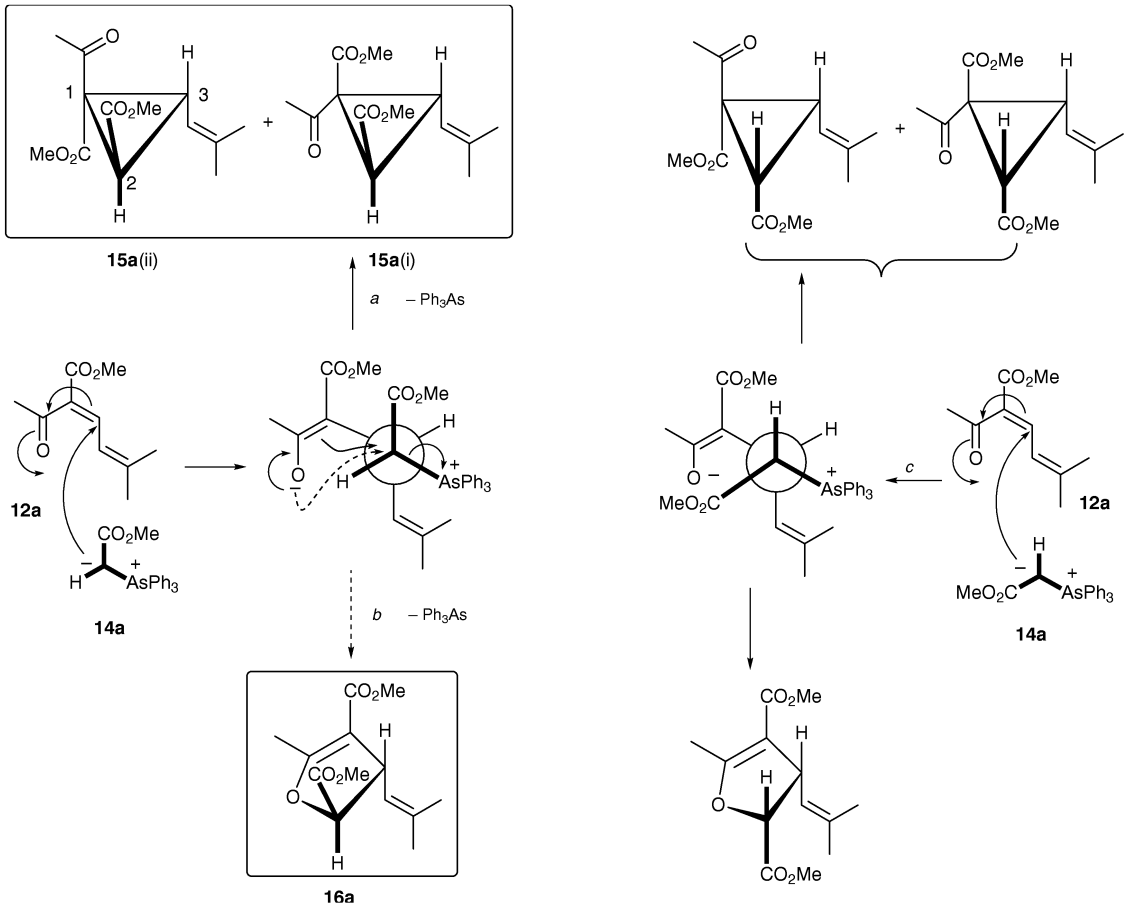



4 : 1
15b(i) : **15b**(ii)

and

15f(i) : **15f**(ii)(R = Et)

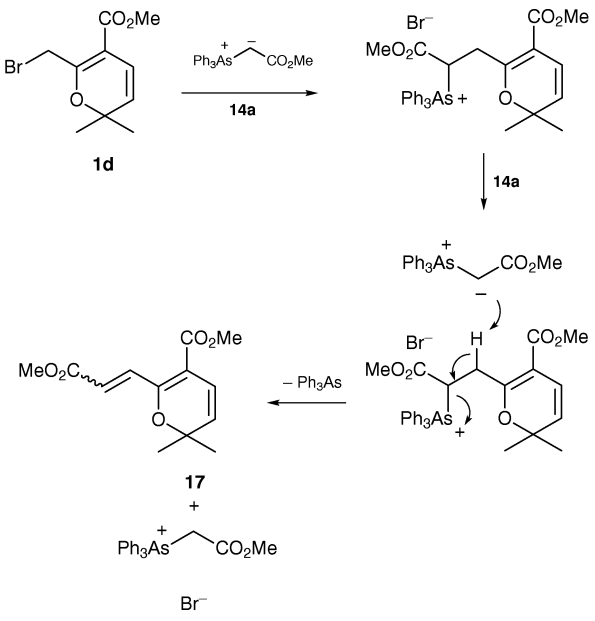


Scheme 3 The mechanism of cyclopropanation of arsonium ylides **14** and 2*H*-pyrans **1**

10b and **10c** showed some ectoparasiticidal activity, but **5d**, **10d**, **10e** and **10f** showed no activity (Scheme 6).

Conclusions

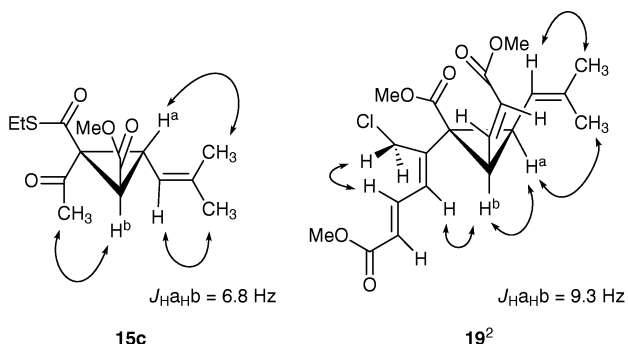
In this article we have described an efficient synthetic method for the preparation of vinylcyclopropane-1,2-dicarboxylates, **15**, from acetatearsonium ylide, **14a**, and 2*H*-pyran-5-carboxylates, **1**. We have not been able to obtain dihydrofurans,[27] **16**, exclusively.



Scheme 4

Experimental

All reactions were carried out under nitrogen. ^{1}H-NMR ($SiMe_4$ as an internal standard) and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz and 50.3 MHz, respectively. High resolution electron ionization (EI) mass spectra and chemical ionization (CI) mass spectra using ammonia were obtained on a Kratos Concept ISQ instrument. Infrared spectra were obtained on a Hitachi 270-30 FTIR spectrophotometer (film, NaCl plates). Ultraviolet absorbance was measured on 96% EtOH solutions on a Shimadzu UV-150 spectrophotometer. Microanalyses were obtained using a Carlo Erba CHNS-O EA 1108 elemental analyser. Column chromatography was performed using Merck Si-60 (40–63 mm) silica gel. Bulb-to-bulb distillations (bp) were carried out on a Büchi GKR-51 apparatus. Diethyl ether (ether) and tetrahydrofuran (THF) were dried and distilled from $LiAlH_4$. Light petroleum is the fraction between 40–60 °C. Arsonium salts were prepared by heating methyl



Scheme 5 Typical nOe's observed in NOESY experiments of **15c** and **19**

Table 2 ^{13}C Chemical shifts (δ_C) of compounds **15a**, **16a**, **15b**, **15c**, *trans*-**17**, *cis*-**17**, **15e**, **16e**, **15f**, **16f**, **15g** and **18**[a,b,c]

Carbon	**15a**(i) 62%	**15a**(ii) 38%	**16a**[d]	**15b**(i) 79%	**15b**(ii) 21%	**15c**	*trans*-**17**	*cis*-**17**	**15e**[e]	**16e**	**15f**(i) major	**15f**(ii)[f] minor	**16f**	**15g**	**18**
1	28.71	29.07	13.89	28.99	29.06	23.98	127.07	127.68	34.57	20.59	48.15	47.79	35.31	29.46	20.34
2	197.03	198.03	167.09	197.22	197.93	197.03	135.85	135.85	193.35	163.64¶	194.96	192.84	164.23¶	197.21	158.31
3	49.74	48.34	≈105.2	49.50	47.88	56.55	155.44	156.62	45.70	107.83	45.71	47.88	104.55	47.26	41.79
4	32.29¶	30.90	45.85	31.81	33.41¶	32.60¶	109.52	106.81	35.34¶	49.56	31.49	34.04¶	54.71	32.89	29.54
5	32.78¶	34.03	83.84	36.15	34.25¶	32.11¶	123.73	125.18	35.46¶	83.66	35.55	34.25¶	83.15	16.58	17.83
6	116.09	116.71	124.67	122.28	122.23	115.92	120.25	119.89	122.68	128.24	116.39	115.81	121.97	114.54	115.08
7	139.11	138.87	134.15	131.69	131.35	138.94	77.48	78.16	132.43	129.20	139.80	140.70	140.23	142.08	140.87
8	25.26	25.26	25.55	17.78	17.72	25.21	27.19	26.98	18.05	17.76	25.67	25.60	25.77	25.65	25.73
9	18.24	18.24	17.75	—	—	18.19	27.19	26.98	—	—	18.53	18.73	18.41	18.72	18.57
10	167.85*	166.99¶	167.48	167.75¶	166.88*	168.93	165.63¶	167.94	166.38*	164.10¶	166.42¶	167.45*	164.24¶	116.35	113.77
11	52.03‡	52.54*	≈51	52.10*	52.06‡	51.85	51.83*	51.50*	52.59‡	52.58*	52.56*	52.61‡	51.56*	—	—
12	169.61*	169.21¶	170.55	169.44¶	167.75*	193.30	166.93¶	167.94	169.34*	168.79	169.75¶	169.00*	172.60	166.65	165.54
13	52.67‡	52.63*	≈51	52.73*	52.66‡	23.98	51.83*	51.53*	53.11‡	52.44*	53.03*	53.22‡	52.59*	53.44	52.98
14	—	—	—	—	—	14.02	—	—	—	—	—	—	—	—	—
15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	101.05
16	—	—	—	—	—	—	—	—	—	—	—	—	—	—	115.47

[a] At 50.3 MHz in $CDCl_3$. [b] Consult Table 1 for compounds. [c] Signal pairs ¶, *, ‡ can be interchanged. [d] Significant signals for **16b** are: 13.89 (C1), 47.93 (C3), 83.27 (C5), 127.0 (C6) and 130.38 (C7). [e] Signals for the minor isomer of **15e** are: 191.73 (C2), 170.04 and 167.38 (C12 and C10), 132.74 (C7), 121.88 (C6), 53.13 and 51.40 (C13 and C11), 47.27 (C3), 37.71 (C5) and 33.52 (C4). C1 was obscured by major compounds. [f] Signals for the ethyl ester of **15f** are in identical ratio 79:21, see experimental.

bromoacetate and bromoacetonitrile, respectively, with triphenylarsine in a melt.[12] Recrystallizations of the crude arsonium salts were carried out from toluene and methanol. Nitroethylene was prepared from 2-nitroethanol.[28] We modified the purification of 2-nitroethanol; filtration of the concentrated crude 2-nitroethanol over silica gel gave after elution with CH_2Cl_2 pure 2-nitroethanol that was safe for vacuum distillation.

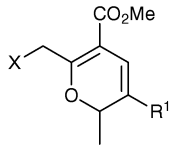
Table 3 ^1H chemical shifts (δ_H) and coupling constants (J in Hz) of compounds **15a**, **16a**, **15b**, **15c**, **15d**, **15e**, **16e**, **15f**, **16f**, **15g**, **18**, *trans*-**17** and *cis*-**17**[a]

Proton	**15a**(i)	*J*	**15a**(ii)	*J*	**16a**	*J*	**15b**(i)	*J*	**15b**(ii)	*J*	**15c**	*J*
1	2.221	s	2.295		2.18	s	2.262	s	2.283	s	2.237	s
4	3.088	dd, 7.1, 8.6	3.046	dd, 7.1, 8.4	≈4.0	m	2.973	m	2.930	m	3.181	dd, 6.8, 8.6
5	2.855	d, 7.1	2.790	d, 7.1	4.532	d, 4.6	2.907	d, 7.0	2.812	d, 7.0	2.904	d, 6.8
6	4.738	dm, 8.6	4.902	dm, 8.4	4.995	dm, 9.7	5.061	ddq, 15.3, 8.3, 0.7	5.219	ddq, 15.3, 8.3, 0.7	4.737	dm, 8.6
7	—	—	—	—	—	—	5.862	dqd, 15.3, 6.5, 0.7	5.862	dqd, 15.3, 6.5, 0.7	—	—
8	1.698	s	1.795	s	1.62	s	1.687	dd, 6.5, 1.6	1.692	dd, 6.5, 1.6	1.702	s
9	1.803	d, 1.2	1.719	s	1.7	s	—	—	—	—	1.847	s
11	3.698	s	3.696	s	3.58	s	3.707	s	3.693	s	3.681	s
13	3.815	s	3.766	s	3.71	s	3.841	s	3.782	s	2.999	q, 7.4
14	—	—	—	—	—	—	—	—	—	—	1.310	t, 7.4

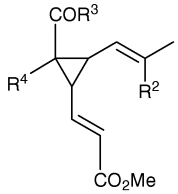
	15d[b]	*J*	**15e**[c]	*J*	**16e**	*J*	**15f**(i)	*J*	**15f**(ii)	*J*	**16f**	*J*
1	4.247,	d, 14.7	4.063,	d, 14.7	4.058	d, 13.4	4.189,	d, 16.3	4.304	s	4.423	d, 12.1
	4.092	d, 14.7	4.228	d, 14.7	4.242	d, 13.4	4.327	d, 16.3	—	—	4.689	d, 12.1
4	3.104	t, ~7.5	2.98–2.95	sm	≈3.6	sm	3.069	dd, 7.2, 8.3	3.295	dd, 7.6, 8.6	5.460	dd, 9.3, 6.7
5	2.949	d, 7.3	2.98–2.95	sm	4.791	d, 4.4	2.942	d, 7.2	3.016	d, 7.6	3.791	d, 6.7
6	4.953	dm, 8.4	5.270	dm, 15.3	5.48	dqd, 15.4, 7.3, 1.4	4.964	dm, 8.3	4.741	dm, 8.6	5.347	dm, 9.3
7	—	—	5.904	dq, 15.3, 6.6	5.67	dq, 15.4, 6.1	—	—	—	—	—	—
8	1.731	d, 0.8	1.704	dd, 6.6, 1.6	1.701	d, 6.1	1.727	s	1.720	s	1.741	s
9	1.794	d, 0.9	—	—	—	—	1.795	d, 1.1	1.815	d, 1.1	1.792	s
11	3.785	s	3.707	s	3.810	s	3.715	s	3.724	s	3.737	s
13	3.721	s	3.791	s	3.690	s	3.775	s	3.845	s	3.757	s

	15g(i)	*J*	**15g**(ii)	*J*	**18**	*J*	*trans*-**17**	*J*	*cis*-**17**	*J*
1	2.208	s	2.450	s	2.150	d, 1.1	6.532	d, 15.5	6.060	d, 12.4
2	—	—	—	—	—	—	8.248	d, 15.5	7.289	d, 12.4
4	3.118	dd, 7.1, 8.9	3.120	dd, 7.3, 8.4	2.470	dd, 9.4, 8.5	—	—	—	—
5	2.591	d, 7.1	2.560	d, 7.3	2.204	d, 9.4	5.481	d, 9.9	5.354	d, 9.9
6	4.426	dm, 8.9, 1.3	4.680	dm, 8.4	5.214	dm, 8.5	6.435	d, 9.9	6.393	d, 9.9
8	1.645	s	1.720	d, 1.0	1.771	s	1.397	s	1.373	s
9	1.724	d, 1.3	1.760	d, 1.1	1.739	d, 1.1	1.397	s	1.373	s
11	—	—	—	—	—	—	3.794	s	3.737	s
13	3.835	s	3.830	s	3.743	s	3.808	s	3.782	s
15	—	—	—	—	5.370	d, 1.1	—	—	—	—

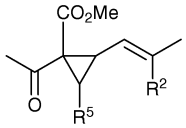
[a] At 200 MHz in $CDCl_3$; see Table 1 for compounds. [b] Only trace amounts, no ^{13}C-NMR data available. [c] A minor isomer of **15e** has ^1H-NMR signals: 5.851 (dqd, J = 15.4, 6.6, 0.8 Hz, 1H), 5.085 (dq, J = 15.4, 1.6 Hz, 1H), 4.481 (dd, J = 10.5, 0.5 Hz, 1H), 4.384 (dd, J = 10.5, 1.1 Hz, 1H), 3.790 and 3.727 (2× s, 6H), 3.141 (dt, $J \doteq$ 8.2, 7.6 Hz, 1H), 3.007 (d, J = 7.6 Hz, 1H), 1.672 (dd, J = 6.6, 1.5 Hz, 3H).



1g R^1 = H, X = Cl
1h R^1 = Me, X = Cl
1i R^1 = Me, X = Br



5a R^2 = Me, R^3 = OMe, R^4 = Ac
5b R^2 = H, R^3 = OMe, R^4 = Ac
5c R^2 = Me, R^3 = OMe, R^4 = $ClCH_2CO$
5d R^2 = H, R^3 = OMe, R^4 = $ClCH_2CO$
5f R^2 = Me, R^3 = SEt, R^4 = Ac
20 R^2 = Me, R^3 = OEt, R^4 = CN



10a R^2 = Me, R^5 = Ac
10b R^2 = H, R^5 = Ac
10c R^2 = Me, R^5 = Bz
10d R^2 = H, R^5 = Bz
10e R^2 = Me, R^5 = Ph
10f R^2 = Me, R^5 = $CH=CH_2$

Scheme 6

Molecular orbital calculations were performed with the MNDO94 semi-empirical molecular orbital program,[29] which is part of the UniChem package.[30] Structures were built using the capabilities of the Sybyl modelling package.[31] Initial structures were optimized with the Tripos force field using Gasteiger–Huckel charges.[32] The bond formed in the postulated reaction between C^{α} and C^3 (Scheme 3) was given a torsion angle in which the triphenylarsine group and acetyl(methoxycarbonyl) group opposed each other. In one structure (that postulated to follow path *a*) this results in the protons lying *trans* to each other. In the other structure (that postulated to follow path *c*) these protons are gauche to each other. These structures were optimized several times with different orientations of the side chains to obtain the structure with the lowest energy. The structures were further optimized with the MNDO94 package using the PM3 Hamiltonian[33] and the PRECISE optimized specification. PM3 was used as it is parameterized for arsenic compounds.

Diels–Alder reactions of nitroethylene and methyl 2,2,6-trimethyl-2*H*-pyran-5-carboxylate (1a)

An excess of nitroethylene (≈10 mmol) in toluene (4 cm^3) was added to 2*H*-pyran **1a** (0.84 g, 4.61 mmol) and stirred under nitrogen for 5 days at room temperature. The reaction mixture was diluted with ether:petroleum ether (1 : 1, 20 cm^3) and filtered over silica gel. Concentration followed by chromatography over silica gel gave the Diels–Alder cycloadduct 1,3,3-trimethyl-6-(methoxycarbonyl)-7-nitro-2-oxabicyclo[2.2.2]-oct-5-ene, **13** (1.01 g, 86%). (Found: C, 56.5; H, 6.8; 5.4. $C_{12}H_{17}NO_5$ requires C, 56.5; H, 6.7; N, 5.5%); [Found: MH^+ (LSI-MS), 256.1164. $C_{12}H_{18}NO_5$ requires 256.1185]; IR (ν_{max}, cm^{-1}): 2983(m), 1723(s), 1620(w), 1550(s), 1437(m), 1368(m), 1251(m), 1203(m), 1079(m), 912(m). ^1H NMR: δ = 1.03 (s, 3H, CH_3-9) 1.29 (s, 3H, CH_3-8), 1.70 (s, 3H, CH_3-10), 1.78 (ddd, 1H, *J* = 13.7, 5.5, 2.6 Hz, CH_2a-7), 2.65 (ddd, 1H, *J* = 13.7, 8.9, 3.1 Hz, CH_2b-7), 2.79 (ddd, 1H, *J* = 7.2, 3.1, 2.6 Hz, CH-4), 3.76 (s, 3H, CH_3-12), 4.84 (dd, 1H, *J* = 8.9, 5.5 Hz, CH-6), 7.66 (d, 1H, *J* = 7.2 Hz, CH-3). ^{13}C NMR: δ = 20.52 (CH_3-10), 26.80, 26.86 (CH_3-8, CH_3-9), 28.50 (CH_2-7), 39.61 (CH-4), 51.56 (CH_3-12), 73.14, 73.88 (C-5, C-1), 87.08 (C-6), 133.13 (C-2), 146.56 (CH-3), 163.65 (C-11).

Typical procedure for the reaction of a substituted 2*H*-pyran-5-carboxylate (1) and methyl 2-(triphenylarsoranylidene)ethanoate (14a)

$KOBu^t$ (0.16 g, 1.43 mmol) was added all at once to a fine suspension of (methoxycarbonylmethyl)triphenylarsonium bromide (0.75 g, 1.63 mmol) in anhydrous THF (5 cm^3) at 0 °C. After 10 min, the solution of the ylide **14a** was treated with methyl 2,2,6-trimethyl-2*H*-pyran-5-carboxylate, **1a**, (0.26 g, 1.43 mmol) in THF (1 cm^3) at 0 °C and stirred under argon for 10 min at 0 °C, then 16 h at 45 °C. The reaction mixture was treated with ether:petroleum ether (1 : 1, 50 cm^3) and the solution was filtered over silica gel. The filtrate was concentrated and the residue was chromatographed on silica gel. Elution with petroleum ether gave triphenylarsine (355 mg, 71%) and further elution with ether : petroleum ether (1 : 9) gave little unreacted 2*H*-pyran **1a** (3 mg) followed by a diastereomeric mixture of dimethyl *trans*-1-acetyl-3-(2-methylprop-1-en-1-yl)-1,2-cyclopropanedicarboxylate (**15a**): (287 mg, 79%); (Found: C, 61.2; H, 7.4. $C_{13}H_{18}O_5$ (mixture) requires C, 61.4; H, 7.1%); λ_{max} (EtOH)/nm 236 (ε/dm^3 mol^{-1} cm^{-1} 12 100). Major isomer, methyl 1-acetyl-*c*-2-(methoxycarbonyl)-*t*-3-(2-methylprop-1-en-1-yl)cyclopropane-*r*-1-carboxylate: [Found: MH^+ (CI), 255.1226. $C_{13}H_{19}O_5$ requires 255.1232]; MS-EI *m*/*z*: 255 (MH^+, 100%), 239 (15), 223 (30), 207 (30), 199 (35), 195 (20), 180 (15), 163 (15); IR (ν_{max}, cm^{-1}): 2978(m), 2933(m), 1733(s), 1666(s), 1634(m), 1582(s), 1445(m), 1378(m), 1264(m), 1192(s), 1032(m), 967(m), 895(m), 851(m). Minor isomer, methyl 1-acetyl-*t*-2-(methoxycarbonyl)-*c*-3-(2-methylprop-1-en-1-yl)cyclopropane-*r*-1-carboxylate: [Found: MH^+ (CI), 255.1226. $C_{13}H_{19}O_5$ requires 255.1232]; MS-CI *m*/*z*: 255 (MH^+, 85%), 223 (100), 211 (10), 195 (35), 180 (15), 163 (10); IR (ν_{max}, cm^{-1}): 2955(m), 1732(vs), 1713(vs), 1441(s), 1358(m), 1285(s), 1249(s), 1164(m), 1100(m). All other condensations, entries 6–14, Table 1, were carried out in THF.

Dimethyl *trans*-1-acetyl-3-(prop-1-en-1-yl)-1,2-cyclopropanedicarboxylate (15b). Major isomer, methyl 1-acetyl-*c*-2-(methoxycarbonyl)-*t*-3-(prop-1-en-1-yl)cyclopropane-*r*-1-carboxylate: (Found: C, 60.05; H, 6.9. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%); λ_{max} (EtOH)/nm 211 (ε/dm^3 mol^{-1} cm^{-1} 9500); [Found: MH^+ (CI), 241.1077. $C_{12}H_{17}O_5$ requires 241.1076]; MS-CI *m*/*z*: 241 (MH^+, 100%), 209 (45), 181 (75), 165 (10), 149 (10); IR (ν_{max}, cm^{-1}): 2954(w), 1734(vs), 1710(vs), 1629(w), 1438(s), 1292(s), 1266(s), 1237(s), 1200(s), 1082(m), 968(m). Minor isomer, methyl 1-acetyl-*t*-2-(methoxycarbonyl)-*c*-3-(2-methylprop-1-en-1-yl)cyclopropane-*r*-1-carboxylate: (Found: C, 59.9; H, 6.9. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%); IR (ν_{max}, cm^{-1}): 3005(w), 2956(m), 1732(vs), 1441(s), 1358(m), 1286(s), 1236(s), 1101(m), 968(m).

Methyl 1-acetyl-*r*-1-ethylsulfanylcarbonyl-*t*-3-(2-methylprop-1-en-1-yl)cyclopropane-*c*-2-carboxylate (15c). (Found: C, 59.3; H, 7.1; S, 11.6. $C_{14}H_{20}O_4S$ requires C, 59.1; H, 7.1; S, 11.3%); λ_{max} (EtOH)/nm 207, 241, 285(sh) (ε/dm^3 mol^{-1} cm^{-1} 13 000, 11 500, 3900); [Found: MH^+ (CI), 285.1171. $C_{14}H_{21}O_4S$ requires 285.1160]; MS-EI *m*/*z*: 285 (MH^+, 95%), 255 (10), 223 (100), 191 (20), 129 (45); IR (ν_{max}, cm^{-1}): 2971(m), 2932(m), 1738(s), 1712(s), 1672(s), 1441(m), 1356(m), 1257(m), 1208(s), 1120(m), 883(m).

***trans*- And *cis*-methyl 6-(2-methoxycarbonyl-1-ethenyl)-2,2-dimethyl-2*H*-pyran-5-carboxylate (17).** *Trans* isomer: λ_{max} (EtOH)/nm 227, 255(sh), 366 (ε/dm^3 mol^{-1} cm^{-1} 10 700, 4300, 5500); [Found: MH^+ (CI), 253.1084. $C_{13}H_{17}O_5$ requires 253.1076]; MS-CI *m*/*z*: 253 (MH^+, 85%), 237 (100), 221 (35), 193 (35); IR (ν_{max}, cm^{-1}): 2952(m), 1723(vs), 1642(m), 1611(m), 1546(m), 1435(m), 1307(m), 1283(m), 1256(s), 1167(m), 1107(s), 1070(m). *cis*-Isomer: λ_{max} (EtOH)/nm 211, 265(sh), 348 (ε/dm^3 dm^{-1} cm^{-1} 10 700, 3000, 3200); [Found: MH^+ (CI), 253.1084. $C_{13}H_{17}O_5$ requires 253.1076]; MS-CI *m*/*z*: 253

(MH^+, 100%), 237 (90), 221 (40), 211 (15), 193 (40); IR (ν_{max}, cm^{-1}): 2952(m), 1709(vs), ≈1700(vs), 1643(m), 1546(m), 1436(m), 1315(m), 1275(s), 1104(s), 1068(s).

Dimethyl 1-(2-bromo-1-oxoethyl)-3-(1-propenyl)-1,2-cyclopropanedicarboxylate (15e). (Found: C, 45.2; H, 4.6. $C_{12}H_{15}BrO_5$ requires C, 45.2; H, 4.7%); λ_{max} (EtOH)/nm 205, 266 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 6040, 5530); [Found: M^+ (CI), 319.0178. $C_{12}H_{16}BrO_5$ requires 319.0181]; MS-CI *m/z*: 319 (MH^+, 60%), 287 (30), 238 (70), 207 (30), 179 (100), 165 (20).

Dimethyl 5-bromomethyl-2,3-dihydro-3-(2-methyl-1-propenyl)-2,4-furandicarboxylate (16e). [Found: MH^+ (CI), 319.0178. $C_{12}H_{16}BrO_5$ requires 319.0181]; MS-CI *m/z*: 319 (MH^+, 60%), 287 (30), 238 (70), 207 (30), 179 (100), 165 (20).

Dimethyl 1-(2-chloro-1-oxoethyl)-3-(2-methyl-1-propenyl)-1,2-cyclopropanedicarboxylate (15f). (Found [mixture]: C, 53.95; H, 6.2. $C_{13}H_{17}ClO_5$ [mixture] requires C, 54.1; H, 5.9%); Major isomer, methyl 1-chloroacetyl-*c*-2-(methoxycarbonyl)-*t*-3-(2-methylprop-1-en-1-yl)cyclopropane-*r*-1-carboxylate: λ_{max} (EtOH)/nm 206, ≈215(sh), ≈260 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 8400, 7960, 3100); [Found: MH^+ (CI), 289.0846. $C_{13}H_{18}ClO_5$ requires 289.0843]; MS-CI *m/z*: 289 (MH^+, 60%), 257 (100), 229 (20), 221 (30), 193 (45), 179 (15). IR (ν_{max}, cm^{-1}): 2955(w), 1730(vs), 1438(m), 1286(m), 1252(m), 1209(m). Minor isomer, methyl 1-chloroacetyl-*t*-2-(methoxycarbonyl)-*c*-3-(2-methylprop-1-en-1-yl)cyclopropane-*r*-1-carboxylate: [Found: MH^+ (CI), 289.0851. $C_{13}H_{18}ClO_5$ requires 289.0843]; MS-CI *m/z*: 289 (MH^+, 65%), 257 (100), 221 (45), 211 (50), 193 (75), 179 (30); IR (ν_{max}, cm^{-1}): 2954(w), 1728(vs), 1654(w), 1439(m), 1250(s), 1209(s), 1167(s).

1-Ethyl, 2-Methyl 1-(2-chloro-1-oxoethyl)-3-(2-methyl-1-propenyl)-1,2-cyclopropanedicarboxylate (15f, Et, Me ester). ^1H NMR: δ = 1.274 (t, *J* = 7.1 Hz, 3H, CH_3-Et), 1.649 (s, 3H, CH_3-9), 1.750 (s, 3H, CH_3-8), 2.947 (d, 1H, *J* = 7.6 Hz, CH-5), 3.210 (dd, 1H, *J* = 7.6, 8.5 Hz, CH-4), 3.656 (s, 3H, CH_3-11), 4.215 (q, *J* = 7.1 Hz, 2H, CH_2-Et), 4.254 (s, 2H, CH_2-1), 4.674 (d, 1H, *J* = 8.5Hz, CH-6). ^{13}C NMR: δ = 13.83 (CH_3-Et), 18.61 (CH_3-9), 25.50 (CH_3-8), 33.94 (CH-4, CH-5), 47.59 (CH_2-1), 47.73 (C-3), 52.33 (CH_3-11), 62.30 (CH_2-Et), 115.89 (CH-6), 140.50 (C-7), 166.74, 168.78 (C-10, C-12), 192.85 (C-2).

Dimethyl 5-chloromethyl-2,3-dihydro-3-(2-methyl-1-propenyl)-2,4-furandicarboxylate (16f). (Found: C, 54.1; H, 6.0. $C_{13}H_{17}ClO_5$ requires C, 54.1; H, 5.9%); λ_{max} (EtOH)/nm 206, 261 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 3700, 4700); [Found: MH^+ (CI), 289.0843. $C_{13}H_{18}ClO_5$ requires 289.0834]; MS-CI *m/z*: 289 (MH^+, 100%), 257 (70), 221 (25), 193 (50); IR (ν_{max}, cm^{-1}): 2953(m), 1739(s), ~1720(s), 1651(s), 1436(s), 1205(s), 1074(m), 735(m).

Reaction of methyl 2,2,6-trimethyl-2*H*-pyran-5-carboxylate (1a) and (cyanomethyl)triphenylarsonium bromide in the presence $KOBu^t$

$KOBu^t$ (0.27 g, 2.41 mmol) was added all at once to a fine suspension of (cyanomethyl)triphenylarsonium bromide (1.00 g, 2.35 mmol) in anhydrous THF (5 cm^3) and stirred for 25 min at 0 °C. Methyl 2,2,6-trimethyl-2*H*-pyran-5-carboxylate, **1a**, (0.43 g, 2.35 mmol) in THF (1 cm^3) was added to the reaction mixture at 0 °C and after 5 min stirred for 1 h at room temperature. The reaction mixture was first treated with ether:petroleum ether (1:1, 20 cm^3), filtered over silica gel and concentrated. The residue was chromatographed with petroleum ether then ether : petroleum ether (1 : 9) and (1 : 4) and gave respectively triphenylarsine (0.45 g, 63%) and a 4 : 1 diastereomeric mixture of *trans*-methyl 1-acetyl-2-cyano-3-(2-methyl-1-propenyl)cyclopropanecarboxylate (**15g**) (124 mg, 24%); (Found: C, 65.2; H, 6.9; N, 5.9. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8, N, 6.3%); λ_{max} (EtOH)/nm 213, 292 ($\varepsilon/dm^3\ dm^{-1}\ cm^{-1}$ 14 100, 1300); [Found: MH^+ (CI), 222.1133. $C_{12}H_{16}NO_3$ requires 222.1131]; MS-CI *m/z*: 222 (MH^+, 100%), 206 (10), 195 (10), 179 (55), 167 (20); IR (ν_{max}, cm^{-1}): 2956(m), 2245(m), 1725(s), 1713(s), 1634(w), 1581(w), 1438(s), 1378(m), 1313(s), 1285(s), 1204(s) 1106(m), 844(w); followed by methyl *c*-2-cyano-1-(2-cyano-1-methyl-1-ethenyl)-*c*-3-(2-methylprop-1-en-1-yl)cyclopropane-*r*-1-carboxylate (**18**): (89 mg, 16%); (Found: C, 68.75; H, 6.8; N, 11.65. $C_{14}H_{16}N_2O_2$ requires C, 68.8 H, 6.6; N, 11.5%); λ_{max} (EtOH)/nm 212 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 14900); [Found: MH^+ (CI), 245.1285. $C_{14}H_{17}N_2O_2$ requires 245.1290]; MS-CI *m/z*: 245 (MH^+, 20%), 229 (100), 213 (15), 197 (20), 185 (15), 170 (20). IR (ν_{max}, cm^{-1}): 2955(m), 2244(m), 2222(m), 1740(s), 1630(m), 1437(m), 1379(m), 1298(m), 1205(s), 1138(m), 735(m).

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