Stereocontrolled Synthesis of Functionalized Bicyclo-[3.3.0], -[4.3.0] and -[5.3.0] Systems by Tin-mediated Radical Cyclization

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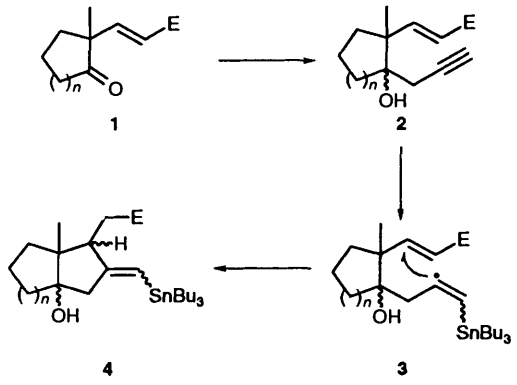
The stereocontrolled synthesis of functionalized *cis*- and *trans*-fused bicyclic systems involving tin-mediated vinyl radical cyclization is reported.

The synthesis of highly functionalized bicyclic systems is an area of sustained interest to synthetic chemists owing to the existence of these frameworks in many naturally occurring compounds.[1] The efficacy of free radical reactions in C–C bond formation in a highly selective manner has led to a number of new methodologies for the synthesis of bicyclic systems.[2] These radical reactions are site specific, requiring mild, neutral reaction conditions, and are known to proceed with a high degree of stereocontrol. We report herein a general method of synthesizing functionalized bicyclo-[3.3.0], -[4.3.0] and -[5.3.0] systems by using tin-mediated vinyl radical cyclization (Scheme 1). The different methods of generating vinyl radicals[3,4] and the preferred modes of cyclization of these radicals[5] have been well documented. With a view to carrying out a preferential 5-*exo*-*trig* cyclization, an α,β-unsaturated ester group was envisaged as the radical acceptor (Scheme 1).



1 2 3 4

Scheme 1 n = 1, 2, 3. E = Electron-withdrawing group

The same group is capable of further functional modifications. Formation of bicyclic systems involving radical ring closure [equation (1)] have been reported to lead to *cis*-ring fusion.[6] In the present methodology, the formation of the bicyclic systems occurs with control of the ring-junction stereochemistry, the latter being fixed at the initial stage of the reaction sequence itself (addition of the prop-2-ynyl equivalent to the ketone). The synthesis of *trans*-fused bicyclic systems has been reported recently.[7] The present study aims at evaluating the extent of stereocontrol obtainable in the radical cyclization (*i.e.*, stereochemical ratio of the newly generated stereocentre).

Results and Discussion

The starting materials required for the present study (n = 1, 2, 3) have been prepared from readily available cycloalkanones by a sequence of reactions: formylation, methylation[8] and Wittig olefination under phase-transfer conditions.[9] The three-carbon side-chain was introduced by the addition of prop-2-ynylaluminium sesquibromide to the ketones in tetrahydrofuran (THF) at −78 °C.

(1)

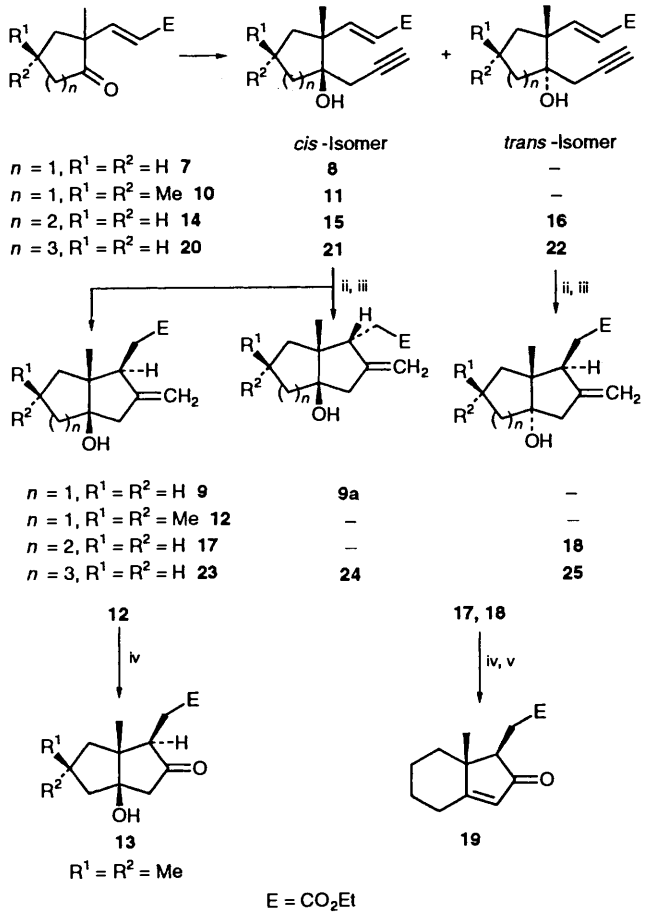
5 6

n = 1, 2, 3

Synthesis of Functionalized Bicyclo[3.3.0]*octanes.*—This carbon framework has formed an integral part in many synthesis of terpenoids, some biologically important molecules,[10] and secondary metabolites.[11]

The alcohol **8** was obtained from the cyclopentanone derivative **7** in 95% yield as a single isomer (HPLC, Scheme 2). The *cis*-stereochemical relationship in the product **8** was ascertained by differential nuclear Overhauser effect (NOE) experiments. Initially, compound **8** was subjected to radical cyclization under normal conditions with no success.† The reaction when carried out under neat conditions was exothermic and went to completion within 5–10 min (TLC). The IR spectrum of the crude product revealed the absence of a C≡CH group and a shift of the ester carbonyl frequency from 1715 to 1730 cm^{-1}, indicating the loss of conjugation. The crude vinylstannane,‡ without purification, was subjected to destannylation with pyridinium toluene-*p*-sulfonate (PPTS) in CH_2Cl_2 at room temperature for 48 h. Significantly, the tertiary alcohol was found to be stable under these conditions. However, HPLC analysis of the product showed it to be a diastereoisomeric mixture (95:5). The major isomer **9** was separated in a pure form by preparative HPLC. Structural assignment for compound **9** was based on ^1H NMR spectroscopy including homonuclear proton-decoupling studies, ^{13}C NMR spectroscopy including an off-resonance spectrum, and mass spectral and elemental analyses (see Experimental section). The minor isomer separated showed the presence of the above major isomer in the ratio 70:30. The stereochemistry of compounds **9** and **9a** was established by differential NOE experiments. For the major isomer **9**, irradiation of the angular methyl-group signal (δ 0.87) showed substantial enhancement of methylene protons signals at C-2 (δ 2.40–2.42). Similarly, irradiation of the angular methyl-group signal at δ 1.02 due to compound **9a** in the mixture (70:30) caused an enhancement of the methine proton signal at C-2′ (δ 2.89). These results clearly imply that, in the major isomer **9**, the ethoxycarbonylmethylene and the angular methyl groups are *cis* orientated, while in its stereoisomer **9a** they are *trans*. Thus, compound **8**, after radical cyclization and destannylation, gave the bicyclo[3.3.0]octane **9** and a small amount of the diastereoisomer **9a** (epimeric configuration at C-2′) in good yield.

† Treatment of compound **8** with 0.02 mol dm^{-3} Bu_3SnH in benzene under reflux conditions led only to recovery of the starting material.
‡ The stereochemistry of the addition of $Bu_3Sn^{\cdot}$ radical to the triple bond was not determined.



Scheme 2 *Reagents and conditions:* i, ≡–CH_2Br, Al, $HgCl_2$ (cat.), THF, –78 °C, 3 h; ii, Bu_3^nSnH, AIBN, 80–85 °C; iii, PPTS, CH_2Cl_2, room temp., 48 h; iv, $RuCl_3$, $NaIO_4$, MeCN–CCl_4–water; v, PTSA (cat.), PhH, reflux, 12 h

The methodology was extended to the ketone **10** in view of its ready availability from isophorone. Incidentally, it has the required structural features present in many linearly fused triquinanes.[1a] Compound **11** was obtained in 90% yield as a single diastereoisomer (HPLC) and the *cis*-stereochemical relationship of the substituents was established by differential NOE experiments. Radical cyclization of compound **11** furnished initially the vinyl stannane,[12] which was destannylated to give compound **12** in 90% yield as a single diastereoisomer (HPLC). The structure of compound **12** was established with the aid of spectral data (see Experimental section). The *cis*-stereochemical relationship as indicated in structure **12** was determined by differential NOE studies. Further, oxidative cleavage of the *exo*-methylene bond in compound **12** by using $RuCl_3$–$NaIO_4$–water [1 : 1 : 1.5][13] gave the ketone **13** in 90% yield which can serve as a precursor for linearly fused triquinanes.[14]

Theoretically, the radical cyclization could have furnished two racemic diastereoisomeric pairs. The marked selectivity observed provided us with a basis for extending the study to other systems.

Synthesis of Functionalized Bicyclo[4.3.0]*nonanes.*—Many complex, naturally occurring molecules, such as ikarguamycin and alliacolides, possess the above basic ring system,[1] thus rendering them interesting synthetic targets.

Prop-2-ynylation of the cyclohexanone derivative **14** gave a mixture of isomeric alcohols (65:35, HPLC) in almost quantitative yield (Scheme 2). The major isomer, **15**, and minor isomer, **16**, were separated by preparative HPLC and characterized by spectral methods. Based on literature analogy,[15] it was assumed that the major product was the *cis*-isomer **15**, arising by an axial attack on the carbonyl group, while the minor product, the *trans*-isomer **16**, resulted from an equatorial attack. Further support for structural assignments was available from differential NOE studies, and ^1H NMR and ^{13}C NMR studies. Compound **15** was subjected to radical cyclization as described earlier. Destannylation furnished compound **17** in 80% yield as a single diastereoisomer (HPLC). The isomer **16** also underwent the stannylation–cyclization–destannylation sequence smoothly to furnish product **18** in 75% yield as a single diastereoisomer (HPLC). The structures of compounds **17** and **18** were confirmed by spectral data. The individual proton assignments in the ^1H NMR spectrum for both the compounds were made by homonuclear proton-decoupling experiments. The stereochemical features of compounds **17** and **18** was established by differential NOE experiments. It may be noted that irrespective of the ring-junction stereochemistry, the cyclization is highly diastereoselective, the methoxycarbonylmethylene group and the methyl group ending up orientated as shown in their respective structures.

Further proof for the ring-junction stereochemistry of compounds **17** and **18** was available from the ^{13}C NMR δ_C-values of C-1′ and C-5′ carbons (see Experimental section) which are in agreement with the literature values[16] for similar systems arising from the fact that the *cis*-fused ring carbons will be shielded compared with those of the *trans*-system. Compounds **17** and **18** differ only with respect to the fusion at C-5′. This was confirmed by the following chemical transformation. Radical cyclization of the mixture of diastereoisomers **15** and **16** (65:35) without separation followed by destannylation gave the cyclized products **17** and **18** as a mixture in 80% yield. Oxidative cleavage of the *exo*-methylene group using $RuCl_3$–$NaIO_4$ (0.1/5 mol equiv.) in a CCl_4–MeCN–water (1 : 1 : 1 : 5)[13] system gave the mixture of ketones in 90% yield, which was dehydrated using toluene-*p*-sulfonic acid (PTSA) (cat.) in benzene under reflux for 12 h. The bicyclic enone **19** was obtained in quantitative yield. The method thus provides an efficient route for the synthesis of functionalized bicyclo-[4.3.0]non-6-en-8-ones.[17]

Synthesis of Functionalized Bicyclo[5.3.0]*decanes.*—A variety of sesquiterpenes contain highly functionalized bicyclo-[5.3.0]decanes.[18] The synthesis of the above ring system in a stereoselective manner is thus desirable.

Prop-2-ynylation of ketone **20** furnished the alcohol product in 90% yield as a mixture of isomers **21** and **22** (35:65, Scheme 2) which was separated by preparative HPLC. The structure of products **21** and **22** was established based on differential NOE experiments and by correlation of ^1H NMR and ^{13}C NMR spectral data. In the present case, the ratio of the stereoisomeric alcohols obtained indicates that the pseudo-equatorial attack on the ketone is seemingly a more favourable process. Compounds **21** and **22** were subjected separately to radical cyclization–destannylation as per the procedure described earlier. In each case a 90:10 mixture of diastereoisomers was obtained (HPLC). From compound **21**, the diastereoisomeric compounds **23*** and **24** could be separated in pure form by column chromatography in 80% combined yield, while from compound **22** only the diastereoisomer **25** could be separated from the mixture in 70% yield. Attempts to isolate the other diastereoisomer were not successful. For each compound, stereochemical assignments were made based on differential NOE experiments.

* The compound was found to be unstable at room temperature. See ref. 15*e*.

It is pertinent to note that increasing the ring size has little effect on the stereoselectivity that accompanies the cyclization. The high degree of diastereoselectivity observed during the course of cyclization can be explained along with the stereoselectivity of hexenyl-radical cyclization[19] as per the guidelines proposed by Beckwith *et al.* and Rajanbabu *et al.*, utilizing the favourable mode of orbital overlap and steric interaction. The cumulative effect of the above mentioned factors may lead to a high degree of diastereoselectivity with the major isomers being formed *via* a chair-like transition state. This is in accordance with the experimental findings.

The present study provides a method for the construction of functionalized bicyclic systems. It is also noteworthy, for systems with $n = 1,2$ a good deal of stereocontrol was available by this method which involves a vinyl radical effecting a 5-*exo-trig* cyclization onto an α,β-unsaturated ester system, and in the process, creating a new stereogenic centre. When $n = 3$, only a moderate amount of stereocontrol was available. The non-selectivity of the addition of the organometallic reagent to the ketones **14** and **20** can be considered to be one of the limitations of this method, but can be employed successfully if one wishes to synthesize bicyclic enones as exemplified by conversion into enone **19**. We are currently engaged in the process of extending this methodology to specific target molecules.

Experimental

All b.p.s are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer. ^{1}H NMR spectra were either recorded at 400 MHz on a JEOL GSX 400 NMR spectrophotometer or at 90 MHz on Varian EM 390 NMR spectrophotometer. ^{13}C NMR spectra were either recorded at 100.6 MHz on a JEOL GSX 100 or at 22.5 MHz on a JEOL FX 90 Q NMR spectrophotometer as indicated. Chemical shifts were reported in ppm (δ) using Me_4Si as standard, and coupling constants were expressed in Hz. Percentage NOE enhancements were obtained by integrating the affected resonance relative to the irradiated resonance in the difference spectrum in each case. Mass spectra were recorded on both a GCMS QP 1000 A spectrometer and a JEOL JMS-DX 303 HF mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 B elemental analyser. HPLC studies were made on Shimadzu LC-4A and LC-5A instruments with a Zorbax ODS column, UV detector, and methanol–water (3:2) or acetonitrile–water (3:2) as solvent at a flow rate of 4 mm^3 min^{-1}. Thin-layer chromatograms (TLC) were developed on glass plates coated with silica gel-G (ACME) of 0.25 mm thickness and were visualized with iodine. Column chromatography was carried out either with SiO_2 (silica gel, ACME, 100–200 mesh) or with neutral Al_2O_3 (alumina, ACME, washed with ethyl acetate and activated). For dry experiments, glassware was thoroughly dried in an oven, cooled, and assembled under a stream of nitrogen. The organic extracts of crude products were dried over anhydrous magnesium sulfate. Solvents were of reagent grade and purified according[20] to the literature procedure prior to use, and Bu_3SnH was prepared[21] according to the literature procedure.

General Experimental Procedure[9] *for the Synthesis of Ketones* **7**, **10**, **14** *and* **20**.—To a solution of a 2-formyl-2-methylcycloalkanone (0.062 mol) in CH_2Cl_2 (60 cm^3) along with ethoxycarbonylmethyl(triphenyl)phosphonium bromide (0.078 mol, 1.3 mol equiv.) in water (60 cm^3) was added potassium carbonate (0.09 mol, 1.5 mol equiv.) in small portions over a period of 5 min. The resulting mixture was stirred for 2 h, and the organic layer was separated, washed with water, and dried. Removal of solvent gave a residue which solidified on cooling. Digestion of the solid with light petroleum (40–60 °C) (10 × 25 cm^3) and evaporation of the solvent gave a residue, which was chromatographed (silica gel) to give the ketone.

Ethyl 3-(1′-*methyl*-2′*oxocyclopentyl*)*acrylate* **7**. Following the general procedure, treatment of 2-formyl-2-methylcyclopentanone[8] (7.80 g) gave *compound* **7** (7.30 g, 60%) as a liquid, R_f 0.53 [AcOEt–hexane (1:10)]; $\nu_{max}(CCl_4)$/cm^{-1} 1740, 1715 and 1640; $\delta_H(CCl_4$; 90 MHz) 1.1 (3 H, s, Me), 1.2 (3 H, t, *J* 7.3, CO_2CH_2*Me*), 1.5–1.9 (6 H, m, methylenes), 4.15 (2 H, q, *J* 7.3, CO_2CH_2Me), 5.8 (1 H, d, *J* 17.0, 2-H) and 7.1 (1 H, d, *J* 17.0, 3-H) (Found: C, 67.3; H, 8.2. $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22%).

Ethyl 3-(1′,4′,4′-*trimethyl*-2′-*oxocyclopentyl*)*acrylate* **10**. Following the general procedure, treatment of 2-formyl-2,4,4-trimethylcyclopentanone[8] (9.55 g) gave *compound* **10** (9.0 g, 65%) as a liquid, R_f 0.6 [AcOEt–hexane (1:20)]; $\nu_{max}(CCl_4)$/cm^{-1} 1740, 1720 and 1640; $\delta_H(CDCl_3$; 400 MHz) 1.06 (3 H, s), 1.14 (3 H, s), 1.25 (3 H, s), 1.26 (3 H, t, *J* 7.3), 1.82 (1 H, d, *J* 13.6, 5′-H^a), 2.14 (1 H, d, *J* 13.6, 5′-H^b), 2.23 (2 H, d, *J* 3.4, 3-H$_2$), 4.61 (2 H, q, *J* 7.3), 5.84 (1 H, d, *J* 15.6, 2-H) and 6.93 (1 H, d, *J* 16.1, 3-H) (Found: C, 69.6; H, 9.0. $C_{13}H_{20}O_3$ requires C, 69.90; H, 8.90%).

Ethyl 3-(1′-*methyl*-2′-*oxocyclohexyl*)*acrylate* **14**. Following the general procedure, treatment of 2-formyl-2-methylcyclohexanone[8] (8.68 g) gave *compound* **14** (7.80 g, 60%) as a liquid, R_f 0.78 [AcOEt–hexane (1:10)]; $\nu_{max}(CCl_4)$/cm^{-1} 1705–1710 and 1640; δ_H ($CDCl_3$, 400 MHz) 1.23 (3 H, s), 1.30 (3 H, t, *J* 7.3), 1.69–1.81 (4 H, m, methylenes), 1.94–2.07 (2 H, m, methylenes), 2.41–2.48 (2 H, m, methylenes), 4.19 (2 H, q, *J* 7.3), 5.77 (1 H, d, *J* 16.1, 2-H) and 7.13 (1 H, d, *J* 16.1, 3-H) (Found: C, 68.5; H, 8.6. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.63%).

Ethyl 3-(1′-*methyl*-2′-*oxocycloheptyl*)*acrylate* **20**.—Following the general procedure, treatment of 2-formyl-2-methylcycloheptanone[8] (9.54 g) gave *compound* **20** (9.73 g, 70%) as a liquid, R_f 0.6 [AcOEt–hexane (1:20)]; $\nu_{max}(CCl_4)$/cm^{-1} 1705–1715 and 1640; $\delta_H(CCl_4$; 90 MHz) 1.1 (3 H, s, Me), 1.2 (3 H, t, *J* 7.3), 1.5–2.2 (10 H, m, methylenes), 4.15 (2 H, q, *J* 7.3), 5.8 (1 H, d, *J* 16.2, 3-H) and 7.0 (1 H, d, *J* 16.2, 2-H) (Found: C, 69.7; H, 8.9. $C_{13}H_{20}O_3$ requires C, 69.60; H, 8.90%).

General Procedure for Prop-2-*ynylation of Ketones* **7**, **10**, **14** *and* **20**.—An aluminium amalgam was prepared from aluminium foil (0.36 mol, 3 mol equiv.) and mercury(II) chloride [10 mg (cat.)] in dry THF (15 cm^3) by vigorous stirring of the mixture at room temperature for 1 h under nitrogen. A solution of prop-2-ynyl bromide (0.036 mol, 3 mol equiv.) in dry THF (25 cm^3) was slowly added to the stirred suspension at such a rate as to maintain the temperature between 30 and 40 °C, and after the addition the mixture was stirred at 40 °C was continued until a dark grey solution was obtained (*ca.* 1 h). The prop-2-ynylaluminium sesquibromide solution thus obtained was added to a solution of a ketone (0.012 mol) in dry diethyl ether (100 cm^3) at −78 °C and the reaction mixture was then poured into ice–water and extracted with diethyl ether. The extract was washed with brine, dried, and concentrated. The residual liquid was subjected to column chromatography (silica gel) with hexane–ethyl acetate (10:1) as eluent to give the prop-2-ynyl carbinol.

Ethyl 3-[2′-*hydroxy*-1′-*methyl*-2′-(*prop*-2″-*ynyl*)*cyclopentyl*]-*acrylate* **8**. Following the general procedure, addition of prop-2-ynylaluminium sesquibromide solution to compound **7** (2.35 g) gave *compound* **8** (2.70 g, 95%), R_f 0.51 [AcOEt–hexane (1:10)]; $\nu_{max}(CCl_4)$/cm^{-1} 3460, 3300, 2100, 1715 and 1640; $\delta_H(CDCl_3$; 400 MHz) 1.20 (3 H, s), 1.30 (3 H, t, *J* 7.3), 1.74–1.97 (6 H, m), 2.10 (1 H, dd ⟶ t, *J* 2.4, 3″-H), 2.29 (1 H, dd, *J* 17.0, 2.4, 1″-H^b), 2.38 (1 H, dd, *J* 17.0 and 2.4, 1″-H^a), 2.45 (1 H, br s, OH), 4.19 (2 H, q, *J* 7.3), 5.83 (1 H, d, *J* 15.8, 2-H) and 6.96 (1 H, d, *J*

15.8, 3-H); δ_C($CDCl_3$; 100.6 MHz) 14.25 (q), 18.40 (q), 18.80 (t), 27.46 (t), 36.57 (t), 37.14 (t), 51.21 (s), 60.29 (t), 71.55 (d), 80.78 (s), 81.95 (s), 119.23 (d), 153.32 (d) and 166.68 (s); *m/z* 236 (M^+), 221, 219, 211, 199 and 167 (Found: C, 71.1; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

General Procedure for Radical Cyclization and Protiodestannylation.—A flame-dried, 100 cm^3, round-bottomed flask equipped with a magnetic stirring bar was charged with AnalaR nitrogen, a prop-2-ynyl carbinol (0.0021 mol), and tributyltin hydride (0.0022 mol, 1.05 mol equiv.), and azoisobutyronitrile (AIBN), (0.0001 mol) was added. The entire assembly was lowered into an oil-bath maintained at between 75 and 85 °C, and the mixture was stirred. After an induction period of less than 5 min, an exothermic reaction occurred which produced a small amount of gas, and the reaction mixture was stirred for an additional 10 min, at which point TLC showed that the reaction was essentially complete (also by IR). The crude vinylstannane thus obtained was suitable for protiodestannylation.

To a solution of crude vinylstannane in CH_2Cl_2 (20 cm^3) was added PPTS (2 mol equiv.) and the reaction mixture was stirred at room temperature for 48 h, at which time TLC analysis showed complete consumption of starting material and formation of a polar product. The solvent was removed under reduced pressure, and the residue was thoroughly extracted with hexane–ethyl acetate (3:2). The combined extracts were concentrated under reduced pressure, and the crude product was chromatographed (silica gel) with hexane–ethyl acetate (10:1) as eluent to give the destannylated product.

Ethyl (5'-hydroxy-1'-methyl-3'-methylenebicyclo[3.3.0]*octan-2'-yl)acetate* **9**. Following the general procedure, radical cyclization of compound **8** (0.50 g) and then destannylation gave the cyclized compound **9** (0.40 g, 80%). HPLC analysis showed it to be a mixture of isomers in the ratio 95:5. Pure product **9** was separated by HPLC, followed by stereoisomers **9a** and **9** as a mixture in the ratio 70:30.

For *compound* **9**: R_f 0.49 [AcOEt–hexane (1:10)]; ν_{max}(CCl_4)/cm^{-1} 3600, 3060, 1730 and 1650; δ_H($CDCl_3$; 400 MHz) 0.87 (3 H, s), 1.27 (3 H, t, *J* 7.3), 1.50–1.98 (7 H, m), 2.40 (1 H, dd, *J* 7.8 and 2.9, 2-H^a), 2.42 (1 H, dd, *J* 7.8 and 2.9, 2-H^b), 2.45 (1 H, d, *J* 16.6, 4'-H^a), 2.64 (1 H, d, *J* 16.6, 4'-H^b), 2.71 (1 H, m, 2'-H), 4.15 (2 H, q, *J* 7.3), 4.7 (1 H, br s, =C*H*H) and 4.86 (1 H, br s, =CH*H*); δ_C($CDCl_3$; 100.6 MHz) 14.21 (q), 15.95 (q), 21.40 (t), 34.46 (t), 37.66 (t), 40.33 (t), 45.55 (t), 48.71 (d), 53.96 (s), 60.47 (t), 87.76 (s), 106.53 (t), 151.44 (s) and 173.55 (s); *m/z* 238 (M^+), 220, 196, 165, 121, 107, 98 and 69 (Found: C, 70.4; H, 9.15. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30%).

Compounds **9** and **9a** were isolated as a mixture in the ratio 70:30. However, it was possible to assign the peaks from ^1H NMR and ^{13}C NMR spectra, since the peaks for the two compounds do not overlap with each other.

For compound **9a**: δ_H($CDCl_3$; 400 MHz) 1.02 (3 H, s), 1.27 (3 H, t, *J* 7.3), 1.33–1.67 (5 H, m), 1.80 (1 H, dd ⟶ t, *J* 7.3, 6'-H^a), 2.02 (1 H, br m, OH), 2.35 (1 H, dd, *J* 7.3 and 1.9, 2-H^a), 2.42 (1 H, dd, *J* 7.3 and 1.9, 2-H^b), 2.48 (1 H, d, *J* 16.1, 4'-H^a), 2.56 (1 H, d, *J* 16.1, 4'-H^b), 2.89 (1 H, m, 2'-H), 4.16 (2 H, q, *J* 7.3), 4.71 (1 H, br s, =C*H*H) and 4.84 (1 H, br s, =CH*H*); δ_C($CDCl_3$; 100.6 MHz) 14.19 (q), 20.22 (q), 20.40 (t), 33.42 (t), 33.85 (t), 39.04 (t), 47.53 (t), 48.53 (d), 53.22 (s), 60.52 (t), 87.09 (s), 105.68 (t), 151.56 (s) and 173.59 (s).

Ethyl 3-[*2'-hydroxy-1',4',4'-trimethyl-2'-(prop-2''-ynyl)-cyclopentyl*]*acrylate* **11**. Following the general procedure, addition of prop-2-ynylaluminium sesquibromide solution to compound **10** (2.70 g) gave *compound* **11** (2.85 g, 90%), R_f 0.55 [AcOEt–hexane (1:20)]; ν_{max}(CCl_4)/cm^{-1} 3580, 3300, 2100, 1720 and 1640; δ_H($CDCl_3$; 400 MHz) 1.07 (3 H, s), 1.14 (6 H, s), 1.23 (3 H, t, *J* 7.3), 1.62 (1 H, d, *J* 13.6, 3'-H^a), 1.79 (2 H, d, *J* 13.6, 7'-H_2), 1.93 (1 H, d, *J* 13.6, 3'-H^b), 2.03 (1 H, dd ⟶ t, *J* 4.3, 3''-H), 2.24 (3 H, br q, 1''-H_2 and OH), 4.15 (2 H, q, *J* 7.3), 5.74 (1 H, d, *J* 16.1, 2-H) and 7.04 (1 H, d, *J* 16.1, 3-H); δ_C($CDCl_3$; 100.6 MHz) 14.11 (q), 18.42 (q), 27.71 (t), 30.60 (q), 33.21 (q), 34.35 (s), 52.21 (t), 52.55 (t), 52.99 (s), 60.21 (t), 71.55 (d), 80.58 (s), 82.89 (s), 118.86 (d), 153.67 (d) and 166.69 (s); *m/z* 264 (M^+), 249, 247, 239, 219, 195, 165 and 132 (Found: C, 72.5; H, 9.1. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%).

Ethyl (5'-hydroxy-1',7',7'-trimethyl-3'-methylenebicyclo[3.3.0]*octan-2'-yl)acetate* **12**. Following the general procedure, radical cyclization of compound **11** (0.55 g) and then destannylation gave the cyclized *compound* **12** (0.50 g, 90%), R_f 0.52 [AcOEt–hexane (1:20)]; ν_{max}(CCl_4)/cm^{-1} 3600, 3060, 1735 and 1650; δ_H($CDCl_3$; 400 MHz) 0.80 (3 H, s), 1.05 (3 H, s), 1.10 (3 H, s), 1.20 (3 H, t, *J* 7.3), 1.43 (1 H, d, *J* 13.7, 8'-H^a), 1.52 (1 H, s, OH), 1.59 (1 H, d, *J* 13.6, 8'-H^b), 1.77 (1 H, d, *J* 14.1, 6'-H^a), 1.89 (1 H, d, *J* 14.6, 6'-H^b), 2.28 (1 H, d, *J* 17.0, 4'-H^a), 2.30 (2 H, dd, *J* 6.3 and 5.3, 2-H_2), 2.66 (1 H, d, *J* 17.0, 4'-H^b), 2.80 (1 H, br s, 2'-H), 4.09 (2 H, q, *J* 7.3), 4.68 (1 H, dd, *J* 2.4 and 1.9, =C*H*H) and 4.80 (1 H, dd, *J* 2.4 and 1.9, =CH*H*); δ_C($CDCl_3$; 100.6 MHz) 14.13 (q), 15.59 (q), 33.01 (q), 33.39 (q), 34.29 (t), 37.05 (s), 44.76 (t), 49.34 (d), 51.86 (t), 54.45 (t), 55.87 (s), 60.42 (t), 89.04 (s), 106.90 (t), 151.15 (s) and 173.43 (s); *m/z* 266 (M^+), 254, 251, 249, 222, 219, 165, 111 and 67 (Found: C, 72.1; H, 9.8. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84%).

Ethyl (5'-hydroxy-1',7',7'-trimethyl-3'-oxobicyclo[3.3.0]*octan-2'-yl)acetate* **13**. To a solution of compound **12** (0.150 g, 56 mmol) in a CCl_4–MeCN–water mixture (1:1:1.5; 14 cm^3) was added sodium metaperiodate (0.5 g, 4.1 mol equiv.). To this biphasic solution was added ruthenium trichloride hydrate (5 mg)[14] and the entire mixture was stirred vigorously for 12 h at room temperature. Then CH_2Cl_2 (10 cm^3) was added and the phases were separated. The upper, aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were dried and concentrated. The resulting residue was diluted with diethyl ether (20 cm^3), and the mixture was filtered through a Celite pad and concentrated. The crude product was purified by chromatography (silica gel) with hexane–ethyl acetate (10:1) as eluent to afford *compound* **13** (0.14 g, 90%), R_f 0.4 [AcOEt–hexane (1:10)]; ν_{max}(CCl_4)/cm^{-1} 3565 and 1730; δ_H($CDCl_3$; 400 MHz) 0.87 (3 H, s), 1.10 (3 H, s), 1.16 (3 H, s), 1.21 (3 H, t, *J* 7.1), 1.61 (1 H, d, *J* 13.9, 8'-H^a), 1.73 (1 H, d, *J* 13.9, 8'-H^b), 1.90 (1 H, d, *J* 14.5, 6'-H^a), 2.00 (1 H, s, OH), 2.01 (1 H, d, *J* 14.5, 6'-H^b), 2.19 (1 H, d, *J* 19.2, 4'-H^a), 2.21 (1 H, dd, *J* 6.4 and 6.5, 2-H^a), 2.55 (1 H, dd, *J* 6.6 and 6.6, 2-H^b), 2.61 (1 H, d, *J* 19.3, 4'-H^b), 2.79 (1 H, dd ⟶ t, *J* 6.6 and 6.5, 2'-H) and 4.11 (2 H, q, *J* 7.1) (Found: C, 67.1; H, 9.0. $C_{15}H_{24}O_4$ requires C, 67.13; H, 9.00%).

Ethyl 3-[*2'-hydroxy-1'-methyl-2'-(prop-2''-ynyl)cyclohexyl*]-*acrylate* **15** *and* **16**. Following the general procedure, addition of prop-2-ynylaluminium sesquibromide solution to compound **14** (2.50 g) gave the compounds **15** and **16** (3.0 g, in quantitative yield). HPLC showed this was a mixture of isomers in the ratio 65:35, and they were separated by preparative HPLC.

cis-*Isomer* (*major*) **15**: R_f 0.6 [AcOEt–hexane (1:10)]; ν_{max}(CCl_4)/cm^{-1} 3530, 3300, 2100, 1720 and 1630; δ_H($CDCl_3$; 400 MHz) 1.16 (3 H, s), 1.30 (3 H, t, *J* 7.3), 1.40–1.91 (8 H, m), 2.02 (1 H, br s, OH), 2.09 (1 H, dd ⟶ t, *J* 2.4, 3''-H), 2.33 (1 H, dd, *J* 17.0 and 2.4, 1''-H^a), 2.46 (1 H, dd, *J* 17.0 and 2.4, 1''-H^b), 4.20 (2 H, q, *J* 7.3), 5.80 (1 H, d, *J* 16.1, 2-H) and 7.28 (1 H, d, *J* 16.1, 3-H); δ_C($CDCl_3$; 100.6 MHz) 14.28 (q), 20.20 (q), 21.07 (t), 21.93 (t), 27.66 (t), 32.77 (t), 34.29 (t), 43.63 (s), 60.37 (t), 72.22 (d), 73.30 (s), 80.46 (s), 119.93 (d), 153.69 (d) and 166.80 (s); *m/z* 250 (M^+), 235, 233, 213, 181, 144 and 78 (Found: C, 71.9; H, 8.8. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

trans-*Isomer* (*minor*) **16**: R_f 0.59 [AcOEt–hexane (1:10)]; ν_{max}(CCl_4)/cm^{-1} 3530, 2100, 1720 and 1630; δ_H($CDCl_3$; 400 MHz) 1.10 (3 H, s), 1.30 (3 H, t, *J* 7.3), 1.44–2.00 (8 H, m), 2.06 (1 H, br s, OH), 2.11 (1 H, dd ⟶ t, *J* 2.4, 3''-H), 2.32 (1 H, dd, *J* 16.6 and 2.4, 1''-H^a), 2.45 (1 H, dd, *J* 16.6 and 2.4, 1''-H^b), 4.19

(2 H, q, *J* 7.3), 5.82 (1 H, d, *J* 16.3, 2-H) and 7.38 (1 H, d, *J* 16.3, 3 H); δ_C($CDCl_3$; 100.6 MHz) 14.30 (q), 19.57 (q), 20.96 (t), 21.28 (t), 28.54 (t), 32.62 (t), 34.26 (t), 43.56 (s), 60.28 (t), 72.30 (d), 73.35 (s), 80.49 (s), 120.01 (d), 155.15 (d) and 166.94 (s); *m/z* 250 (M^+), 235, 233, 213, 181, 144 and 78 (Found: C, 71.7; H, 8.7%).

Ethyl (1′-*hydroxy*-6′-*methyl*-8′-*methylenebicyclo*[4.3.0]*nonan*-7′-*yl*)*acetate* **17**. Following the general procedure, radical cyclization of compound **15** (0.53 g) and then destannylation gave the cyclized *compound* **17** (0.42 g, 80%), R_f 0.58 [AcOEt–hexane (1 : 10)]; ν_{max}(CCl_4)/cm^{-1} 3600, 3060, 1730 and 1650; δ_H($CDCl_3$; 400 MHz) 0.85 (3 H, s), 1.27 (3 H, t, *J* 7.3), 1.30–1.73 (8 H, m), 1.93 (1 H, br s, OH), 2.42 (1 H, dd, *J* 17.0 and 2.4 9′-H^a), 2.45 (2 H, d, *J* 6.8, H_2), 2.53 (1 H, d, *J* 17.0, 9′-H^b), 2.99 (1 H, m, 7′-H), 4.15 (2 H, q, *J* 7.3), 4.87 (1 H, d, *J* 2.4, =C*H*H) and 4.95 (1 H, d, *J* 2.4, =CH*H*); δ_C($CDCl_3$; 100.6 MHz) 14.19 (q), 16.73 (q), 21.19 (t), 22.50 (t), 33.36 (t), 34.82 (t), 35.82 (t), 44.63 (t), 45.92 (d,s), 60.41 (t), 78.57 (s), 108. 26 (t), 151.17 (s) and 173.07 (s); *m/z* 252 (M^+), 235, 207, 165, 105, 97, 77 and 58 (Found: C, 71.3; H, 9.5. $C_{15}H_{24}O_3$ requires C, 71.39, H, 9.58%).

Ethyl (1′-*hydroxy*-6′-*methyl*-8′-*methylenebicyclo*[4.3.0]-*nonan*-7′-*yl*)*acetate* **18**. Following the general procedure, radical cyclization of compound **16** (0.53 g) and then destannylation gave the cyclized compound **18** (0.40 g, 75%), R_f 0.57 [AcOEt–hexane (1 : 10)]; ν_{max}(CCl_4)/cm^{-1} 3600, 3060, 1730 and 1650; δ_H($CDCl_3$; 400 MHz) 0.79 (3 H, s), 1.27 (3 H, t, *J* 7.3), 1.30–1.79 (9 H, m, methylenes and OH), 2.25 (1 H, d, *J* 6.8, 2-H^a), 2.29 (1 H, d, *J* 6.8, 2-H^b), 2.43 (1 H, d, *J* 15.1, 9′-H^a), 2.45 (1 H, d, *J* 15.1, 9′-H^b), 3.10 (1 H, dd ⟶ t, *J* 2.9, 7′-H), 4.15 (2 H, q, *J* 7.3), 4.90 (1 H, d, *J* 1.9, =C*H*H) and 5.01 (1 H, d, *J* 1.9. =CH*H*); δ_C($CDCl_3$; 100.6 MHz) 14.21 (q),, 17.17 (q), 20.13 (t), 20.46 (t), 30.02 (t), 30.24 (t), 33.62 (t), 43.87 (t), 46.04 (s), 46.84 (d), 60.41 (t), 79.22 (s), 108.83 (t), 151.52 (s) and 173.82 (s); *m/z* 252 (M^+), 235, 207, 165, 105, 97, 77 and 58 (Found: C, 71.2; H, 9.4%).

Ethyl (6′-*methyl*-8′-*oxobicyclo*[4.3.0]*non*-1′(9′)-*en*-7′-*yl*)*acetate* **19.** Following the general procedure, radical cyclization of the mixture of **15** and **16** (2.5 g, 0.01 mol) with Bu_3SnH (3.2 g, 1.1 mol equiv.) gave the cyclized compounds, as a mixture of compounds **17** and **18** (2.0 g, 80%). To a solution of compounds **17** and **18** in a CCl_4–MeCN–water mixture (1 : 1 : 1.5; 35 cm^3) was added sodium metaperiodate (7.0 g, 4.1 mol equiv.). To this biphasic solution was added ruthenium trichloride heptahydrate [14] (20 mg) and the entire mixture was stirred vigorously for 20 h at room temp. The upper, aqueous phase was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried, filtered through a Celite pad, and concentrated. The crude product (1.80 g, 90%) was pure enough to be used for the next step; ν_{max}(CCl_4)/cm^{-1} 3580 and 1730.

A solution containing a mixture of the above alcohols (1.80 g, 0.0072 mol), hydroquinone (2 mg) and PTSA (2 mg) in degassed benzene (100 cm^3) was heated for 12 h at reflux under nitrogen with a Dean–Stark water separator. The solution was washed successively with aq. sodium hydrogen carbonate and brine, then was dried and concentrated. The residue was purified by chromatography (silica gel) to afford *compound* **19** (1.7 g, quantitative), R_f 0.61 [AcOEt–hexane (1 : 10)]; ν_{max}(CCl_4)/cm^{-1} 1725, 1685 and 1615; δ_H($CDCl_3$; 300 MHz) 1.03 (3 H, s), 1.21 (3 H, t, *J* 7.3), 1.28–2.10 (6 H, m, 3′-, 4′- and 5′-H_2), 2.21–2.40 (2 H, m, 2′-H_2), 2.56–2.82 (3 H, m, 7′-H and H_2), 4.11 (2 H, q, *J* 7.3) and 5.73 (1 H, s, 9-H) (Found: C, 71.1; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

Ethyl 3-[2′-*hydroxy*-1′-*methyl*-2′-(*prop*-2″-*ynyl*)*cycloheptyl*]-*acrylate* **21** *and* **22**. Following the general procedure, addition of prop-2-ynylaluminium sesquibromide solution to compound **20** (2.70 g) gave the compounds **21** and **22** (2.85 g, 90%). HPLC analysis showed that the product was a mixture of isomers in the ratio 35 : 65 and they were separated by preparative HPLC.

cis-*Isomer* (*minor*) **21**: R_f 0.55 [AcOEt–hexane (1 : 20)]; ν_{max}(CCl_4)/cm^{-1} 3560, 3300, 2100, 1720 and 1640; δ_H($CDCl_3$; 400 MHz) 1.18 (3 H, s), 1.30 (3 H, t, *J* 7.3), 1.46–1.82 (10 H, m, methylenes), 1.99 (1 H, br s, OH), 2.08 (1 H, dd ⟶ t, *J* 2.4, 3″-H), 2.31 (1 H, dd, *J* 17.0 and 2.4, 1″-H^a), 2.44 (1 H, dd, *J* 17.0 and 2.4, 1″-H^b), 4.20 (2 H, q, *J* 7.3), 5.82 (1 H, d, *J* 15.8, 2-H) and 7.18 (1 H, d, *J* 15.8, 3-H); δ_C($CDCl_3$; 100.6 MHz) 14.28 (q), 20.78 (q), 20.81 (t), 21.60 (t), 26.72 (t), 29.07 (t), 35.08 (t), 36.51 (t), 46.74 (s), 60.37 (t), 72.13 (d), 75.94 (s), 80.84 (s), 119.61 (d), 154.77 (d) and 166.89 (s); *m/z* 264 (M^+), 247, 225, 198, 180, 150, 111 and 83 (Found: C, 72.7; H, 9.15. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%).

trans-*Isomer* (*major*) **22**: R_f 0.54 [AcOEt–hexane (1 : 20)]; ν_{max}(CCl_4)/cm^{-1} 3560, 3300, 2100, 1720 and 1640; δ_H($CDCl_3$; 400 MHz) 1.07 (3 H, s), 1.3 (3 H, t, *J* 7.3), 1.05–2.07 (10 H, m, methylenes), 1.76 (1 H, br s, OH), 2.09 (1 H, dd ⟶ t, *J* 2.4, 3″-H), 2.88 (1 H, dd, *J* 16.6 and 2.4, 1″-H^a), 2.43 (1 H, dd, *J* 16.6 and 2.4, 1″-H), 4.20 (2 H, q, *J* 7.3), 5.78 (1 H, d, *J* 16.3, 2-H) and 7.25 (1 H, d, *J* 16.3, 3-H); δ_C($CDCl_3$; 100.6 MHz) 14.31 (q), 19.79 (q), 20.59 (t), 21.78 (t), 26.44 (t), 29.57 (t), 34.97 (t), 36.13 (t), 46.89 (s), 60.31 (t), 72.34 (d), 75.99 (s), 80.90 (s), 118.85 (d), 158.87 (d) and 167.12 (s); *m/z* 264 (M^+), 247, 225, 198, 180, 150, 111 and 73 (Found: C, 72.7; H, 9.15%).

Ethyl (1′-*hydroxy*-7′-*methyl*-9′-*methylenebicyclo*[5.3.0]*decan*-8′-*yl*)*acetate* **23** *and* **24**. Following the general procedure, radical cyclization of compound **21** (0.55 g) and then destannylation gave the cyclized compounds **23** and **24** (0.45 g, 80% combined yield). HPLC analysis showed the product was a mixture of isomers in the ratio 90 : 10 and they were separated by column chromatography (silica gel).

Major isomer **23**: R_f 0.53 [AcOEt–hexane (1 : 20)]; ν_{max}-(CCl_4)/cm^{-1} 3560, 3060, 1730 and 1650; δ_H($CDCl_3$; 400 MHz) 0.81 (3 H, s), 1.27 (3 H, t, *J* 7.3), 1.30–1.99 (11 H, m, methylenes and OH), 2.36 (2 H, dd, *J* 8.3 and 5.8, H_2), 2.44 (1 H, dd, *J* 18.0 and 2.4, 10′-H^a), 2.55 (1 H, dd, *J* 18.0 and 2.4, 10′-H^b), 2.84 (1 H, m, 8-H), 4.16 (2 H, q, *J* 7.3), 4.69 (1 H, d, *J* 1.9, =C*H*H) and 4.80 (1 H, d, *J* 1.9, =CH*H*); δ_C($CDCl_3$; 22.5 MHz) 14.06 (q), 17.71 (q), 20.40 (t), 21.91 (t), 26.10 (t), 29.56 (t), 34.29 (t), 37.66 (t), 39.07 (t), 49.21 (s), 52.67 (d), 60.33 (t), 81.29 (s), 104.84 (t), 150.48 (s) and 173.44 (s); *m/z* 266 (M^+), 251, 239, 234, 222, 195, 144 and 77 (Found: C, 72.5; H, 9.9. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84%).

Minor isomer **24**: R_f 0.52 [AcOEt–hexane (1 : 20)]; ν_{max}-(CCl_4)/cm^{-1} 3560, 3060, 1730 and 1650; δ_H($CDCl_3$; 400 MHz) 1.03 (3 H, s) 1.27 (3 H, t, *J* 7.3), 1.39–1.81 (11 H, m, methylenes and OH), 2.31 (2 H, dd, *J* 8.1 and 5.8, H_2), 2.38 (1 H, dd, *J* 18.0 and 2.4, 10′-H^a), 2.78 (1 H, dd, *J* 18.0 and 2.4, 10′-H^b), 3.15 (1 H, m, 8′-H), 4.16 (2 H, q, *J* 7.3), 4.76 (1 H, d, *J* 2.4, =C*H*H) and 4.87 (1 H, d, *J* 2.4, =CH*H*); δ_C($CDCl_3$; 100.6 MHz) 14.21 (q), 18.02 (q), 20.67 (t), 21.24 (t), 26.76 (t), 29.14 (t), 33.11 (t), 38.07 (t), 43.66 (t), 49.80 (s), 50.32 (d), 60.49 (t), 82.93 (s), 105.83 (t), 151.27 (s) and 173.71 (s); *m/z* 266 (M^+), 251, 239, 234, 195, 144 and 77 (Found: C, 72.1; H, 9.8%).

Ethyl (1′-*hydroxy*-7′-*methyl*-9′-*methylenebicyclo*[5.3.0]-*decan*-8′-*yl*)*acetate* **25**. Following the general procedure, radical cyclization of compound **22** (0.55 g) and then destannylation gave the cyclized compound (0.40 g, 70%). HPLC analysis showed it was a mixture of isomers in the ratio 90 : 10. By preparative HPLC we were able to separate only the major isomer.

For *compound* **25**: R_f 0.52 [AcOEt–hexane (1 : 20)]; ν_{max}(CCl_4)/cm^{-1} 3600, 3060, 1730 and 1650; δ_H($CDCl_3$; 400 MHz) 0.78 (3 H, s), 1.27 (3 H, t, *J* 7.3), 1.32–1.81 (11 H, m, methylenes and OH), 2.32 (2 H, d, *J* 6.3, H_2), 2.36 (1 H, dd, *J* 17.5 and 2.4, 10′-H^a), 2.50 (1 H, dd, *J* 17.5 and 2.4, 10′-H^b), 3.11 (1 H, dd ⟶ t, *J* 2.9, 8′-H), 4.16 (2 H, q, *J* 7.3), 4.79 (1 H, d, *J* 2.4, =C*H*H) and 4.88 (1 H, d, *J* 2.4, =CH*H*); δ_C($CDCl_3$; 100.6 MHz) 14.21 (q), 17.03 (q), 24.18 (t), 25.35 (t), 26.53 (t), 32.47 (t), 33.77 (t), 34.67 (t), 47.83 (t), 49.76 (t), 50.43 (s), 60.49 (t), 83.59

(s), 106.88 (t), 152.18 (s) and 173.92 (s); *m/z* 266 (M^+) (Found: C, 72.0; H, 9.8%).

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