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Synthesis of diethyl 2-methyl-bicyclo[3.1.1]hept-2-ene-6,6-dicarboxylate by Pd-catalyzed intramolecular allylic alkylation. Stereoselective preparation of its optically homogeneous form from *R*-(−)-carvone

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ABSTRACT

A new route to racemic diethyl 2-methyl-bicyclo[3.1.1]hept-2-ene-6,6-dicarboxylate (±)-**1a** by means of a palladium-catalyzed intramolecular allylic alkylation exercised on malonate-ester derivatives has been developed from *R*-(−)-carvone. The stereocontrolled synthesis of the enantiomerically pure (−)-**1b** by application of a six-step reactions sequence with a 28% overall yield from acetal **8**, has been accomplished.

1. Introduction

Expansolides A (**I**) and B (**II**) and Massarinolin A (**III**) were isolated by Bodo and Gloer from cultures of the soil fungus *Penicillium expansun* and the aquatic fungus *Massarina tunicata* Shearer and Fallah, respectively, (Fig. 1). These sesquiterpenoids display an antagonistic activity in vitro toward various bacteria and fungi and one of them (**III**), also proved to be active against *Staphylococcus aureus* (ATCC 29213).[1]

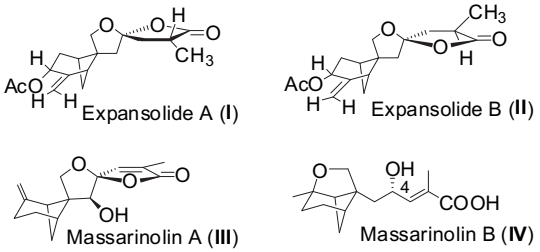

Figure 1.

In 2006 we successfully achieved the first total synthesis of massarinolin B (**IV**) and its 4-*epi* isomer, which are structurally close related to **III**.[2] We now wish to propose the bicyclic malonates **1a** and **1b** (Fig. 2) as appropriate starting materials for the synthesis of massarinolin A, the most demanding synthetic challenge among the components of this family of biologically active sesquiterpenoids. Additionally, palladium-catalyzed allylic alkylation has been shown to be a versatile reaction for generating quaternary chiral centers. The intramolecular version of this process has the potential to generate two new stereocenters in a single reaction and can allow a rapid increase in molecular complexity, generating polycycles in a stereospecific manner.[3] Recently, Trost et al. have reported intramolecular palladium-catalyzed asymmetric allylic alkylation to generate [2.2.2] bicycles with good enantio- and diastereoselectivity.[4]

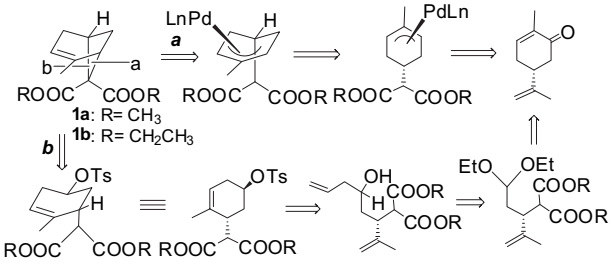

Figure 2.

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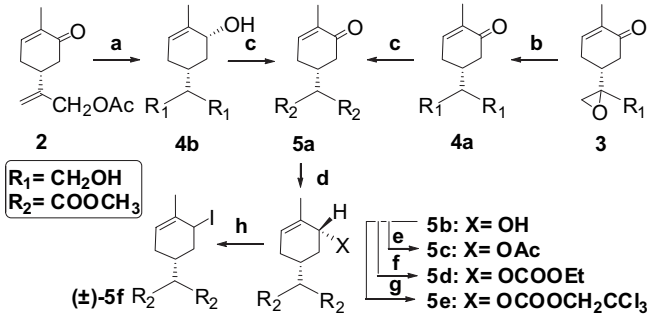
2. Results and discussion

We were prompted to access the bicyclo[2.2.1]heptane present in malonates **1a**,**b** through two different types of strategies based on disconexion types a and b (Fig. 2).[5]

According to disconexion type a the bicyclic malonate **1a** should be accessible through the Pd-catalyzed intramolecular allylic alkylation of monocyclic malonates **5c**–**e** (Scheme 1). These derivatives were easily accessible either from the epoxide **3** or the acetate **2**[6] by oxidation of either the keto diol **4a** or the triol **4b**. The keto diol **4a** was obtained in 85% yield by the Ti(III)-promoted epoxide opening of hydroxy epoxide **3** in the presence of either water or cyclohexadiene.[7] Additionally, reaction of acetate **2** with 3 equiv of 9-BBN followed by oxidative work up of the resulting trialkyl borane allowed us to isolate the triol **4b**, with 76% isolated yield. Extensive oxidation of either **4a** or **4b** by treatment with the Jones reagent led to the isolation of keto malonate **5a**, after treatment of the resulting malonic acid with an ethereal diazomethane solution. The oxidative route to **5a** through the keto diol **4a** proved to be advisable since the yield obtained in this case (70%) was more convenient than that obtained through the triol **4b** (42%). With the keto malonate **5a** in our hands we proceeded to prepare the malonate esters needed for the intramolecular cyclization reaction. Cerium trichloride-promoted sodium borohydride reduction of **5a** led to the hydroxy malonate **5b** quantitatively, and subsequent transformation of **5b** into the malonoester **5c** and carbonates **5d**,**e**, was successfully achieved by following standard procedures. The isolation of malonates **5c**–**e** provided the opportunity to perform the intramolecular Pd-catalyzed allylic alkylation to generate highly functionalized pinenes, such as **1**.

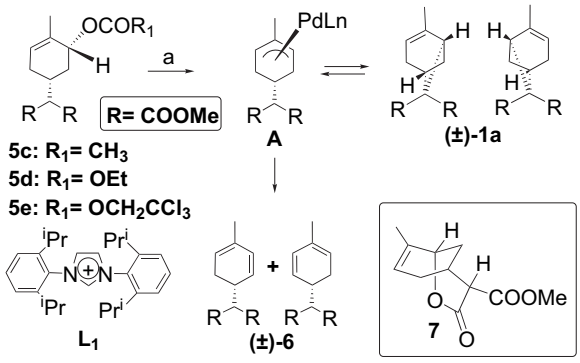


Scheme 1. (a) 9-BBN, THF, rt, 15 h; CH_3OH, 3 N NaOH, 30% H_2O_2, 60 °C, 1 h, 76%; (b) Cp_2TiCl_2, Zn THF, rt, 1 h; 3, 1,4-CHD, THF, $NaPO_4H_2$, 85%; (c) i: Jones, acetone, 0°C, 45 min, 70% (from **4a**), 42% (from **4b**); ii: CH_2N_2, ether, rt, 100%; (d) $NaBH_4$, $CeCl_3$, CH_3OH, −20 °C, 15 min, 100%; (e) Ac_2O, pyr, CH_2Cl_2, rt, 24 h, 88%; (f) ClCOOEt, pyr, DMAP, CH_2Cl_2, rt, 24 h, 85%; (g) $ClCOOCH_2CCl_3$, pyr, DMAP, CH_2Cl_2, rt, 3 h, 83%. (h) imidazole, Ph_3P, I_2, toluene, 0 °C, 86% (from **5b**).

The intramolecular alkylation of malonates **5c**–**e** failed at room temperature in the presence of 10 mol % palladium catalyst [Pd$(PPh_3)_4$, Pd_2dba_3] when triphenylphosphine was used as ligand, NaH as a base, and THF as a solvent (entries 1,3, and 5). An increase in temperature led to mixtures of starting material and the β-hydrogen elimination product (±)-**6** (entries 2, 4, and 6). The reaction was run with carbonates **5d** and **5e** in the absence of exogeneous base (entries 3 and 5).

Combination of Cs_2CO_3 or *N*,*O*-bis(trimethylsilyl) trifluoroacetamide (BSTFA)[8] as bases and the nucleophilic carbene L_1[9] or 1,2-bis(diphenylphosphino) ethane (dppe) as ligands in the presence of either Pd_2dba_3 (entry 7) or the allylpalladium chloride dimer (entry 8) did not modify our previous results. However, in these cases the formation of the elimination product (±)-**6** was accompanied by the formation of lactone **7**, which should result from deacylation[10] followed by transesterification under the reaction conditions. The use of palladium acetate and a variety of solvents, including DMF and toluene, provided no improvement (entries 8–11).

Since the palladium(0)-catalyzed ring cleavage of vinylcyclopropanes to generate an intermediate π-allylpalladium complex **A** has been observed previously,[11] we considered the low stability of vinyl cyclobutanes under Pd(0)-catalysis to explain the formation of the diene (±)-**6** under the reaction conditions (Scheme 2). By carefully monitoring the reaction by TLC it was observed that the vinyl cyclobutane (±)-**1a** is an intermediate in the transformation of **5c** to (±)-**6**.



Scheme 2. (a) Pd, catalyst, base, solvent, temperature, see Table 1.

This requires the vinyl cyclobutane to be opened by palladium (0) and to be in equilibrium with the π-allylpalladium complex.

The kinetic product of the system is (±)-**1a**, which in prolonged reaction times will be transformed to (±)-**6**.

The reaction of **5c** with 10 mol % palladium(II) acetate in the presence of NaH and Ph_3P (1 equiv) as ligand at 0 °C led to recovery of the starting material when DMF was used as solvent (entry 9).

When the reaction was run at room temperature, the elimination product (±)-**6** was obtained in 45% yield (entry 10) and a further increase to 50 °C led to the lactone **7** in 83% yield.

However, since the β-elimination requires coordinative unsaturation of Pd complexes, an increase in ligand up to 0.25 equiv (dppe instead of Ph_3P), using THF as solvent, allowed us to isolate the malonate (±)-**1a** in 65% yield (entry 13).

This is by far the most convenient system, since palladium acetate is a readily available compound, that is, completely stable in air. An increase in temperature did not improve our first result, but led to higher yields of the elimination product (entry 14).

Furthermore, in combination with imidazole by reaction of **5b** with triphenylphosphine and iodine we were able to isolate the racemic iodide **5f** in 86% yield which, by reaction with LDA at −78 °C, led to racemic **1a** in 60% yield.[12]

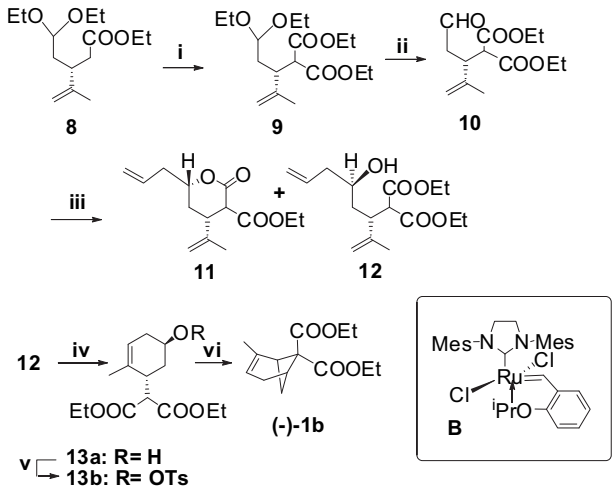
The enantioselective synthesis of (−)-**1b** was developed from acetal ester **8**[13] according to disconexion type b (Fig. 2).

LDA deprotonation of **8** at −78 °C in THF was followed by the addition of ethyl chloroformate to yield the malonate **9** in 85% yield. The acetal deprotection of **9** by treatment with *p*-toluene sulphonic acid yielded the aldehyde **10** in quantitative yield (Scheme 3).

The stereoselective allylation of **10** was first attempted by titanium tetrachloride-promoted addition of allyltrimethylsilane to the aldehyde, to yield a mixture of lactone **11** and hydroxy malonate **12** at a **12**/**11**=2:1 ratio in 87% yield.

The addition of allyl bromide in the presence of Cp_2TiCl under Barbier conditions[14] yielded the same mixture but with the opposite stereoselectivity (**11**/**12**=4.5:1) in 78% yield.

Finally, boron trifluoride-promoted addition of allyltrimethylsilane to **10** afforded a mixture of products at a **12**/**11**=5:1 ratio, which allowed us to isolate **12** in 80% yield.



Scheme 3. (a) THF, LDA, −78 °C, $ClCO_2Et$ (85%); (b) pTSA, CH_3COCH_3, rt, 100%, (c) CH_2Cl_2,$BF_3{\cdot}Et_2O$, allylSiMe$_3$, −78 °C, 96%; (**11**/**12**=16: 80); (d) CH_2Cl_2, Hoveyda catalyst (**B**), rt, 75%, (e) CH_2Cl_2, pyr, tosyl chloride, rt, 73%; (f) THF, NaH, rt, 75%.

With the hydroxy malonate **12** in our hands, attention was turned to the crucial cyclization step. Gratifyingly, we successfully achieved the bis olefin metathesis process with the Hoveyda catalyst **B** and were able to isolate the cyclohexenol **13a** in 75% yield. Quantitative transformation of hydroxyderivative **13a** into the tosylate **13b** allowed us to access the target (−)-**1b** by treatment with NaH in THF with 75% yield.

3. Conclusion

In sum, we have developed a new route to the highly functionalized pinene (±)-**1a** by means of a palladium-catalyzed intramolecular allylic alkylation exerted on malonate derivatives readily obtained from *R*-(−)-carvone. The stereocontrolled synthesis of the enantiomerically pure (−)-**1b** starting from the acetal ester **8**[12] is described.

4. Experimental

4.1. General experimental methods

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where indicated otherwise. IR spectra were recorded for $CHCl_3$ solution samples on NaCl plates, unless otherwise noted, on an FT-IR instrument. HRMS determinations (EI) were recorded at the Mass Spectrometry Service of the University of Salamanca, Spain. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for handling of air-sensitive materials. Chemicals and solvents were obtained from commercial sources and used as received with the exception of benzene, toluene and dioxane, which were distilled from sodium and benzophenone. Yields reported are for chromatographic pure isolated products unless mentioned otherwise.

4.1.1. (R)-5-[(R,S)-2-(Hydroxymethyl)oxiran-2-yl]-2-methylcyclohex-2-enone ***3***. To a solution of (*R*)-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-enone, **2a** (1.6 g, 9.5 mmol) and vanadyl acetyl acetonate (24 mg, 0.095 mmol) in 12 mL of toluene at 80 °C, was added dropwise a solution of 6 M *tert*-butyl hydroperoxide in decane (1.75 mL, 10.5 mmol). The reaction was stirred for 1 h at 80 °C. When the reaction was finished (TLC), the mixture was cooled to room temperature and 3 mL of 10% $Na_2S_2O_3$ was added. The crude mixture was extracted with ether, and the combined organic layers were washed whit brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was flash chromatographed on a silica gel column. Elution with hexane/ethyl acetate (1:3) afforded (*R*)-5-((*R*,*S*)-2-(hydroxymethyl)oxiran-2-yl)-2-methylcyclohex-2-enone **3** (1 g, 60%). R_f 0.40 (hexane/ethyl acetate 1:3); $[\alpha]_D^{20}$ −42.2 (*c* 1.32, $CHCl_3$); IR (film): ν 3472, 2926, 2891, 1738, 1713, 1672, 1433, 1370, 1165, 1109, 1049 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (m, 1H), 1.59 (s, 3H), 2.05 (m, 2H), 2.30 (m, 2H), 2.59 (dd, 1H, J_1=3, J_2=4.5 Hz), 2.67 (dd, 1H, J_1=1.6, J_2=4.5 Hz), 3.57 (dd, 2H, J_1=12.5, J_2=19.5 Hz), 6.60 (t, 1H, J=1.4 Hz) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ 15.7 (CH_3), 27.8 (CH_2), 36.5 (CH), 39.8 (CH_2), 48.9 (CH_2), 60.9 (C), 62.5 (CH_2), 135.5 (C), 144.9 (CH), 199.3 (C) ppm; MS (EI) (*m*/*z*, %): 182 (M^+, 2); 164 (4), 151 (10), 108 (100); 82 (64); 67 (20). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.89; H, 7.71.

4.1.2. (R)-5-(1,3-Dihydroxypropan-2-yl)-2-methylcyclohex-2-enone ***4a***. A suspension of Cp_2TiCl_2 (0.85 g, 3.5 mmol) with Zinc (0.5, 8 mmol) in 24 mL of deoxygenated and dry THF was stirred under an argon atmosphere for 1 h. When the reaction mixture turned from red to green, it was added dropwise via a Teflon cannula to a deoxygenated solution of **3** (250 mg, 1.4 mmol) with 1,4-cyclohexadiene (0.8 mL, 8.2 mmol) in 7 mL of THF. When the initial green color of the Ti(III) solution turned to red [Ti(IV)], the reaction was completed. Then, a satd solution of NaH_2PO_4 was added and the mixture was stirred overnight. The Ti salts were filtered and washed with ethyl acetate. The filtrate was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated off. The residue was flash-chromatographed in a silica gel column. Elution with ethyl acetate afforded **4a** (213 mg, 85%); R_f 0.5 (hexane/ethyl acetate); $[\alpha]_D^{20}$ −26 (*c* 1.4, $CHCl_3$); IR (neat): ν 3378, 2920, 2851, 1655, 1450, 1370, 1060 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09–1.24 (m, 1H), 1.54 (m, 1H), 1.68 (s, 3H), 2.19 (m, 2H), 2.48 (m, 2H), 3.73 (m, 4H), 6.71 (t, 1H, J=1.4 Hz) ppm.; ^{13}C NMR (200 MHz, $CDCl_3$): δ 15.8 (CH_3), 30.5 (CH_2), 33.8 (CH), 42.3 (CH_2), 46.0 (CH), 62.4 (CH_2), 62.6 (CH_2), 135.4 (C), 146.3 (CH), 201.0 (C) ppm; HRMS-EI (M^++Na): Calculated for $C_{10}H_{16}O_3Na$: 207.0991; found: 207.0996.

4.1.3. (5R)-5-(1,3-Dihydroxypropan-2-yl)-2-methylcyclohex-2-enol ***4b***. To a solution of 9-BBN (1.8 g, 14.4 mmol) in 30 mL of dry, freshly distilled THF was dropwise added the acetate 2 (1 g, 4.8 mmol) dissolved in THF (10 mL) and stirred for 15 h at room temperature. Then, the reaction mixture was chilled and, methanol (15 mL), aq 3 N NaOH (15 mL) and 30% H_2O_2 (15 mL) were consecutively added, warmed up to 60 °C and stirred for 1 h. The reaction mixture was cooled down to room temperature, satd with K_2CO_3, and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the organic solvent at reduced pressure afforded a crude product (0.8 g), which was fractionated by flash chromatography on silica gel. By elution with ethyl acetate/methanol (95/5) and evaporation of the solvent, the triol **4b** (0.7 g, 76%) was obtained as colorless oil. R_f 0.15 (ethyl acetate); $[\alpha]_D^{20}$ −30 (*c* 1.1, $CHCl_3$); IR (film): ν 3336, 2916, 2886, 1449, 1373, 1036, 965, 916, 809 cm^{-1}; ^{1}H NMR ($CHCl_3$): δ 1.62 (s, 3H), 1.70–2.50 (m, 6H), 3.48 (s, 1H), 3.70–4.00 (m, 4H), 4.10–4.30 (m, 3H), 5.45 (s, 1H) ppm; ^{13}C NMR ($CHCl_3$): δ 19.3 (q), 30.8 (t), 33.1 (d), 37.8 (t), 48.6 (d), 2×61.8 (t), 71.5 (d), 124.6 (d), 138.2 (s) ppm; HRMS-EI (M^++Na) Calculated for $C_{10}H_{18}O_3Na$: 209.1148, found: 209.1147.

4.1.4. Dimethyl 2-[(R)-4-methyl-5-oxocyclohex-3-enyl]-malonate ***5a*** *(from* ***4a****).* A solution of 2.67 M Jones reagent (2.2 mL, 5.83 mmol) was added dropwise to a solution of **4a** (325.0 mg, 1.76 mmol) in

acetone (21 mL) at 0 °C. The solution was stirred for 45 min at room temperature, after which isopropanol was added and the solution turned to green. Saturated NaCl (10 mL) was added, the acetone was evaporated off under reduced pressure, and the reaction mixture was extracted with ether. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude, which was treated with an ethereal solution of diazomethane to yield the malonate **5a** (268.5 mg, 70%) as a colorless oil. R_f=0.5 (hexane/ethyl acetate 1:1); $[\alpha]_D^{20}$ −37 (*c* 1.5, $CHCl_3$); IR: *ν* 2954, 2926, 2852, 1742, 1735, 1675, 1437, 1253, 1159, 1022, 918, 743 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 1.8 (s, 3H), 2.1–2,7 (m, 5H), 3.4 (d, 1H, *J*=8 Hz), 3.7 (s, 6H), 6.6–6.8 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): *δ* 15.4 (q), 29.6 (t), 34.9 (d), 41.7 (t), 52,3 (2×q), 55.7 (d), 135.6 (s), 143.4 (d), 167.9 (2×s), 197.5 (s) ppm; HRMS-EI (M^++Na) Calculated for $C_{12}H_{16}O_5Na$: 263.0889, found: 263.0877.

4.1.5. Dimethyl 2-[(1R,5R)-5-hydroxy-4-methylcyclohex-3-enyl] malonate ***5b****.* $NaBH_4$ (75 mg, 1.99 mmol) was added to a solution of **5a** (478.9 mg, 1.99 mmol) and cerium trichloride (503.4 mg, 1.99 mmol) in 2 mL of methanol at −20 °C. After 15 min the reaction was quenched with 5 mL of ethyl ether and 5 mL of water. The mixture was cooled to room temperature and the aqueous layer was extracted with ethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue in a silica gel flash column, with hexane/ethyl acetate (1:1) as eluent, afforded (*R*)-dimethyl 2-(5-hydroxy-4-methylcyclohex-3-enyl)malonate **5b** (485 mg, 100%). R_f 0.45 (hexane/ethyl acetate 8:2); $[\alpha]_D^{20}$ −24.51 (*c* 1.06, $CHCl_3$); IR: *ν* 3419, 2953, 2921, 1733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.74 (s, 3H), 1.12–2.55 (m, 6H), 3.31 (d, 1H, J_1=9.1 Hz), 3.72 (s, 3H), 3.73 (s, 3H), 4.15–4.27 (m, 1H), 5.39–5.47 (m, 1H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): *δ* 18.7 (q), 29.4 (t), 33.3 (d), 36.9 (t), 52.2 (q), 56.6 (d), 69.6 (d), 122.3 (d), 136.5 (s), 168.7 (s) ppm; HRMS-EI (M^++Na): Calculated for $C_{12}H_{18}O_5Na$: 265.1046; found: 265.1048.

4.1.6. Dimethyl-2-[(1R,5R)-5-acetoxy-4-methylcyclohex-3-enyl]-malonate ***5c****.* Pyridine (0.1 mL, 1.2 mmol) and 0.09 mL (0.9 mmol) of acetic anhydride were added to a solution of **5b** (145 mg, 0.6 mmol) in 4 mL of CH_2Cl_2. The reaction mixture was stirred for 24 h at room temperature. Then, crushed ice was added to the mixture, which was stirred for an additional hour. The reaction was extracted with ether and the organic layer was washed with 1 M HCl, satd $NaHCO_3$, satd NaCl, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue in a flash silica gel column, with hexane/ethyl acetate (9:1) as eluent, afforded (*R*)-dimethyl-2-(5-acetoxy-4-methylcyclohex-3-enyl) malonate **5c** (162 mg, 88%). R_f 0.45 (hexane/ethyl acetate 9:1); $[\alpha]_D^{20}$ −20.71 (*c* 0.97, $CHCl_3$); IR: *ν* 3000, 2954, 2858, 1734, 1437, 1371, 1236, 1158, 1016, 937, 827 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.40–2.55 (m, 5H), 1.56 (s, 3H), 2.03 (s, 3H), 3.38 (d, 1H, J_1=9.1 Hz), 3.71 (s, 6H), 5.35–5.45 (m, 1H), 5.50–5.54 (m, 1H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): *δ* 18.9 (q), 20.9 (q), 28.8 (t), 32.3 (d), 32.5 (t), 52.2 (q), 56.0 (d), 71.2 (d), 124.5 (d), 132.7 (s), 168.4 (s), 168.5 (s), 170.4 (s) ppm; HRMS-EI (M^++Na): Calculated for $C_{14}H_{20}O_6Na$: 307.1152; found 307.1144.

4.1.7. (1R,5R)-5-(Di(methoxycarbonyl)methyl)-2-methylcyclo hex-2-enyl ethyl carbonate ***5d****.* Pyridine (0.2 mL, 2.5 mmol), ethyl chloroformate (0.2 mL, 1.9 mmol), and dimethylaminopyridine (DMAP) (6 mg, 0.04 mmol) were successively added to a solution of **5b** (150 mg, 0.6 mmol) in 5 mL of dichloromethane at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 h. Then, 15 mL of a mixture of ether/water (95:5) was added. The organic layer was consecutively washed with 1 M $KHSO_3$, water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated off under reduced pressure to afford a crude mixture (162 mg), which was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate (9:1) and evaporation of the solvent the carbonate **5d** (166 mg, 85%) was isolated as a colorless oil. R_f 0.5 (hexane/ethyl acetate 9: 1); $[\alpha]_D^{20}$ +22.6 (*c* 0.85, $CHCl_3$); IR (film): *ν* 2940, 2858, 1734, 1436, 1371, 1238, 1158, 1018, 937, 827 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 1.33 (t, 3H, *J*=4.5 Hz), 1. 67 (s, 3H), 1.80–2.60 (m. 5H). 3.36 (d, 1H; *J*=9 Hz), 3.72 (s, 6H), 4.18 (q, 2H, J_1=7, J_2=14 Hz), 5.23–5.29 (m, 1H), 5.50–5.54 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): *δ* 14.1 (q), 18.6 (q), 28.8 (t), 29.5 (t), 32.5 (d), 52.2 (q), 56.0 (d), 63.7 (t), 75.4 (d), 124.8 (d), 132.5 (s), 155.0 (s), 168.4 (s) ppm; HRMS (M^++Na) calculated for $C_{15}H_{22}O_7Na$: 337.1257, found: 337.1263.

4.1.8. (1R,5R)-5-[Di(methoxycarbonyl)methyl]-2-methylcyclohex-2-enyl-1-(2,2,2-trichloroethyl carbonate) ***5e****.* To a solution of **5b** (210 mg, 0.9 mmol) in pyridine (2 mL) and DMAP (5 mg, 0.04 mmol) at 0 °C and under argon atmosphere was dropwise added 2,2,2-trichloroethyl chloroformate (0.15 mL, 1 mmol). The reaction mixture was stirred for 3 h at room temperature. Then, a mixture of ether/water (15:1) (15 mL) was added. The organic layer was consecutively washed with 1 M $KHSO_3$, water and brine, then, dried over Na_2SO_4. Evaporation of the organic solvent at reduced pressure led to the isolation of a crude (0.5 g), which was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate (85:15) and evaporation of the solvent the carbonate **5e** (0.3 g, 83%) was isolated as a yellow oil. R_f 0.45 (hexane/ethyl acetate 85: 15); $[\alpha]_D^{20}$ −0.15 (*c* 1.37, $CHCl_3$); IR: *ν* 2941, 1743, 1450, 1259, 1005 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 1.71 (s, 3H), 1.90–2.55 (m, 5H), 3.38 (d, 1H, *J*=9 Hz), 3.74 (s, 6H), 4.72 (d, 1H, J_1=12 Hz), 4.82 (d, 1H, J_1=12 Hz), 5.31–5.37 (m, 1H), 5.58 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): *δ* 18.8 (q), 29.1 (t), 32.4 (t), 32.5 (d), 52.5 (q), 52.6 (q), 56.0 (d), 76.7 (t), 77.3 (d), 94.5 (s), 125.6 (d), 131.9 (s), 153.9 (s), 168.5 (s), 168.5 (s) ppm; HRMS (M^++Na) calculated for $C_{15}H_{19}Cl_3O_7Na$: 439.0094, found: 439.0092.

4.1.9. (±)-Dimethyl 2-[(1R,5S)-5-iodo-4-methylcyclohex-3-enyl]malonate (±)- ***5f****.* To a solution of **5b** (0.13 g, 0.5 mmol) in toluene (3 mL) at 0 °C and under an argon atmosphere were consecutively added, imidazole (100 mg, 1.5 mmol), triphenylphosphine (200 mg, 0.8 mmol), and iodide (190 mg, 0.75 mmol). Then, dichloromethane (3.5 mL) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was filtered and the solids were washed with pentane. The organic solvents were evaporated at reduced pressure and the crude (1.8 g) was fractionated by flash chromatographed on silica gel. By elution with hexane/ethyl acetate (8:2), the iodide (±)-**5f** was isolated (160 mg, 86%) as a yellow oil. R_f 0.5 (hexane/ethyl acetate 8:2); IR(film): *ν* 2949, 2916, 1734, 1434, 1337, 1251, 1156 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 1.69–1.77 (m, 2H), 1.83 (s, 3H), 2.15–2.35 (m. 2H), 2.86–2.96 (m, 1H), 3.35 (d, 1H, *J*=8 Hz), 3.75 (s, 3H), 3.76 (s, 3H), 4.94 (t, 1H, *J*=2 Hz), 5.53–5.55 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): *δ* 22.1 (q), 29.3 (t), 31.0 (d), 35.2 (d), 37.9 (t), 52.4 (q), 56.2 (d), 124.0 (d), 136.4 (s), 168.5 (s), 168.5(s) ppm; HRMS-EI (M^++Na) Calculated for $C_{12}H_{17}O_4NaI$: 375.0063; found 375.0070.

4.1.10. (1S,5R*)-Dimethyl 2-methylbicyclo[3.1.1]hept-2-ene-6,6-dicarboxylate (±)-* ***1a*** *(from (±)-* ***5f****).* To a solution of diisopropylamine (0.1 mL, 0.7 mmol) in anhydrous THF (3 mL) at 0 °C and under an argon atmosphere, a solution of 1.1 M BuLi in hexane (0.4 mL, 0.64 mmol) was added at −78 °C. The mixture was stirred at that temperature and then cooled down to −78 °C, Then, a solution of (±)-**5f** (115 mg, 0.3 mmol) in THF (2 mL) was added dropwise via cannula and the reaction mixture was stirred for 1 h and warmed up to room temperature. Then, a solution of satd NH_4Cl (4 mL) was added and the reaction mixture was extracted with ether and

washed with brine, dried over anhydrous Na_2SO_4, the organic solvent was evaporated under reduced pressure to afford a residue (0.9 g), which was fractionated by flash chromatography. By elution with hexane/ethyl acetate (75:25) the bicyclic malonate (±)-**1a** was obtained (31 mg, 44%) as a colorless oil. R_f 0.45 (hexane/ethyl acetate 7:3); IR: ν 2948, 2859, 1705, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66–2.25 (m, 4H), 1.76 (s, 3H), 3.00–3.03 (m, 1H), 3.66 (s, 3H), 3.76 (s, 3H), 4.58 (t, 1H, J_1=3.5 Hz), 5.59–5.61 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 21.1 (q), 25.0 (d), 27.9 (t), 33.6 (t), 50.6 (q), 54.6 (q), 75.0 (d), 83.4 (s), 126.9 (d), 129.7 (s), 163.5 (s), 167.7 (s) ppm; HRMS-EI (M^++ Na): Calculated for $C_{12}H_{16}O_4Na$: 247.0940, found: 247.0959.

4.1.11. Methyl 8-methyl-3-oxo-2-oxa-bicyclo[3.3.1]non-7-ene-4-carboxylate ***7*** *(from* ***5b****).* To a suspension of NaH (3 mg, 0.12 mmol) in THF (1 mL) at 0 °C and under an argon atmosphere a solution of **5b** (24 mg, 0.12 mmol) in THF (2 mL) was added via cannula. Then, the reaction mixture was warmed at reflux and stirred for 1 h at that temperature. Then, the reaction was cooled to room temperature, a solution of satd NH_4Cl (2 mL) was added, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with satd NaCl and dried over Na_2SO_4. The organic solvent was evaporated at reduced pressure to afford **7** (28 mg, 100%) as a colorless oil. R_f 0.2 (hexane/ethyl acetate 8:2); $[\alpha]_D^{20}$ +77.8 (*c* 1.3, $CHCl_3$); IR(film): ν 2952, 1724, 1437, 1375, 1264, 1219, 1152, 1053, 1264, 1220, 1152, 1054, 1034, 960 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.82 (s, 3H), 1.86–2.59 (m, 5H), 3.30 (s, 1H), 3.75 (s, 3H), 4.57 (s, 1H), 5.55–5.56 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 21.2 (q), 26.9 (t), 28.7 (d), 33.5 (t), 52.8 (q), 53.8 (d), 75.3 (d), 123.2 (d), 134.6 (s), 167.7 (s), 170.3 (s) ppm; HRMS-EI (M^++Na): Calculated for $C_{11}H_{14}O_4Na$: 233.0784, found: 233.0780.

4.1.12. (R)-Diethyl 2-(5,5-diethoxy-2-methylpent-1-en-3-yl) malonate ***9****.* To a round-bottom flask equipped with septum inlet, magnetic stirrer, and argon inlet, was placed a solution diisopropylamine (0.9 mL, 6.6 mmol) in dry THF (32 mL) at 0 °C. To this solution was added dropwise a solution of 1.6 M Buli in hexane (3.8 mL, 6 mmol). The solution was stirred at 0 °C for 30 min and then cooled to −78 °C. After 30 min of stirring at that temperature, a solution of (*R*)-ethyl 3-(2,2-diethoxyethyl)-4-methylpent-4-enoate **8** (0.78 g, 3 mmol) in anhydrous THF (15 mL). After 30 min of stirring ethyl chloroformate (0.6 mL, 6 mmol) was added and the resultant mixture was stirred for 14 h at −78 °C and quenched with satd aq NH_4Cl (30 mL). The aqueous phase was extracted with ether and the combined layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography hexane/ethyl acetate (9:1) to afford **9** (0.85 g, 85%) as colorless oil. R_f 0.25 (hexane/ethyl acetate 9:1); $[\alpha]_D^{20}$ +2.7 (*c* 1.51, $CHCl_3$); IR: ν 2965, 1740, 1452, 1374, 1242, 1141, 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15–1.26 (m, 9H), 1.69 (t, 2H, J_1=6.6 Hz), 2.36 (d, 2H, J=2.13 Hz), 2.71–2.85 (m, 1H), 3.46–3.65 (m, 4H), 4.09 (q, 2H, J=7.07 Hz), 4.44 (m, 1H), 4.79 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 15.2 (q), 18.8 (q), 36.8 (t), 39.1 (t), 39.9 (d), 60.0 (t), 61.0 (t), 101.3 (d), 112.1 (t), 145.9 (s), 172.1 (s) ppm; MS-EI (M^+, %): 285 (M^+−EtOH, 10), 257 (15), 239 (25), 165 (45), 116 (50), 103 (100), 75 (90). Anal. Calcd for $C_{17}H_{30}O_6$: C, 61.80; H, 9.15. Found: C, 61.76; H, 9.12.

4.1.13. (R)-Diethyl 2-(2-methyl-5-oxopent-1-en-3-yl) malonate ***10****. p*-Toluenesulphonic acid PTSA (0.24 g, 1.3 mmol) was added to a solution of (*R*)-diethyl 2-(5,5-diethoxy-2-methylpent-1-en-3-yl) malonate **9** (1.2 g, 3.5 mmol) in 75 mL acetone/water (2:1). The resultant mixture was stirred for 22 h at room temperature then, the acetone was removed under reduced pressure. The aqueous phase was extracted with ether and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel. By elution with hexane/AcOEt (4:1) the malonate **10** (0.9 g, 100%) was isolated as colorless oil. R_f 0.5 (hexane/ethyl acetate 8:2); $[\alpha]_D^{20}$ −27.6 (*c* 0.94, $CHCl_3$); IR: ν 2928, 1735, 1452, 1377, 1252, 1157, 1037 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13–1.29 (m, 6H), 1.73 (s, 3H), 2.54–2.63 (m, 2H), 3.42–3.55 (m, 2H), 4.10–4.24 (m, 4H),4.87 (s, 2H), 9.63 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.9 (q), 19.7 (q), 40.8 (d), 44.8 (t), 55.1 (d), 61.6 (t), 114.5 (t), 143.2(s), 167.8 (s), 200.2 (d) ppm; HRMS-EI (M^++Na): Calculated for $C_{13}H_{20}O_5Na$: 279.1202, found: 279.1202.

4.1.14. Diethyl 2-[(3R,5R)-5-hydroxy-2-methylocta-1,7-dien-3-yl]malonate ***11****, and (4R,6S)-ethyl 6-allyl-tetrahydro-2-oxo-4-(prop-1-en-2-yl)-2H-pyran-3-carboxylate* ***12****. Method* 1: To a solution of aldehyde **10** (0.9 g, 3.48 mmol) in dry dichloromethane (175 mL) was added dropwise a solution of 1 M $TiCl_4$ in dichloromethane (5 mL, 5 mmol) via syringe at −78 °C and under an argon atmosphere. The reaction mixture was stirred for 15 min and allyltrimethylsilane (0.7 mL, 4.3 mmol) was added. The reaction mixture was stirred at −78 °C for 7 h and then, quenched with 70 mL of satd $NaHCO_3$. The aqueous phase was extracted with ether and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product (0.9 g) was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate 3:1, the lactone **11** (0.3 g, 35%) and the hydroxy malonate **12** (0.6 g, 65%) were isolated.

Method 2: Strictly deoxygenated THF (8 mL) was added to a mixture of $TiCl_2Cp_2$ (0.23 g, 0.9 mmol) and Mn dust (0.2 g, 3.4 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green. Then, a solution of aldehyde **10** (0.1 g, 0.4 mmol) in THF (0.5 mL) was slowly added. Subsequently, a solution of allylic bromide (73 μL, 0.85 mmol) in THF (0.5 mL) was slowly added and the mixture was stirred for 20 h. The reaction was quenched with brine and the resulting solution was filtered. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the organic solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel. By elution with hexane/ethyl acetate 3:1, the lactone **11** (71.5 mg, 68%), and the hydroxy malonate **12** (18.4 mg, 15%) were isolated.

Method 3: To a solution of aldehyde **10** (0.12 g, 0.5 mmol) in dry dichloromethane (25 mL), $BF_3{\cdot}OEt_2$ (86 μL, 0.69 mmol) was slowly added at −78 °C under an argon atmosphere. After 15 min, allyltrimethylsilane (93 μL, 0.6 mmol) was added and the resulting solution was stirred for 15 h at −78 °C. The reaction was poured into satd $NaHCO_3$ aq (12 mL) and extracted with Et_2O. The extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 0.15 g of a crude product, which was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate 3:1, the lactone **11** (18 mg, 16%) and the hydroxy malonate **12** (109 mg, 80%) were isolated.

Compound **11**: R_f 0.5 (hexane/ethyl acetate 7: 3); $[\alpha]_D^{20}$ −27.5 (*c* 1.5, $CHCl_3$); IR (neat): ν 3080, 2980, 2927, 1746, 1645, 1252, 1155, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (t, J=7 Hz, 3H), 1.55 (m, 1H), 1.72 (s, 3H), 1.98 (m, 1H), 2.41 (m, 1H), 2.49 (m, 1H), 3.00 (dt, J_1=12 Hz; J_2=4 Hz, 1H), 3.41 (d, J=12 Hz, 1H), 4.2 (q, J=7 Hz, 2H), 4.46 (m, 1H), 4.83 (m, 1H), 4.85 (m, 1H), 5.14 (m, 1H), 5.17 (m, 1H), 5.80 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.0 (q), 19.1 (q), 32.8 (t), 39.9 (t), 42.9 (d), 52.6 (t), 61.7 (t), 79.8 (d), 113.0 (t), 119.0 (t), 131.9 (d), 143.6 (s), 167.1 (s), 168.4 (s) ppm; HRMS-EI (M^++Na): Calculated for $C_{14}H_{20}O_4Na$: 275.1254, found: 275.1257.

Compound **12**: R_f 0.25 (hexane/ethyl acetate 7: 3); $[\alpha]_D^{20}$ −20.1 (*c* 0.98, $CHCl_3$); IR: ν 3450, 3020, 2928, 1733, 1279, 1249, 1175 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (s, 3H), 1.24 (s, 3H), 1.6 (m, 2H), 1.70 (s, 3H), 2.05

(m. 1H), 2.15 (m, 1H), 2.93 (dt, J_1=12, J_2=4 Hz, 1H), 3.42 (d, J=12 Hz, 1H), 3.54 (m, 1H), 4.14 (q, J=7 Hz, 2H), 4.17 (q, J=7 Hz, 2H), 4.82 (m, 2H), 5.03 (m, 1H), 5.06 (m, 1H), 5.80 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.2 (q), 14.2 (q), 19.1 (q), 37.8 (t), 41.1 (t), 44.8 (d), 56.4 (d), 61.5 (t), 61.7 (t), 69.3 (d), 115.0 (t), 118.4 (t), 134.7 (d), 144.6 (s), 168.2 (s), 168.6 (s) ppm; HRMS-EI (M^++Na): Calculated for $C_{16}H_{26}O_5Na$: 321.1672, found: 321.1665.

4.1.15. Diethyl 2-((1R,5R)-5-hydroxy-2-methylcyclohex-2-enyl) malonate ***13a***. In a round-bottom flask equipped with septum inlet, magnetic stirring bar, and argon inlet was placed the catalyst (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloride(*o-iso*-propoxyphenylmethylene) ruthenium (**B**, see text) (22.5 mg, 0.036 mmol). A solution of **12** (0.2 g, 0.7 mmol) in dry dichloromethane (8 mL) was added. The reaction mixture was stirred for 24 h at room temperature and then, quenched with 1 mL of ethyl vinyl ether. The solvent was removed under reduced pressure and the crude product was fractionated by flash chromatography on silica gel. By elution with hexane/AcOEt (8:2) and evaporation of the organic solvent at reduced pressure, the hydroxy malonate **13a** (0.15 g, 75%) was obtained as colorless oil. R_f 0.3 (hexane/ethyl-acetate 7:3); $[\alpha]_D^{20}$ −29.6 (*c* 0.8, $CHCl_3$); IR (neat): ν 3422, 2924, 1731 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$): δ 1.21–1.27 (6H, m), 1.66 (3H, s), 1.77–2.01 (4H,m), 2.28–2.34 (1H, m), 3.01–3.02 (1H, m), 3.67 (1H, d, J=6 Hz), 4.04–4.06 (1H, m), 4.12–4.21 (4H, m), 5.38–5.40 (1H, m); ^{13}C NMR (200 Hz, $CDCl_3$): δ 169.0 (s), 168.4 (s), 133.0 (s), 122.0 (d), 64.4 (d), 61.3 (t), 61.1 (t), 53.6 (d), 36.8 (d), 33.7 (t), 33.2 (t), 21.7 (q), 14.0 (q) ppm; HRMS-EI (M^++Na): Calculated for $C_{14}H_{22}O_5Na$: 293.1359; found: 293.1356.

4.1.16. Diethyl 2-[(1R,5R)-2-methyl-5-(tosyloxy)cyclohex-2-enyl] malonate ***13b***. To a solution of alcohol **13a** (0.15 g, 0.5 mmol) in dichloromethane (3 mL) were consecutively added pyridine (130 μL, 1.6 mmol) and *p*-toluenesulfonyl chloride (0.25 g, 1.3 mmol). The reaction mixture was stirred for 17 h under argon and quenched with satd aq $NaHCO_3$. The aqueous phase was extracted with ether. The combined organic layers were washed with 1 M HCl, aq satd $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate 7:3 the tosylate **13b** (0.17 g, 73%) was isolated as colorless oil. R_f 0.45 (hexane/ethyl acetate 7: 3); $[\alpha]_D^{20}$ −18.4 (*c* 1.1, $CHCl_3$); IR (neat): ν 3345, 2928, 1735 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$): δ 1.19–1.29 (6H, m), 1.65 (3H, s), 1.89–2.23 (4H, m), 2.43 (3H, s), 2.97–3.10 (1H, m), 3.68 (1H, d, J=5 Hz), 4.06–4.22 (4H, m), 4.84–4.89 (1H, m), 5.29–5.31 (1H, m), 7.32 (2H, d, J=9 Hz), 7.78 (2H, d, J=8 Hz); ^{13}C NMR (200 Hz, $CDCl_3$): δ 168.9 (s), 168.4 (s), 144.6 (s), 134.7 (s), 133.4 (s), 130.0 (d), 127.9 (d), 120.7 (d), 77.3 (d), 61.8 (t), 61.5 (t), 53.1 (d), 36.6 (d), 31.2 (t), 30.5 (t), 21.8 (q), 21.8 (q), 14.3 (q), 14.2 (q) ppm; HRMS: Calculated for $C_{21}H_{28}O_7NaS$ 447.1448, found 447.1436.

4.1.17. Diethyl 2-methylbicyclo[3.1.1]hept-2-ene-6,6-dicarboxylate (−)- ***1b***. To a magnetically stirred suspension of (60%) NaH 60% (20 mg, 0.5 mmol) in THF (3 mL) at 0 °C was added a solution of **13b** (0.17 g, 0.4 mmol) in dry THF (7 mL). The reaction mixture was stirred for 15 h at room temperature under argon and quenched with 10 mL of satd aq NH_4Cl. The aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate (9:1), the bicyclic malonate (−)-**1b** (0.05 g, 50%) was isolated as colorless oil. R_f 0.45 (hexane/ethyl acetate 0.45); $[\alpha]_D^{20}$ −103.0 (*c* 0.9, $CHCl_3$); IR (neat): ν 2931, 1667, 1602, 1380, 1235, 1086 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$): δ 1.22–1.33 (6H, m), 1.74 (3H, s), 1.80–1.83 (2H, m), 2.32–2.36 (2H, m), 3.28–3.30 (1H, m), 4.06–4.19 (4H, m), 4.87–4.89 (1H, m), 5.06–5.07 (1H, m) ppm; ^{13}C NMR (200 Hz, $CDCl_3$): δ 167.0 (s), 164.4 (s), 141.8 (s), 114.5 (d), 84.4 (s), 73.9 (d), 63.6 (t), 59.0 (t), 34.2 (t), 30.2 (d), 27.8 (t), 22.6 (q), 14.8 (q), 14.4 (q) ppm; HRMS: Calculated for $C_{14}H_{20}O_4Na$ 275.1254; found 275.1245.

4.1.18. Catalytic intramolecular allylic alkylation. General procedure: The catalyst (see Table 1 in the text) (0.024 mmol), the ligand (0.03 mmol), the base (256.5 mg, 0.8 mmol), and freshly distilled THF (2.5 mL) were placed in a 50-mL round-bottom flask equipped with a magnetic stirring bar and a condenser. The reaction mixture was stirred under an Argon atmosphere at 0 °C. Then, a solution of the substrate (**5c**,**d**) (0.23 mmol) in THF (1.5 mL) was added dropwise and the reaction mixture was driven at the temperature described and indicated reaction times. The reaction was cooled to room temperature and a satd NH_4Cl (2.5 mL) solution was added. The reaction mixture was extracted with ether and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude, which was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate (3:1) and evaporation of the solvent, the products (**1**, **6**, and **7**) were isolated (isolated yields: see the Table 1).

Table 1
Catalytic intramolecular allylic alkylation

Rxn	SM	Sol.	Base	Temp. °C	Catalyst (equiv)	Ligand (equiv)	Products (%)
1	**5c**	THF	NaH	24	$Pd(PPh_3)_4$ (0.1)	PPh_3 (0.3)	**5c** (100%)
2	**5c**	THF	NaH	60	$Pd(PPh_3)_4$ (0.1)	PPh_3 (0.3)	**7** (15%); **6** (65%)
3	**5d**	THF	–	60	$Pd(PPh_3)_4$ (0.2)	PPh_3 (0,8)	**5d** (35%); **6** (35%)
4	**5d**	THF	NaH	60	$Pd(PPh_3)_4$ (0.1)	PPh_3 (0.4)	7 (15%); **6** (45%)
5	**5e**	THF	–	60	$Pd(PPh_3)_4$ (0.1)	PPh_3 (0.4)	**5e** (35%); **6** (40%)
6	**5e**	THF	NaH	60	$Pd(PPh_3)_4$ (0.1)	PPh_3 (0.4)	**7** (5%); **6** (50%)
7	**5e**	THF	Cs_2CO_3	60	Pd_2dba_3 (0.025)	L_1 (0.05)	**5e** (65%); **6** (15%)
8	**5e**	Tol	BSTFA	60	$(allylPdCl)_2$ (0.03)	dppe (0.075)	**5e** (70%); **6** (15%)
9	**5c**	DMF	NaH	0	$Pd(OAc)_2$ (0.1)	PPh_3 (0.5)	**5c** (90%)
10	**5c**	DMF	NaH	20	$Pd(OAc)_2$ (0.1)	PPh_3 (0.4)	**5c** (40%); **6** (45%);
11	**5c**	DMF	NaH	50	$Pd(OAc)_2$ (0.1)	PPh_3 (0.4)	**7** (83%)
12	**5c**	THF	NaH	50	$Pd(OAc)_2$ (0.1)	PPh_3 (0.4)	**5c** (50%); **6** (15%)
13	**5c**	THF	NaH	50	$Pd(OAc)_2$ (0.1)	Dppe (0.25)	**5c** (15%); **1** (65%)
14	**5c**	THF	NaH	70	$Pd(OAc)_2$ (0.1)	Dppe (0.25)	**5c** (10%); **7** (5%); **6** (40%); **1** (10%)

Compound (±)-**1a** colorless oil. R_f 0.45 (hexane/ethyl acetate 7:3); $[\alpha]_D^{20}$ 0 (*c* 1.3 $CHCl_3$) with identical spectroscopic properties as those described above.

Compound (±)-**6**: colorless oil. R_f 0.5 (hexane/ethyl acetate 3:1); $[\alpha]_D^{20}$ 0 (*c* 1.5, $CHCl_3$); IR: ν 2953, 2923, 1731 cm^{-1}. ^{1}H RMN ($CDCl_3$): δ 1.73 (s, 3H), 1.90–2.40 (m, 2H), 2.87–3.05 (m, 1H), 3.49 (d, 1H, J_1=9.7 Hz), 3.72 (s, 3H), 3.73 (s, 3H), 5.38–5.47 (m, 1H), 5.73 (dd, 1H,

J_1=4.3, J_2=9.1 Hz), 5.87 (d, 1H, J_1=9.7 Hz) ppm; ^{13}C RMN ($CDCl_3$): δ 20.9 (q), 26.5 (t), 32.7 (d), 52.4 (q), 54.2 (d), 119.3 (d), 126.7 (d), 129.5 (d), 131.5 (s), 168.8 (s) ppm. IR: ν 2953, 2923, 1731 cm^{-1}; HRMS-EI (M^++Na): Calculated for $C_{12}H_{16}O_4Na$: 247.0940; found: 247.0944.

Compound **7**: colorless oil. R_f 0.2 (hexane/ethyl acetate 8:2); $[\alpha]_D^{20}$ +77.8 (*c* 1.3, $CHCl_3$); IR(film): ν 2952, 1724, 1437, 1375, 1264, 1219, 1152, 1053, 1264, 1220, 1152, 1054, 1034, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H), 1.86–2.59 (m, 5H), 3.30 (s, 1H), 3.75 (s, 3H), 4.57 (s, 1H), 5.55–5.56 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 21.2 (q), 26.9 (t), 28.7 (d), 33.5 (t), 52.8 (q), 53.8 (d), 75.3 (d), 123.2 (d), 134.6 (s), 167.7 (s), 170.3 (s) ppm; HRMS-EI (M^++Na): Calculated for $C_{11}H_{14}O_4Na$: 233.0784, found: 233.0780.

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Supplementary data

Supplementary spectroscopic data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.08.051. These data include MOL files and InChIKeys of the most important compounds described in this article.

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