Sequential Michael addition/biscyclization reactions leading to the formation of highly substituted polycyclic substrates: some preliminary studies

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Dedicated to Professor Moreno-Mañas on the occasion of his 60th birthday with regards and best wishes

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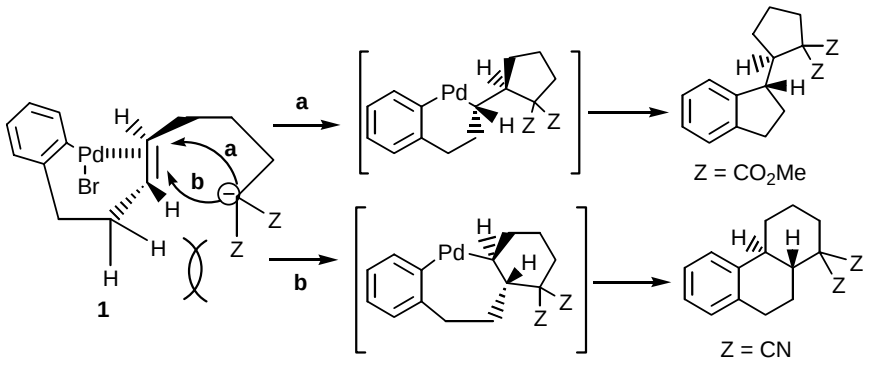
Abstract

An intermolecular Michael addition reaction of a malonate or malononitrile to unsaturated carbonyl substrates **Z2a**, **E2a** and **E2b** followed by a palladium-mediated biscyclization reaction led to the formation of highly functionalised tricyclic compounds with, in general, a high level of selectivity**.** A preliminary study on the transformation of one of these resulting substrates into a tetracyclic compound is also presented.

Keywords: Intermolecular Michael additions, palladium, biscyclization, polycyclics

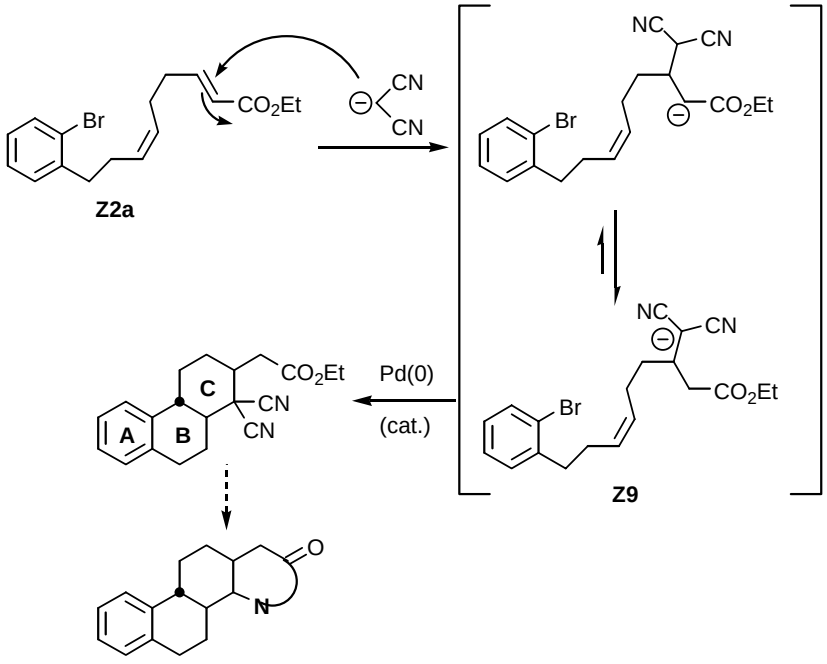
Introduction

In recent years, transition metal-mediated tandem or cascade reactions have become a powerful method for the one-step synthesis of various carbo- and heterocyclic systems. Many groups have made important contributions to this area and the scope and limitation of such reactions have been the subject of recent reviews.[1] As a part of our ongoing effort to expand the synthetic utility of a new palladium-mediated cyclization reaction developed in our group,[2] we recently reported efficient strategies for the construction of tricyclic structures.[3] In particular, we have demonstrated that the palladium-catalysed cyclization of linear compounds of type **1** (Z or E) proceeds with complete retention of the stereochemistry in a stereocontrolled mode since it involves attack of the carbon nucleophile onto the double bond electrophilically activated by the organopalladium species. Moreover, the regiochemistry of the cyclisation (5 exo versus 6 endo) can be controlled by the steric bulk of the nucleophile part (Scheme 1).[4]



Scheme 1

We now report further progress based on the use of an intermolecular Michael addition reaction coupled with this palladium mediated biscyclization reaction. The motivation of this study emanates from the view that this would permit suitable functionalisation of ring C and thereby provide potential intermediates for the synthesis of various tetracyclic compounds by way of several synthetic transformations (Scheme 2).[5] Another challenging aspect of this tandem reaction lies in the level of selectivity on this palladium biscyclization reaction with respect to the relative configuration of the three newly formed chiral centers.

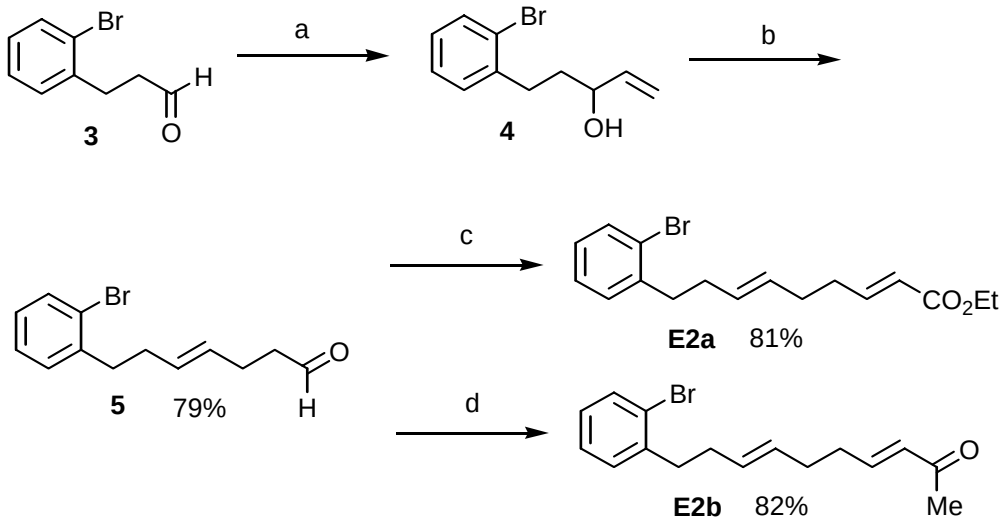


Scheme 2

Results and Discussion

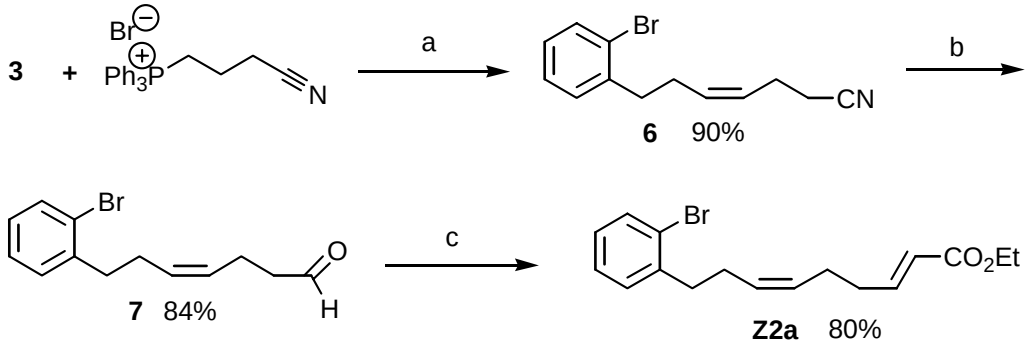
In order to test the feasibility of this Michael addition-biscyclization reaction, we needed access to α-β-unsaturated carbonyl compounds **E2a** and **Z2a**. They were readily prepared from the known aldehyde **3** [6] as summarized in Schemes 3 and 4.

The synthesis of **E2a** began with the addition of vinylmagnesium bromide to **3** which provided the allylic alcohol **4**. To effect the Claisen rearrangement, this alcohol was placed in refluxing butyl vinyl ether, in the presence of mercuric acetate.[7] To complete the sequence, the resulting aldehyde **5** was treated with carbomethoxymethylene triphenylphosphorane to afford **E2a** in 81% yield. In order to introduce another functional group for further transformation, we also prepared the unsaturated ketone **E2b** (82%) using a mild olefination procedure,[9] conventional methods giving poor results.



Scheme 3. (a) vinyl magnesium bromide, THF, 0°C. (b) butyl vinyl ether, $Hg(OAc)_2$, Δ. (c) NaH, THF, 0°C, $(EtO)_2P(O)CH_2CO_2Et$. (d) $(MeO)_2P(O)CH_2COMe$, DIPEA, LiCl, CH_3CN.

The synthesis of the isomerically pure **Z2a** was realized through a three-step sequence. Wittig olefination of aldehyde **3** with the phosphorane derived from 4-bromobutyronitrile[8] proceeded smoothly at 0°C to provide olefin **6** in 90% yield. The nitrile function was then converted to the aldehyde **7** by reduction with diisobutylaluminium hydride. Introduction of the conjugated carboethoxy group was also carried out by a Wittig reaction.

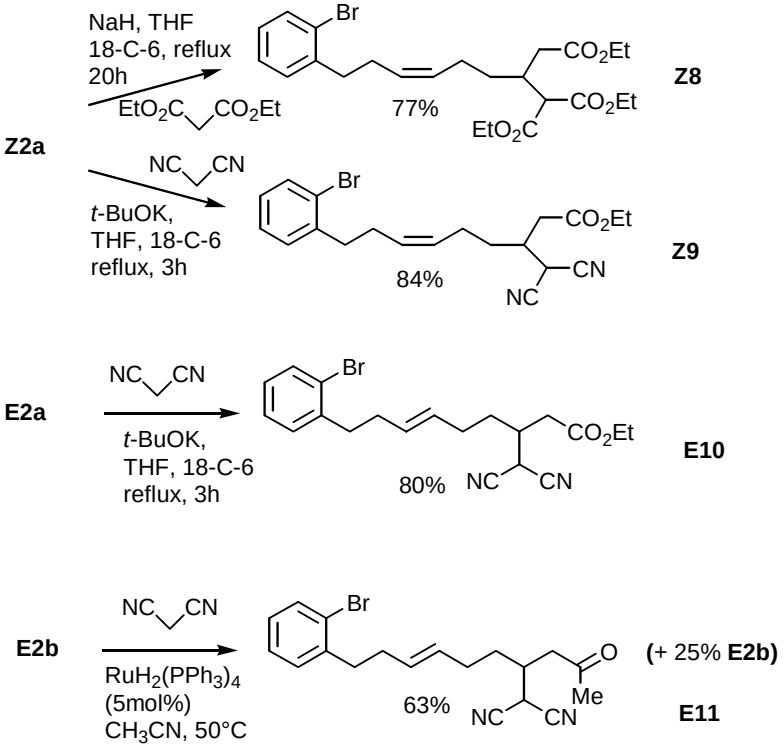


Scheme 4. (a) KHMDS, THF, 0°C; (b) DIBAL-H, Et_2O, -78°C; (c) NaH, THF, °C, $(EtO)_2P(O)CH_2CO_2Et$.

We initially attempted the sequential Michael addition / biscyclization reaction via a one pot procedure. We envisaged that Michael addition of active methylene compounds such as malonate and malononitrile to the α-β-unsaturated carbonyl compound such as **Z2a** would lead to the expected stabilised anionic intermediate **Z9** by proton transfer. Addition of an appropriate palladium(0) complex to the reaction mixture would allow the biscyclization process to take place according to Scheme 2. [10]

First of all, we studied the reaction of **Z2a** with the malonic enolate prepared from diethyl malonate and potassium hydride in THF as solvent. Although Michael addition of methylmalonate was nearly complete, as observed by GC, this solvent was not suitable for the biscyclization reaction. After addition of the palladium catalyst, no reaction occurred even after prolonged times at reflux of the solvent. Attempted modification of this standard method was unsuccessful in spite of variations of the solvent, the base, the temperature, the nature of the palladium catalyst and of the nucleophile (malononitrile in place of diethyl malonate). Consequently, we decided to overcome these problems by studying first the conjugate addition of active methylene compounds and secondly the biscyclization of the resulting adducts.

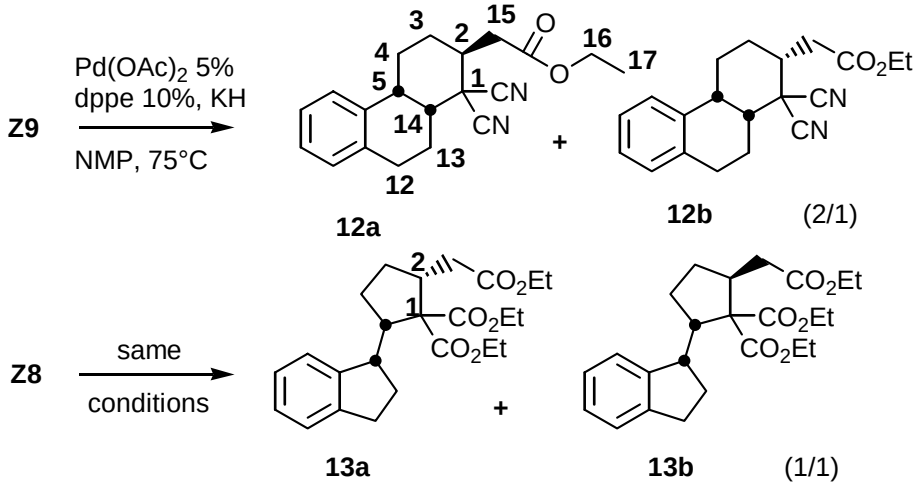
Michael addition of the sodium salt of diethylmalonate to **Z2a** in refluxing THF containing a catalytic amount of 18-crown-6 afforded adduct **Z8** in 77% yield. Addition of malononitrile to the same substrate and to the *trans* analogue **E2a** required the use of -*t*BuOK as base instead of NaH, adducts **Z9** and **E10** were then obtained in respectively 84% and 80% yield. When these conditions were used for addition of malononitrile to the α,β-unsaturated ketone **E2b**, the yield of the adduct **E11** was very low (25%). However, by employing the ruthenium(II) catalyzed conditions developed by Echavarren, the yield of **E11** could be improved to 63%.[11] A significant amount (23%) of the starting material was also recovered (Scheme 5)



Scheme 5

We next examined the palladium mediated biscyclization of these four cyclization precursors, aryl bromides **Z8**, **Z9**, **E10** and **E11**. They were subjected to the conditions that had been determined optimum for the cyclization of the linear homologous substrates.[4] The reaction was carried out by heating of a substrate in NMP at 60°C in the presence of 5%mole Pd(dppe), 1.1 equivalent of KH and 0.2 equivalent of 18-crown-6. Under these conditions, the less sterically demanding nucleophile **Z9** underwent a clean regiospecific cyclization to afford a 2:1 mixture of C_2 epimeric perhydrophenanthrene substrates **12a** and **12b** in 73% total yield without formation of 5-exo-trig cyclization products. The structure of the cyclization products have been elucidated by analysis of the ^1H and ^{13}C NMR spectra in comparison with those of the linear analogues having no CH_2CO_2Et side chain whose structure had been confirmed by X-ray crystallography.[4] As anticipated, a high degree of stereocontrol was observed during the cyclisation. The geometry of the newly formed ring junction is *cis*, this being in accord with the reaction mechanism proposed above. The major isomer could be isolated from the mixture by careful medium pressure liquid chromatography. Its structure has been deduced on the basis of NMR spectroscopic data. Indeed, 2D homo- and heteronuclear experiments allowed for identification of most of the hydrogens and carbons and in particular the small ^1H NMR coupling (^3J = 4.6 Hz) observed between the two adjacent ring methine protons(H_5 and H_{14}) confirmed the *cis* fused configuration. In the NOESY experiments, the presence of a cross peak between the two vicinal methine protons confirmed the *cis* ring fusion. The lack of signals between these two protons and the third methine C_2 proton and the presence of a cross peak between H_2 and one proton H_{13} indicated that the side chain CH_2CO_2Et and the two vicinal methine protons were on the same face of the molecule. (Scheme 6)

The palladium-catalysed cyclization of the bulkier nucleophile **Z8**, under the same conditions led to the exclusive formation of cyclopentanic compounds **13a** and **13b** with no selectivity at the C_2 center (1:1 mixture according to GC) (Scheme 6). The stereostructural assignments for these tricyclic compounds were based on the close resemblance of their ^1H and ^{13}C NMR to those of the linear homologue having no side chain.[4]

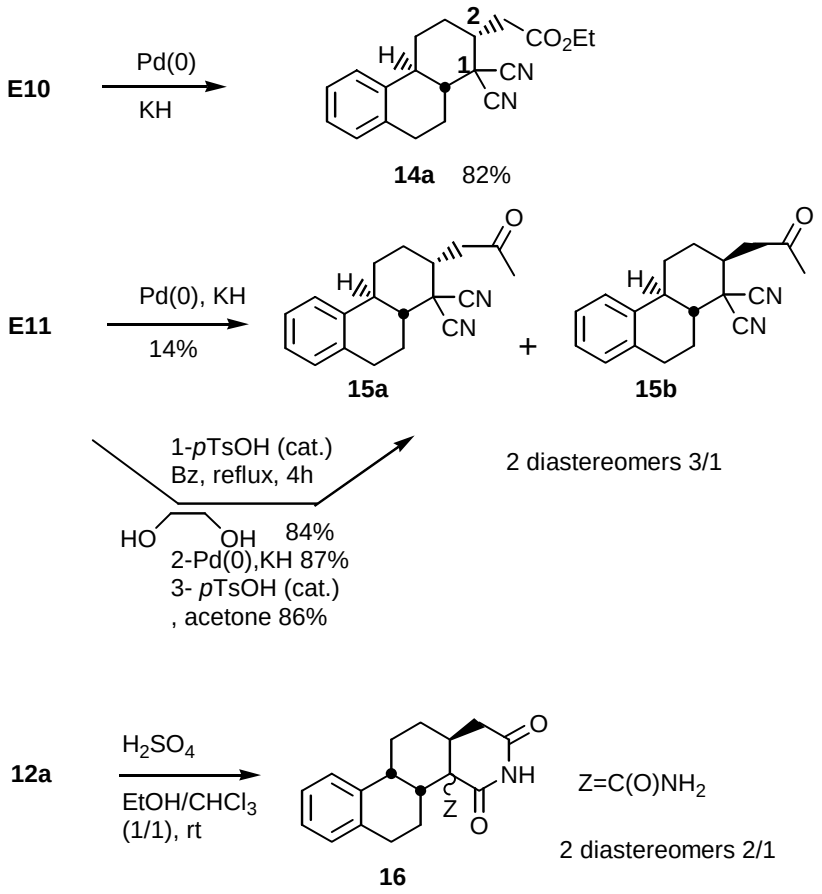


Scheme 6

Under identical reaction conditions (60°C, 3h) the cyclization of **E10** resulted in the formation of the tricyclic compound **14** as a single isomer as indicated by GC, ^{1}H and ^{13}C NMR. The structural and stereochemical assignments for this isomer were made on the basis of the HSQC, TOCSY and NOESY spectra. In particular, in the NOESY spectra, the presence of a cross peak between the two methine protons on both side of the carbon bearing the nitrile group allowed to assign the stereochemistry as shown in Scheme 7.

It is noteworthy that the palladium-mediated cyclization reaction of linear alkenes (having no CH_2CO_2Et side chain) bearing a malononitrile were generally considerably slower (60h) than that of the corresponding malonates (5h).[4,12] Concerning the cyclization of **Z9** and **E10**, we observed a significantly faster biscyclisation of these two compounds compared to the linear dinitrile substrates (3.5h). This can be interpreted as a consequence of the Thorpe-Ingold effect.

When the same cyclisation reaction conditions were applied to the ketone **E11**, an intense degradation was observed and several by-products were formed along with the expected tricyclic compound **15** which could be isolated in only 14%. These failures seemed due to the presence of the keto group since performing this reaction on the corresponding protected ketone was successful and afforded a 3:1 mixture of C_2 epimeric compounds in 89% combined yield. The major isomer could be isolated by recrystallization from diethyl ether and mild acidic treatment liberated the ketone. The assigned structure of the resulting major isomer **15a** has been elucidated from its NMR spectrum and by analogy to **14a**.



Scheme 7

As mentioned in the introduction, the three highly functionalized perhydrophenanthrenes obtained in these two-step procedure may undergo further transformations to give tetracyclic substrates. As an example, we decided to prepare a tetracyclic lactam from the tricyclic nitrile ester **12a**. Therefore, **12a** was treated with concentrated H_2SO_4 in absolute EtOH to provide the target compound as an inseparable 2:1 mixture of diastereomers **16** in 66 % combined yield. The assigned structure of these resulting tetracyclic products were corroborated by their IR, ^{1}H and ^{13}C NMR as well as their CI mass spectra.

Further extension of the scope of this Michael-addition/biscyclization reaction will be reported in due course.

Experimental Section

General Prpcedures. All reactions were carried out under a nitrogen atmosphere using standard syringe, cannula and septa techniques. All reactions were monitored by thin layer chromatography carried out on aluminium plates precoated with silica gel 60 F_{254} (Merck) or by gas chromatography on a DB 1 capillary column 30 m. Column chromatographies were performed on silica gel SI 60 (40-60 μ, MERCK). Melting points (uncorrected) were determined on a Büchi Melting Point 510. IR spectra were recorded on a Perkin-Elmer 337 instrument. Nuclear Magnetic Resonance spectra were obtained on a Brucker ALS 300 spectrometer (^{1}H : 300 MHz or ^{13}C : 75 MHz) using TMS as an internal standard. Chemical shifts were expressed in ppm downfield from TMS and coupling constants (J) in Hertz. Microanalysis were performed by Service Central d'Analyse du CNRS, Solaize, France. THF was distilled from Na/benzophenone, N-methylpyrrolidone (NMP) and DMSO (dimethylsulfoxide) were distilled from CaH_2, DMF was distilled from P_2O_5 and Et_2O was distilled from LAH prior to use.

Preparation of 4. Vinyl magnesium bromide 1M in THF (11.1 mL, 11.1 mmol) was added dropwise at –30°C to a solution of aldehyde **3** (1.57 g, 7.37 mmol) in 20 mL of THF. At the end of the addition, the solution was warmed up to room temperature and stirred for two hours. The mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O. After drying under $MgSO_4$ and evaporation under vacuum, the crude oil was purified by flash chromatography (PE/Et_2O 7:3) to afford allyl alcohol **4** as an oil in 90% yield. ^{1}H-NMR δ 1.75 (1H, s), 1.75 (H, m), 1.83-1.91 (2H, m), 2.77-2.95 (2H, m), 4.18-4.2 (1H, m), 5.15-5.33 (2H, m), 5.95 (1H, ddd, *J* = 17.2, 10.4, 6), 7.04-7.10 (1H, m), 7.22-7.28 (2H, m), 7.55 (1H, d, *J* = 7.8); ^{13}C-NMR δ 32.2, 37.1, 72.6, 115.7, 124.6, 127.6, 127.8, 130.6, 133.0, 141.0, 141.3; IR *ν* 3400, 3060, 2920, 2860, 1640, 1570, 1470, 1020, 990, 920, 900;

Preparation of 5. To a solution of allyl alcohol **4** (1.34 g, 5.56 mmol), in 14 mL of butylvinyl ether was added mercuric acetate (1.72 g, 5.42 mmol). The resulting mixture was stirred at reflux for 18 h. The reaction was quenched with sodium carbonate (20 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organics were washed with brine and dried over $MgSO_4$. Purification by flash chromatography (PE/Et_2O 9:1) furnished the aldehyde **5** as an oil in 79% yield. ^{1}H-NMR δ 2.07-2.40 (m, 4H), 2.46-2.51 (2H, m), 2.78 (2H, dd, *J* = 6.5, 8.7), 5.39-5.58 (2H, m),

7.02-7.08 (1H, m), 7.16-7.27 (2H, m), 7.52 (1H, dd, *J* = 1.1, 8), 9.75 (1H, s); ^{13}C-NMR δ 25.5, 33.0, 36.5, 43.8, 124.8, 127.7, 128.0, 129.2, 130.9, 133.1, 141.4, 202.7; IR *v* 3040, 2920, 2720, 1720, 1040, 965, 750.

Preparation of E2a. Same procedure as for **Z2a**: scale 1.26 g, 4.72 mmol of **5**. Purification by flash chromatography (PE/Et_2O 9:1) led to the ester **E2a** as an oil in 81% yield. ^{1}H-NMR δ 1.31 (3H, t, *J* = 7.2), 2.14-2.36 (H, m), 2.8 (2H, t, *J* = 7.5), 4.20 (q, 2H, *J* = 7.2), 5.39-5.58 (2H, m), 5.83 (1H, d, *J* = 15.6), 6.91-7.09 (2H, m), 7.19-7.28 (2H, m), 7.54 (1H, d, *J* = 8.3); ^{13}C-NMR δ 14.7, 31.3, 32.5, 33.1, 36.6, 60.6, 122.0, 124.9, 127.7, 127.9, 129.9, 130.6, 130.8, 133.1, 141.5, 149.0, 167.1; IR *v* 3050, 2920, 1715, 1660, 1440, 1370, 1270, 1170, 970, 750.

Preparation of E2b. To a solution of aldehyde **5** (1.48 g, 5.59 mmol) in 40 mL of CH_3CN was successively added LiCl (0.284 g, 6.7 mmol), dimethylacetylmethyl phosphonate (0.956 mL, 6.7 mmol) and diisopropylethyl amine (0.976 mL, 5.59 mmol). The resulting solution was stirred overnight at room temperature. Water was added and the mixture extracted twice with Et_2O. Combined organic phases were washed with brine and dried over $MgSO_4$. Purification by flash chromatography (PE/Et_2O 8:2) led to the methyl ketone **E2b** as an oil in 82% yield. ^{1}H-NMR δ 2.12-2.40 (9H, m), 2.77-2.85 (2H, m), 5.4-5.6 (2H, m), 6.08 (1H, d, *J* = 16), 6.79 (1H, dt, *J* = 6.6, 16), 7.02-7.11 (1H, m), 7.18-7.28 (2H, m), 7.54 (1H, d, *J* = 8.3); ^{13}C-NMR δ 27.3, 31.4, 32.7, 33.1, 36.6, 124.9, 127.7, 128.0, 129.8, 130.8, 131.9, 133.1, 141.5, 148.1, 199.1.

Preparation of phosphonium salt. 4-bromobutyronitrile(6.7 mL, 67.5 mmol) and triphenylphosphine (17.7 g, 67.5 mmol) were dissolved in toluene (150 mL). The resulting solution was stirred at reflux for 2 days. A white precipitate appeared during the reaction and was filtered and washed with Et_2O. The phosphonium salt was dried under vacuum to give 13.7 g, 49 % yield .

Preparation of 6. KHMDS (4 g, 20 mmol) and the phosphonium salt (8.2 g, 20 mmol) are dissolved in anhydrous THF (100 ml) at 0°C. The mixture was stirred for 15 minutes and then the aldehyde **3** (2.13 g, 10 mmol) in 20 mL of THF is added dropwise to the solution of the ylide. After 2 hours at 0°C, the mixture was pourred in petroleum ether (200 mL) to precipitate triphenylphosphine oxide. The solution was filtered through a pad of silica gel, evaporated and purified by flash chromatography (PE/Et_2O 9:1) to afford nitrile **6** in 90% yield as a pale yellow oil. ^{1}H-NMR δ 2.15-2.45 (6H, m), 2.82 (2H, t, *J* = 7.5), 5.35-5.48 (1H, m), 5.58-5.70 (1H, m), 7.03-7.11 (1H, m), 7.16-7.29 (2H, m), 7.56 (1H, dt, *J* = 8.5, 1); ^{13}C-NMR δ 17.4, 23.2, 27.6, 35.9, 119.3, 127.4, 127.8, 124.4, 126.3, 130.8, 131.8, 132.9, 140.7; IR *v* 3060, 3010, 2920, 2860, 2240, 1565, 1470, 1440, 1025, 750.

Preparation of 7. Nitrile **6** (1.17 g, 4.44 mmol) was dissolved in 50 mL of Et_2O. The solution was cooled down to –78°C and then DIBAL-H (1M in hexane, 8.9 mmol) was added dropwise. The resulting mixture was stirred at this temperature for 30 minutes and warmed up to RT for 4 hours. The reaction was quenched at 0°C with methanol and a solution of sodium and potassium tartrate (0.7 M). The medium was extracted with Et_2O (2 x 50 mL) and the solvent removed under vacuum. The crude oil was purified by flash chromatography (PE/Et_2O 4:1) to afford aldehyde **7** in 90% yield as a pale yellow oil. ^{1}H-NMR δ 2.34–2.45 (6H, m), 2.80 (2H, t, *J* = 7.5), 5.35-5.48 (1H, m), 5.58-5.70 (1H, m), 7.03-7.11 (1H, m), 7.16-7.29 (2H, m), 7.56 (1H, dt, *J* = 8.5, 1), 9.70 (1H, s); ^{13}C-NMR δ 20.1, 27.5, 36.0, 43.7, 124.5, 127.4, 127.7, 128.5, 129.8, 130.7, 132.8, 141.0, 202.0; IR *v* 3060, 3010, 2920, 2720, 1725, 1570, 1470, 1440, 1025, 750.

Preparation of Z2a. Triethyl phosphonoacetate (1.06 mL, 5.33 mmol) was added dropwise to a suspension of NaH 60% in mineral oil (234 mg, 5.84 mmol) in anhydrous THF (12 mL) at 0°C. After 10 minutes, aldehyde **7** (1.42g, 5.31 mmol) in 3.5 mL of THF was added dropwise to the previous solution. After 2 hours at 0°C, the starting material was consumed and the reaction quenched with a saturated NH_4Cl solution and extracted twice with Et_2O. Combined organic phases were washed with brine dried with $MgSO_4$ and concentrated under vacuum. The crude oil was purified by flash chromatography (PE/Et_2O 9:1) to afford ester **Z2a** in 80% yield. ^{1}H-NMR δ 1.28 (3H, t, *J* = 7), 2.13-2.16 (4H, m), 2.32-2.40 (2H, m), 2.78 (2H, t, *J* = 7.5), 4.18 (2H, q, *J* = 7), 5.34-5.53 (2H, m), 5.80 (1H, d, *J* = 15), 6.87-6.97 (1H, m), 7.02-7.08 (1H, m), 7.17-7.24 (2H, m), 7.53 (1H, d, *J* = 8); ^{13}C-NMR δ 14.3, 25.7, 27.6, 32.2, 36.1, 60.2, 121.7, 124.5, 127.3, 127.7, 129.1, 129.5, 130.6, 132.8, 141.1, 148.5, 166.7; IR *v* 3050, 2920, 1715, 1660, 1440, 1370, 1270, 1170, 970, 750.

Preparation of Z9. Malonitrile (324 mg, 4.45 mmol), 18-crown-6 (116 mg, 0.44 mmol), and *t*BuOK (549 mg, 4.9 mmol) were dissolved in 16 ml of THF and stirred for 15 minutes. A solution of **Z2a** (1.5 g, 4.45 mmol) in 10 mL of THF was added via a canula and the resulting mixture was heated at reflux for 3 hours. The reaction was quenched with saturated NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The organic layer was washed with brine, dried with $MgSO_4$ and evaporated under vacuum. The crude oil was purified by flash chromatography (PE/Et_2O 9:1) to afford ester **Z9** in 84% yield. ^{1}H-NMR δ 1.27 (3H, t, *J* = 7), 1.44-1.58 (1H, m), 1.65-1.76 (1H, m), 1.96-2.15 (2H, m), 2.32-2.49 (4H, m), 2.56-2.63 (H, m), 2.79 (2H, t, *J* = 8), 4.17 (2H, q, *J* = 7), 4.33 (H, d, *J* = 5), 5.31-5.39 (1H, m), 5.50-5.59 (1H, m), 7.04-7.1 (1H, m), 7.17-7.27 (2H, m), 7.53 (1H, dd, *J* = 8, 1); ^{13}C-NMR δ 14.5, 27.2, 24.4, 28.0, 31.2, 34.9, 36.4, 36.8, 61.8, 112.0, 112.4, 124.7, 128.2, 128.5, 127.8, 130.8, 131.1, 133.2, 141.1, 171.2; IR *v* 3100, 2920, 2860, 2240, 1720, 1560, 1430, 1370, 1020, 750.

Preparation of Z8. The procedure was similar as for **Z9** except that we used NaH (2 eq.) instead of *t*BuOK and 2 equiv. of dimethylmalonate. The expected product was obtained after 20 hours at reflux.The residue was purified by flash chromatography (PE/Et_2O 8:2) giving **Z8** as an oil in 80% yield. ^{1}H-NMR δ 1.23 (3H, t, *J* = 7), 1.25 (6H, t, *J* = 7), 1.43-1.51 (2H, m), 2.00-2.07 (2H, m), 2.27-2.53 (4H, m), 2.57-2.64 (1H, m), 2.76 (2H, t, *J* = 7), 3.57 (1H, d, *J* = 6), 4.11 (2H, q, *J* = 7), 4.18 (4H, q, *J* = 7), 5.32-5.49 (2H, m), 7.01-7.08 (1H, m), 7.19-7.24 (2H, m), 7.51 (1H, d, *J* = 8); ^{13}C-NMR δ 14.1, 14.3, 24.6, 27.6, 31.6, 34.6, 36.2, 54.2, 61.3, 61.4, 61.8, 124.5, 127.4, 127.6, 129.0, 129.7, 130.6, 132.8, 141.1, 168.5, 168.7, 172.4; IR *v* 3060, 2920, 2860, 1720, 1570, 1440, 1370, 1050, 1020, 860, 750.

Preparation of E10. Same procedure as for **Z9**. Scale 1.48 mmol of **E2a**. The residue was purified by flash chromatography (PE/Et_2O 6:4) giving **E10** as an oil in 80% yield. ^{1}H-NMR δ 1.33 (3H, t, *J* = 7.2), 1.56-1.68 (1H, m), 1.73-1.85 (1H, m), 2.00-2.22 (2H, m), 2.32-2.53 (4H, m), 2.61-2.68 (1H, m), 2.82 (2H, t, *J* = 7.6), 4.2 (2H, q, *J* = 7.2), 4.39 (1H, d, *J* = 4.9), 5.33-5.42 (1H, m), 5.52-5.62 (1H, m), 7.05-7.10 (1H, m), 7.19-7.28 (2H, m), 7.56 (1H, d, *J* = 8); ^{13}C-NMR δ 14.5, 27.2, 29.7, 31.1, 33.1, 34.9, 36.3, 36.5, 61.8, 112.1, 112.5, 124.9, 127.8, 128.1,128.9, 130.9, 131.8, 133.2, 141.3, 175.3; IR *v* 3100, 2920, 2860, 2240, 1720, 1560, 1430, 1370, 1020, 750.

Preparation of E11. Under argon atmosphere, **E2b** (0.614 g, 2 mmol) was dissolved in acetonitrile. Malonitrile (0.132 g, 2 mmol) and subsequently $RuH_2(PPh_3)_4$ (0.115 g, 0.1 mmol)

were added. The mixture was stirred at 45°C for 20 hours. The solvent was removed under vacuum and the residue purified by flash chromatography (PE/Et_2O 6:4) giving the desired adduct in 63% yield along with 25% of unreacted starting material. ^{1}H-NMR δ 1.52-1.80 (2H, m), 1.96-2.17 (2H, m), 2.21 (3H, s), 2.29-2.37 (2H, m), 2.44-2.51 (1H, m), 2.57-2.82 (4H, m), 4.31 (1H, d, *J* = 4.7) , 5.31-5.40 (1H, m), 5.49-5.59 (1H, m), 7.03-7.08 (1H, m), 7.17-7.24 (2H, m), 7.52 (1H, dd, *J* = 8, 1.1); ^{13}C-NMR δ 28.3, 28.7, 29.1, 31.5, 32.3, 32.7, 34.6, 50.9, 108.8, 109.6, 120.6, 125.0, 125.2, 129.1, 129.2, 130.6, 131.8, 140.9, 204.8.

Protection of the ketone function in E11. Methyl ketone **E11** (642 mg, 1.72 mmol) was treated with ethylene glycol (320 mg, 5.16 mmol), *p*-toluene sulfonic acid (33 mg, 0.17 mmol) in 5 mL of benzene at reflux in a Dean-Stark apparatus for 3 hours. After filtration of the catalyst and evaporation, the crude oil was purified by flash chromatography (PE/Et_2O 7:3) giving the protected ketone in 84% yield. ^{1}H-NMR δ 1.32 (3H, s), 1.57-1.66 (1H, m), 1.73-1.87 (2H, m), 1.96 (1H, dd, *J* = 2.5, 15.3), 2.00-2.13 (1H, m), 2.17-2.26 (2H, m), 2.35 (2H, dd, *J* = 7, 15), 2.80 (2H, dd, *J* = 7, 9.4), 4.00 (4H, s), 4.58 (1H, d, *J* = 3.6), 5.38-5.47 (1H, m), 5.54-5.63 (1H, m), 7.05-7.10 (1H, m), 7.22-7.28 (2H, m), 7.54 (1H, d, *J* = 8.1); ^{13}C-NMR δ 23.9, 27.6, 29.5, 31.8, 32.7, 35.4, 36.2, 38.8, 64.4, 64.9, 109.2, 112.1, 113.3, 124.5, 127.4, 127.7, 128.9, 130.5, 131.2, 132.8, 141.1.

Cyclisation of adducts-general procedure

On one hand, $Pd(OAc)_2$ (6 mg, 0.025 mmol), dppe (20 mg, 0.05 mmol) and heptene (7 μl, 0.05 mmol) were dissolved in 2 mL of NMP and stirred at 50°C until the solution turned red. On the other hand, **Z9** (200 mg, 0.496 mmol), KH (22 mg, 0.55 mmol) and 18-crown-6 (13 mg, 0.05 mmol) were dissolved in 2 mL of NMP and stirred until the termination of gas evolution. Then palladium solution was added to the enolate solution and the mixture stirred at 75°C for 3 h. The reaction was quenched with a few drops of 1M HCl solution and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was purified flash chromatography (PE/Et_2O 9:1) to afford a mixture of 2 diastereomers **12a** and **12b** (2/1 ratio) in 73% yield; mp 126-128°C; ^{1}H-NMR (major diastereomer) δ 1.30 (3H, t, *J* = 7), 1.50-1.72 (H_3, H_4, m), 1.85-1.93 ($H_{4'}$, m), 1.97-2.11 ($H_{3'}$, H_{13}, m), 2.14-2.24 ($H_{13'}$, m), 2.46 (H_{15}, d, *J* = 15.3), 2.49-2.55 (H_2, m), 2.66 (H_{14}, ddd, *J* = 12.8, 4.6, 2.7), 2.88 ($H_{15'}$, dd, *J* = 15.3, 2), 2.92-3.00 (H_{12}, m), 3.05 ($H_{12'}$, ddd, *J* = 20, 5.8, 2), 3.14-3.19 (H_5, m), 4.20 (2H, q, *J* = 7), 7.13-7.20 (4H, m); ^{13}C-NMR δ 14.2, 19.9, 28.1, 29.2, 30.1, 35.0, 36.6, 37.9, 41.9, 43.7, 61.3, 114.1, 114.8, 126.4, 126.8, 129.0, 129.1, 134.1, 138.4, 170.5; IR *ν* 3020, 2980, 2940, 2860, 2220, 1730, 1450, 1380, 1270, 1200, 1010, 770, 750; Anal. Calcd. For $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69. Found C, 74.64; H, 6.92; N, 8.53.

Cyclisation of Z8. The procedure is similar to that previously described. The expected product was obtained, after 2 hours at 75°C, in 72% yield as a mixture of 2 diastereomers **13 a** and **13b** (1/1). ^{1}H-NMR δ 1.22-1.32 (9H, m), 1.45-1.54 (1H, m), 1.57-2.10 (5H, m), 2.56-2.67 (2H, m), 2.74-2.98 (3H, m), 3.05-3.13 (1H, m), 3.74-3.79 (1H, m), 4.06-4.35 (6H, m), 7.15 (3H, br s), 7.33 (1H, d, J = 8); ^{13}C-NMR δ 14.4, 14.6, 22.7, 26.1, 29.3, 32.6, 36.4, 44.1, 44.2, 45.7, 60.7, 61.5, 61.6, 124.2, 124.6, 126.6, 126.8, 143.7, 147.4, 170.3, 171.8, 173.4; IR *ν* 3060, 2920, 2860, 1760, 1460, 1370, 1260, 1100, 1060, 910, 740; MS/EI : 57 (30), 117 (50, indenyl radical), 210

(100), 282 (27), 324 (32), 370 (44), 416 (20); Anal. Calcd. For $C_{24}H_{32}O_6$: C, 69.20; H, 7.74. Found C, 68.98; H, 8.01.

Cyclisation of E10. The procedure is similar to that previously described. The expected product **14a** was obtained, after 3.5 hours at 75°C, in 82% yield as a sole diastereomer: mp 88-90°C; ^{1}H-NMR (C_6D_6) δ 0.81 (1H, ddd, *J* = 25.4, 13.1, 3.5), 1.07 (3H, t, J = 7), 1.20-1.28 (1H, m), 1.25 (1H, td, *J* = 12, 2.6), 1.62 (1H, ddd, *J* = 23.5, 12, 7), 1.86-1.90 (1H, m), 1.94-1.97 (1H, m), 2.05-2.09 (1H, m), 2.31-2.52 (4H, m), 2.90 (1H, dd, *J* = 15.8, 2.8), 4.03 (2H, q, J = 7), 6.90-6.96 (2H, m), 7.11-7.13 (2H, m); ^{13}C-NMR δ 14.6, 26.9, 28.6, 29.5, 29.7, 38.3, 38.9, 41.9, 45.5, 47.2, 61.6, 112.9, 115.7, 126.2, 126.8, 127.1, 129.5, 135.7, 136.9, 170.8; IR *v* 3020, 2980, 2940, 2220, 1730, 1450, 1270, 1010.

Cyclisation of E11 (protected ketone). The procedure is similar to that previously described. The expected product was obtained, after 2.5 hours at 75°C, in 87% yield as a mixture of two diastereomers (3/1). The major diastereomer crystallized from diethyl ether and was easily separated: mp 184-186°C, ^{1}H-NMR δ 1.28-1.40 (1H, m), 1.40 (3H, s), 1.52-1.65 (1H, m), 1.88-1.99 (3H, m), 2.14-2.27 (2H, m), 2.32-2.55 (3H, m), 2.75-2.81 (1H, m), 3.00 (2H, br s), 3.98 (4H, br s), 7.1-7.27 (4H, m); ^{13}C-NMR δ 24.7,27.0, 29.6, 29.9, 30.1, 38.9, 41.6, 42.5, 47.0, 47.4, 64.8, 65.1, 109.3, 113.4, 116.4, 126.2, 126.7, 127.0, 129.5, 135.8, 137.2; IR *v* 2990, 2948, 2244, 1490, 1379, 1262, 1038, 753.

Deprotection of the ketone, preparation of 15a (major diastereomer). Protected ketone (116 mg, 0.345 mmol) was treated by a catalytic amount of *p*-toluene sulfonic acid (5 mg) in 5 mL of acetone at 50 °C. The mixture was stirred for 15 h. and then acid was removed by filtration and the solution evaporated in vacuum. The crude oil was purified flash chromatography (PE/Et_2O 7:3) to afford **15a** in 95% yield. ^{1}H-NMR δ 1.36-1.53 (2H, m), 1.88-2.03 (2H, m), 2.17-2.26 (1H, m), 2.28 (3H, s), 2.30-2.38 (1H, m), 2.52-2.67 (2H, m), 2.72-2.85 (2H, m), 2.99-3.05 (3H, m), 7.12-7.30 (4H, m); ^{13}C-NMR δ 26.8, 28.5, 29.3, 29.5, 30.8, 38.8, 40.3, 45.4, 46.7, 46.9, 113.0, 115.7, 126.0, 126.6, 126.9, 129.3, 135.5, 136.7, 204.7.

Preparation of 16. 12a (70 mg, 0.217 mmol), was dissolved in a mixture of 1 mL of $CHCl_3$ and 1mL of EtOH at 0°C. 4 mL of H_2SO_4 75% were added slowly at 0°C to the previous solution, and the resulting mixture was stirred at rt for 5 days; The reaction was quenched with saturated solution of $NaHCO_3$ and extracted with 20 mL of Et_2O. The organic layer was washed with water, dried over $MgSO_4$ and concentrated under vacuum. **16** was obtained in 60% yield as a mixture of two diastereomers 2/1. ^{1}H-NMR(DMSO) δ 1.22-1.36 (1H, m), 1.44-1.59 (2H, m), 1.63-1.69 (1H, m), 1.7-1.88 (2H, m), 2.22-2.30 (1H, m, major), 2.39 (1H, dd, major, J = 18, 4.8), 2.43-2.52 (1H, m), 2.75-2.90 (3H, m), 3.21 (1H, dd, minor, J = 17.6, 4.8), 3.35 (1H, dd, major, J = 18, 13.6), 6.89 (4H, br s, minor), 7.07 (4H, br s, major), 7.33 (s, NH amide, major), 7.45 (s, NH amide, minor), 10.89 (s, NH imide, major), 11.02 (s, NH imide, minor); ^{13}C-NMR major δ 129.9, 30.0, 30.5, 31.3, 31.7, 36.6, 38.1, 39.9, 57.4, 126.4, 126.6, 129.5, 129.6, 135.9, 142.2, 171.2, 173.7, 173.8; ^{13}C-NMR major δ 19.4, 27.9, 29.2, 30.0, 31.0, 37.4, 38.3, 39.9, 58.8, 126.5, 126.7, 129.4, 129.7, 135.7, 141.5, 169.9, 173.1, 173.6; IR *v* 3440, 3330, 2920, 2850, 1700, 1685, 1655, 1260, 1225, 765, 735; MS/CI : M-H$^+$ = 313.

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