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Alkylations of tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one by a cuprate reaction

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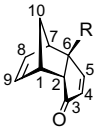
ABSTRACT

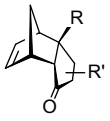
Alkylation at C_6 of tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (R=H) was achieved by treatment of 6-bromotricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one with lithium dimethylcuprate and subsequently with an appropriate electrophile. The best results were obtained in THF as the solvent. A wide range of alkyl halides, bromo ketones and esters, and acetyl chloride resulted in C_6-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ones in moderate to good yields. This alkylation reaction proceeds via a C_6-carbanionic Cu intermediate, which is likely stabilized by the enone olefinic bond. 6-Bromo-*endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, which lacks this double bond, behaves differently. Treatment with lithium dimethylcuprate leads to dehydrobromination to give tricyclo[5.2.1.$0^{2,6}$]deca-2(6),8-dien-3-one in high yield.

1. Introduction

The synthesis of a great variety of naturally occurring cyclopentenoids can be achieved by making use of the *endo*-tricyclo[5.2.1.$0^{2,6}$]decadienone system **1**.[1,2] Stereoselective additions to the enone moiety, followed by chemical transformations to install the desired functionalities lead to tricyclodecenones **2**, which on thermal cycloreversion using the flash vacuum thermolysis technique then lead to cyclopentenones **3**. The availability of both antipodes of **1** in enantiopure form completes this strategy and makes it extremely useful for the enantioselective synthesis of a variety of cyclopentenoids.[1]



1



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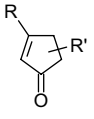

3

Chemical transformations of the Herz ester **4** using the Barton radical decarboxylation process,[3] allow the introduction of several substituents at the C_6 position of the *endo*-tricyclo[5.2.1.$0^{2,6}$]decadienone system[4] as shown in Scheme 1. Although this methodology has resulted in the synthesis of a series of new norbornadiene annulated cyclopentenoids,[5] the simple introduction of an alkyl group at the C_6 position in the tricyclodecadienone **6** (X=alkyl) could not be achieved yet.

The tricyclodecadienones **6** having an alkyl substituent at the C_6 position are important for two reasons. Firstly, they allow the synthesis of cyclopentenoids with simple alkyl substituents, some of which are important industrial fragrances.[6] Secondly, an alkyl substituent at C_6 may influence the stereocontrol of the Michael additions to the enone system.[7]

For the synthesis of 6-alkyl substituted tricyclodecadienones **6** (X=R) Michael addition of an alkyl-type nucleophile to the central enone bond of tricyclodecatrienone **7** looks very attractive.[8] The required tricyclodecatrienone **7** can be obtained by elimination of hydrogen bromide from tricyclic bromide **6a** by treatment with base.[4] The generated tricyclodecatrienone likely undergoes preferential Michael addition at the most reactive central enone unit (Scheme 2).

An elegant manner to accomplish the formal displacement of bromide by an alkyl group via an elimination/addition process would require the use of 2 equiv of lithium dialkylcuprate, one of which serves as the base to generate trienone **7**, with the second equivalent reacting as the nucleophile. It will be shown that this planned chemistry took an unexpected and unprecedented path.

2. Results and discussion

The reaction of tricyclic bromide **6a** with lithium dimethylcuprate did not produce the expected product **8**. This was immediately apparent after quenching the reaction with water after treatment of bromide **6a** with lithium dimethylcuprate in diethyl ether. No methyl group was introduced at all, neither at the C_6 nor at the C_5 position. Instead the bromide at C_6 was fully replaced by a hydrogen as was concluded from the formation of parent tricyclodecadienone **13a**. This result suggests the intermediacy of a C_6-carbanionic copper species, which on aqueous work-up was rapidly protonated. Repeating the reaction but quenching with D_2O unequivocally supports this view as deuterated **13b** was obtained in

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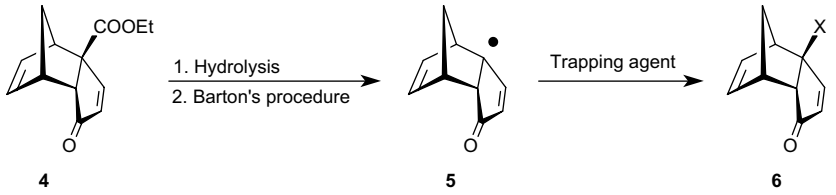
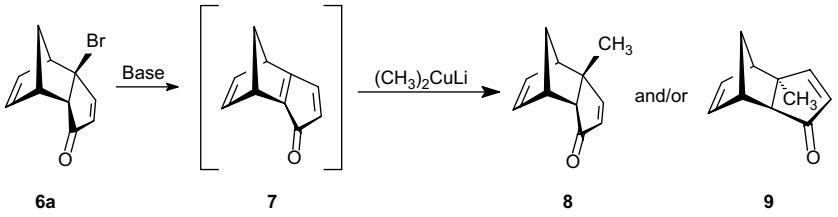


Scheme 1.



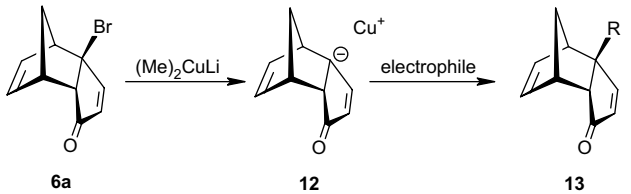
Scheme 2.

almost quantitative yield. Applying methyl iodide as the electrophile further substantiated the intermediacy of a bridgehead C_6-carbanionic intermediate as 6-methyltricyclodecadienone **13c** was obtained in 55% yield using diethyl ether as the solvent (Table 1, entry c).

Table 1
Electrophilic substitution at C_6 in 12

Entry	Electrophile	Product (R=)		Et_2O, −78 °C yield (%)	THF, 0 °C yield (%)
a	H_2O	**13a**	–H	85	95
b	D_2O	**13b**	–D	85	95
c	CH_3I	**13c**	$-CH_3$	55	75
d	CH_3CH_2I	**13d**	$-CH_2CH_3$	0	65
e	$CH_3CH_2CH_2I$	**13e**	$-CH_2CH_2CH_3$	0	60
f	$(CH_3)_2CHI$	**13f**	$-CH(CH)_3$	Not performed	45
g	$CH_2{=}CHCH_2Br$	**13g**	$-CH_2CH{=}CH_2$	60	75
h	$PhCH_2Br$	**13h**	$-CH_2Ph$	0	60
i	$PhC(O)CH_2Br$	**13i**	$-CH_2C(O)Ph$	Not performed	50
j	$EtOOCCH_2Br$	**13j**	$-CH_2COOEt$	Not performed	40
k	$BrCH_2CH_2CH_2Br$	**13k**	$-CH_2CH_2CH_2Br$	Not performed	55
l	$CH_3C(O)Cl$	**13l**	$-C(O)CH_3$	80	50
m	Me_2SO_4	**13c**	$-CH_3$	50	Not performed

Based on these results a conceivable mechanism for the reaction of 6-bromotricyclodecadienone **6a** with lithium dimethylcuprate can be postulated (Scheme 3). The first step is a halogen/metal exchange reaction. The exact nature of the proposed tricyclic carbanionic copper intermediate **12** is unclear but it is most likely stabilized by an orbital interaction with the enone system. A substrate lacking the C_4–C_5 double bond, viz. the corresponding bridgehead 6-bromotricyclodecenone **14**, shows an entirely different behavior as no C_6-carbanionic species are formed upon treatment with lithium dimethylcuprate (Scheme 4, vide infra).



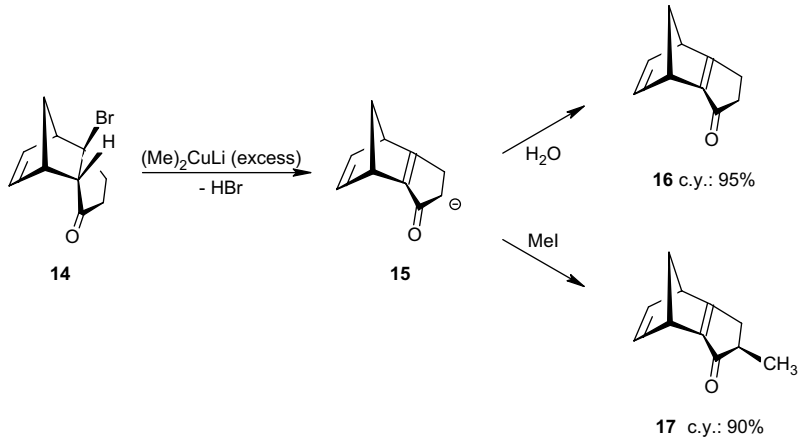
Scheme 3.

The synthetic scope of this alkylation reaction in ether at −78 °C appeared to be rather limited. Only reactive electrophiles are suitable. Good results were obtained for allyl bromide and dimethyl sulfate (Table 1, entries g and m), whilst ethyl iodide and benzyl bromide failed to react. Acylation, however, could be accomplished with acetyl chloride to give the corresponding methyl ketone in 80% yield. Improved results were obtained when THF was used as the solvent. Seemingly, the carbanionic species **12** are more stable in this solvent allowing the electrophilic substitutions to take place at 0 °C. In this solvent, practically all of the substitution reactions studied were successful affording a variety of C_6-alkylated products in moderate to good yields (Table 1).

From these data it is clear that alkylation of **12** is not restricted to reactive primary alkyl halides, such as methyl iodide and allyl bromide, but also less reactive halides can be used. Whereas acylation with acetyl chlorides was successful, attempts to add the copper anion **12** to carbonyl electrophiles, such as aldehydes and ketones, failed. Moreover, 1,4-additions to enones such as tricyclodecadienone **1** (R=H), methyl acrylates, 2-cyclohexen-1-one, and 2-cyclopenten-1-one using **12** could not be accomplished. This result indicates the special nature of this bridgehead carbanionic species, although steric factors may also play a role in preventing the 1,4-addition.

Only lithium dimethyl and di-*n*-butylcuprates could be used in the copper/halogen exchange reaction with **6a**. Heterocuprates and Grignard reagents failed to give this reaction and resulted in complicated product mixtures from which considerable amounts of starting bromide **6a** could be recovered. It should be noted that in all cases the electrophile enters at C_6 in **12**.

The presence of the C_3–C_4–C_5 enone system is apparently crucial for this halogen displacement reaction, as is deduced from the following experiments. Reaction of bromotricyclodecenone **14**, lacking the enone unit, with lithium dimethylcuprate followed by quenching with water led to elimination of hydrogen bromide to give product **16** containing a central enone unit (Scheme 4). This elimination seems to resemble the first step in a similar reaction involving a bridgehead bromide in the tricyclo[3.3.1]decanone system as reported by Kraus and Yi.[9] Remarkably, even when a threefold excess of lithium dimethylcuprate was used, no methyl addition to the enone unit was observed, but instead only product **16** was obtained. Applying excess of cuprate reagent apparently gives proton abstraction at C_4, as was deduced from quenching reaction with methyl iodide, which led to the formation of C_4-methyl substituted product **17** (Scheme 4).



Scheme 4.

It is relevant to note that Michael addition to tricyclodecadienone **16** using excess lithium dimethylcuprate gave the expected 1,4-methyl addition product,[8] exclusively. No deprotonation at C_4 was observed, as was confirmed by quenching the reaction mixture with D_2O, which did not produce any deuteration product. These results strongly suggest that in the reaction of tricyclic bromide **14** with lithium dimethylcuprate, C_4-deprotonation occurs prior to the elimination of hydrogen bromide. It must thus be concluded that the course of the reaction does not resemble the one described by Kraus and Yi. In the present case the following successive steps are taking place: deprotonation at C_4, elimination of hydrogen bromide, quenching with water (proton) or methyl iodide, respectively.

3. Concluding remarks

The initially planned elimination/addition reaction to convert 6-bromotricyclodecadienone **6a** into the corresponding 6-alkylated products **13** takes an entirely different course. The first step is an unpredicted halogen/metal exchange involving lithium dialkylcuprate. Usually, such reagents give Michael type 1,4-addition reactions to enone systems, or direct S_N2 displacement of halogen by an alkyl group.[10] In the present case halide displacement in a S_N2 fashion is simply impossible, leaving a halide/metal exchange reaction as the most likely event to occur. Some successful examples of direct bridgehead methylations using Grignard reagents have been reported.[11] However, this method cannot be applied in the present case because of the reactive enone unit.

One-pot organocopper reactions involving halide/metal exchange have been reported for *gem*-dihalocyclopropanes[12] and α,α′-dihaloketones.[13] In these cases the first halogen is directly replaced by the alkyl nucleophile from the cuprate, whilst the second halogen is subsequently eliminated in a halogen/metal exchange reaction resulting in a reactive carbanion, which is then trapped with an electrophile. In the present case the halogen/metal exchange reaction is restricted to the tricyclodecadienone case, implying that the initially formed carbanion needs the stabilization of the outer enone unit. When such an unit is absent, a different type of reaction is taking place, viz. initial C_4-deprotonation, subsequent dehydrobromination, and finally quenching by an electrophile, either a proton or methyl iodide.

This alkylation procedure expands the scope of the synthetic importance of the tricyclodecadienone system considerably.

4. Experimental section

4.1. General remarks

FTIR spectra were recorded on a Biorad WIN-IR FTS-25 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-400, a Bruker AC-300, and a Bruker AC-100 at T=298 K unless other stated. Chemical shifts were reported relative to TMS. Mass spectrometric (MS) analyses were measured on a double focusing VG Analytical 7070E mass spectrometer. GC–MS analyses were performed using a Varian Saturn II GC–MS ion trap system, equipped with a Varian 8100 autosampler. Separation was carried out on a fused silica HP-1 capillary column (DB-5, 30 m×0.25 mm). Helium was used as a carrier gas and electron impact (EI) was used as ionization mode. Elemental analyses were performed on a Carlo Erba Instruments CHNS-O 1108 Elemental Analyzer. Optical rotations were measured with a Perkin Elmer 241 Polarimeter. Melting points were determined with a Reichert Thermopan microscope and are uncorrected. Gas chromatographic (GC) analyses were performed on a Hewlett-Packard HP5890A or a Hewlett-Packard HP5890II gas chromatograph (flame ionization detector, FID) using a capillary column (HP-1, 25 m×0.32 mm×0.17 μm) and nitrogen at 2 mL/min (0.5 atm) as the carrier gas. The GC temperature programs employed were either from 50 °C (5 min isothermal) to 250 °C at 15 °C/min followed by 2 min at 250 °C (isothermal) or from 100 °C to 250 °C at 15 °C/min followed by 10 min at 250 °C (isothermal). Column chromatography was carried at ambient pressure out using Merck Kieselgel 60. Thin layer chromatography (TLC) was carried out on Merck precoated silicagel 60 F_{254} plates (0.25 mm) using the eluents indicated. Spots were visualized with UV, by reaction with I_2 or molybdate spray. Solvents were dried using the following methods: dichloromethane and hexane were distilled from calcium hydride, diethyl ether was distilled from sodium hydride, ethyl acetate was distilled from potassium carbonate, and toluene was distilled from sodium. THF was distilled first from calcium hydride and then from sodium with benzophenone as indicator under argon, directly prior to use. All other solvents were of analytical grade.

4.2. General procedures for the lithium dimethylcuprate reaction with 6-bromo-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 6a

4.2.1. Procedure A

The experiments were carried out in dry diethyl ether under inert atmosphere. Lithium dimethylcuprate was prepared at 0 °C by

adding methyllithium (ca. 2.4 equiv) to a suspension of CuI (ca. 1.2 equiv) in diethyl ether (10 mL). After stirring for 15 min, the temperature was taken down to −78 °C and bromotricyclodecadienone **6a** (ca. 1 equiv) in a small amount of diethyl ether was added slowly and the reaction mixture was then quenched with an excess (ca. 10 equiv) of the appropriate electrophile. The reaction was monitored by TLC and GC until completion (usually 15 min to 2 h), then quenched with aqueous ammonium chloride and the aqueous phase extracted with ether (3×). The combined organic phase was washed with water (3×), dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica-gel.

4.2.2. Procedure B

The experiments were carried out in dry THF under inert atmosphere. Lithium dimethylcuprate was prepared at 0 °C by adding methyllithium (ca. 2.4 equiv) to a suspension of CuI (ca. 1.2 equiv) in THF (10 mL). After stirring for 15 min, bromotricyclodecadienone **6a** (ca. 1 equiv) in a small amount of THF was added slowly and the reaction mixture was then quenched with an excess (ca. 10 equiv) of the appropriate electrophile. The reaction was monitored by TLC and GC until completion (usually 15 min 2 h), then quenched with aqueous ammonium chloride and the aqueous phase extracted with ether (3×). The combined organic phase was washed with water (3×), dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica-gel.

4.3. 6-Bromo-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 6a

Starting with 5-oxo-*endo*-tricyclo[5.2.1.0^{2,6}]deca-3,8-diene-2-carboxylic acid (0.950 g, 5 mmol), the literature procedure[4] was followed with a slightly modified purification method. The crude product was dissolved in ether and washed several times with 1 M HCl aqueous until complete removal of most of the impurities and the main byproduct 6-pyridylthio-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (checked with pH-paper) was reached. The remaining organic layer was dried with $MgSO_4$, concentrated, and the residue purified by column chromatography on silica-gel (EtOAc/hexane=1:12). Bromotricyclodecadienoneproduct **6a** (1.02 g, 4.53 mmol) was obtained as a white solid in 90% yield. Spectral data of 6-bromo-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one **6a** were in agreement with the reported data.[4]

4.4. *endo*-Tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13a

General procedure A was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.230 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.224 g, 1.00 mmol) and the reaction mixture was quenched with water (0.2 mL, 5 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:6), tricyclodecadienone **13a** (0.124 g, 0.85 mmol) was obtained as a white solid in 85% yield.

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.227 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.225 g, 1.00 mmol) and the reaction mixture was quenched with water (0.2 mL, 5 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:6), tricyclodecadienone **13a** (0.139 g, 0.95 mmol) was obtained as a white solid in 95% yield.

The spectral data were in accordance with the reported data.[4]

4.5. 6-Deutero-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13b

General procedure A was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.232 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.227 g, 1.01 mmol) and the reaction mixture was quenched with D_2O (0.2 mL, 5 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:6), deuterotricyclodecadienone **13b** (0.125 g, 0.85 mmol) was obtained as a white solid in 85% yield.

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.228 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.224 g, 1.00 mmol) and the reaction mixture was quenched with D_2O (0.2 mL, 5 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:6), deuterotricyclodecadienone **13b** (0.140 g, 0.95 mmol) was obtained as a white solid in 95% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, $^3J_{5,4}$=5.6 Hz, 1H, H_5), 5.89 (d, $^3J_{4,5}$=5.6 Hz, 1H, H_4), 5.87 (br s, 1H, H_8), 5.71 (br s, 1H, H_9), 3.15 (br s, 1H, H_1), 2.89 (br s, 1H, H_7), 2.73 (d, $^3J_{2,1}$=4.8 Hz, 1H, H_2), 1.69 (d, $^2J_{10s,10a}$=8.8 Hz, 1H, H_{10s}), 1.55 (d, $^2J_{10a,10s}$=8.8 Hz, 1H, H_{10a}) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.8 (quat.), 164.5, 137.0, 132.6, 132.4 (tert), 52.7 (sec), 50.2, 48.3, 45.0, 44.0 (tert) ppm. IR (CCl_4): ν 2962 (C–H), 2934 (C–H), 2871 (C–H), 1711 (C=O) cm^{-1}. GC–MS (EI): *m*/*e* (%) 147 (35, M^+), 146 (18, M^+-H), 118 (59, $C_9H_8D^+$), 66 (100, $C_5H_6^+$). HRMS (EI): *m*/*z* 147.0795 [calcd for $C_{10}H_9DO$ (M^+) 147.0794].

4.6. 6-Methyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13c

General procedure A was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.232 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.225 g, 1.00 mmol) and the reaction mixture was quenched with methyl iodide (0.7 mL, 30 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:8), methyltricyclodecadienone **13c** (0.088 g, 0.55 mmol) was obtained as a colorless oil in 55% yield.

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.224 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.226 g, 1.00 mmol) and the reaction mixture was quenched with methyl iodide (0.7 mL, 30 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:8), methyltricyclodecadienone **13c** (0.121 g, 0.76 mmol) was obtained as a colorless oil in 75% yield.

General procedure A was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.230 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.226 g, 1.00 mmol) and the reaction mixture was quenched with dimethyl sulfate (1.0 mL, 30 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:8), methyltricyclodecadienone **13c** (0.080 g, 0.50 mmol) was obtained as a colorless oil in 50% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, $^3J_{5,4}$=5.6 Hz, 1H, H_5), 5.95 (br s, 1H, H_8), 5.90 (br s, 1H, H_9), 5.84 (d, $^3J_{4,5}$=5.6 Hz, 1H, H_4), 3.22 (br s, 1H, H_1), 2.57 (br s, 1H, H_7), 2.44 (d, $^3J_{2,1}$=4.4 Hz, 1H, H_2), 1.92 (d, $^2J_{10s,10a}$=8.8 Hz, 1H, H_{10s}), 1.75 (d, $^2J_{10a,10s}$=8.8 Hz, 1H, H_{10a}), 1.45 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.7 (quat.), 169.1, 135.3, 134.4, 132.2, 58.0 (tert), 53.8 (quat.), 51.0 (sec), 50.0, 46.6 (tert), 23.6 (prim.) ppm. IR (CCl_4): ν 2967 (C–H), 2930 (C–H), 2870 (C–H), 1708 (C=O) cm^{-1}. GC–MS (EI): *m*/*z* (%) 160 (14, M^+), 145 (13, M^+-CH_3), 132 (37, M^+-CO), 117 (63, $C_9H_9^+$), 66 (100, $C_5H_6^+$). HRMS (EI): *m*/*z* 160.0887 [calcd for $C_{11}H_{12}O$ (M^+) 160.0888], 117.07028 [calcd for $C_9H_9^+$ 117.0704].

4.7. 6-Ethyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13d

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.228 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.225 g, 1.00 mmol) and the reaction mixture was quenched with ethyl iodide (0.8 mL, 60 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), ethyltricyclodecadienone **13d** (0.113 g, 0.65 mmol) was obtained as a colorless oil in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, $^3J_{5,4}$=5.7 Hz, 1H, H_5), 5.94 (br s, 2H, H_8 and H_9), 5.91 (d, $^3J_{4,5}$=5.7 Hz, 1H, H_4), 3.20 (br s, 1H, H_1), 2.65 (br s, 1H, H_7), 2.50 (d, $^3J_{2,1}$=4.6 Hz, 1H, H_2), 1.86 (d, $^2J_{10s,10a}$=8.6 Hz, 1H, H_{10s}), 1.82 (m, 2H, CH_2CH_3), 1.74 (d, $^2J_{10a,10s}$=8.6 Hz, 1H, H_{10a}), 0.93 (t, ^3J=7.5 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.9 (quat.), 167.9, 135.5, 135.2, 132.6 (tert), 59.0 (quat.), 55.4 (tert), 51.1 (sec), 48.7, 46.3 (tert), 29.7 (sec), 10.6 (prim.) ppm. IR (CCl_4): ν 2979 (C–H), 2927 (C–H), 2871 (C–H), 1709 (C=O) cm^{-1}. GC–MS (EI): *m/z* (%) 174 (15, M^+), 145 (22, M^+-CH_3), 117 (71, $C_9H_9^+$), 66 (100, $C_5H_6^+$). HRMS (EI): *m/z* 174.1044 [calcd for $C_{12}H_{14}O$ (M^+) 174.1044].

4.8. 6-*n*-Propyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13e

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.228 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.226 g, 1.00 mmol) and the reaction mixture was quenched with *n*-propyl iodide (1.0 mL, 60 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), *n*-propyltricyclodecadienone **13e** (0.113 g, 0.60 mmol) was obtained as a colorless oil in 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, $^3J_{5,4}$=5.7 Hz, 1H, H_5), 5.92 (br s, 2H, H_8 and H_9), 5.88 (d, $^3J_{4,5}$=5.7 Hz, 1H, H_4), 3.49 (br s, 1H, H_1), 2.63 (br s, 1H, H_7), 2.50 (d, $^3J_{2,1}$=4.6 Hz, 1H, H_2), 1.90 (d, $^2J_{10s,10a}$=8.7 Hz, 1H, H_{10s}), 1.75 (m, 2H, $CH_2CH_2CH_3$), 1.71 (d, $^2J_{10a,10s}$=8.7 Hz, 1H, H_{10a}), 1.32 (m, 2H, $CH_2CH_2CH_3$), 0.94 (t, ^3J=7.3 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.9 (quat.), 168.3, 135.2, 135.1, 132.6 (tert), 58.4 (quat.), 55.8 (tert), 51.1 (sec), 49.1, 46.4 (tert), 39.5, 19.8 (sec), 14.8 (prim.) ppm. IR (CCl_4): ν 2978 (C–H), 2930 (C–H), 2870 (C–H), 1709 (C=O) cm^{-1}. GC–MS (EI): *m/z* (%) 188 (9, M^+), 145 (14, M^+-CH_3), 117 (65, $C_9H_9^+$), 66 (100, $C_5H_6^+$). HRMS (EI): *m/z* 188.1201 [calcd for $C_{13}H_{16}O$ (M^+) 188.1201].

4.9. 6-*iso*-Propyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13f

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.228 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.225 g, 1.00 mmol) and the reaction mixture was quenched with *iso*-propyl iodide (1.0 mL, 120 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), *iso*-propyltricyclodecadienone **13f** (0.085 g, 0.45 mmol) was obtained as a colorless oil in 45% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, $^3J_{5,4}$=5.8 Hz, 1H, H_5), 5.96 (d, $^3J_{4,5}$=5.8 Hz, 1H, H_4), 5.93 (br s, 2H, H_8 and H_9), 3.18 (br s, 1H, H_1), 2.88 (br s, 1H, H_7), 2.57 (d, $^3J_{2,1}$=4.7 Hz, 1H, H_2), 2.02 (m, 1H, $CH(CH_3)_2$), 1.86 (d, $^2J_{10s,10a}$=8.8 Hz, 1H, H_{10s}), 1.71 (d, $^2J_{10a,10s}$=8.8 Hz, 1H, H_{10a}), 1.13 (d, ^3J=6.8 Hz, 3H, $CH(CH_3)_2$), 0.87 (d, ^3J=6.8 Hz, 3H, $CH(CH_3)_2$) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.7 (quat.), 165.3, 136.6, 135.5, 133.0 (tert), 62.9 (quat.), 55.7 (tert), 50,7 (sec), 46.8, 46.4, 32.9 (tert), 20.3, 19.3 (prim.) ppm. IR (CCl_4): ν 2979 (C–H), 2926 (C–H), 2870 (C–H), 1709 (C=O) cm^{-1}. GC–MS (EI): *m/z* (%) 188 (8, M^+), 145 (38, M^+-CH_3), 117 (100, $C_9H_9^+$), 66 (87, $C_5H_6^+$). HRMS (EI): *m/z* 188.1201 [calcd for $C_{13}H_{16}O$ (M^+) 188.1201].

4.10. 6-Allyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13g

General procedure A was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.230 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.225 g, 1.00 mmol) and the reaction mixture was quenched with allyl bromide (0.9 mL, 30 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:8), allyltricyclodecadienone **13g** (0.112 g, 0.60 mmol) was obtained as a colorless oil in 60% yield.

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.229 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.227 g, 1.01 mmol) and the reaction mixture was quenched with allyl bromide (0.9 mL, 30 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:8), allyltricyclodecadienone **13g** (0.140 g, 0.75 mmol) was obtained as a colorless oil in 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, $^3J_{5,4}$=5.7 Hz, 1H, H_5), 5.95 (br s, 2H, H_8 and H_9), 5.91 (d, $^3J_{4,5}$=5.7 Hz, 1H, H_4), 5.75 (m, 1H, CH_2CH=CH_2), 5.10 (d, ^3J=2.9 Hz, 1H, CH_2CH=CH_2), 5.07 (s, 1H, CH_2CH=CH_2), 3.22 (br s, 1H, H_1), 2.70 (br s, 1H, H_7), 2.60 (dd, ^2J=14.0 Hz, ^3J=7.7 Hz, 1H, CH_2CH=CH_2), 2.51 (s, 1H, H_2), 2.49 (dd, ^2J=14.0 Hz, ^3J=8.0 Hz, 1H, CH_2CH=CH_2), 1.92 (d, $^2J_{10s,10a}$=8.8 Hz, 1H, H_{10s}), 1.77 (d, $^2J_{10a,10s}$=8.8 Hz, 1H, H_{10a}) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.4 (quat.), 167.5, 135.7, 135.0, 134.4, 133.1 (tert), 118.0 (sec), 57.5 (quat.), 55.8 (tert), 51.0 (sec), 48.4, 46.4 (tert), 41.5 (sec) ppm. IR (CCl_4): ν 3065 (C–H_{unsat}), 2979 (C–H), 2927 (C–H), 2871 (C–H), 1709 (C=O) cm^{-1}. GC–MS (EI): *m/z* (%) 187 (100, M^++H), 186 (26, M^+), 145 (31, M^+-CH_2CH=CH_2), 117 (74, $C_9H_9^+$), 66 (69, $C_5H_6^+$). HRMS (EI): *m/z* 186.1042 [calcd for $C_{13}H_{14}O$ (M^+) 186.1044].

4.11. 6-Benzyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13h

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.223 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.227 g, 1.01 mmol) and the reaction mixture was quenched with benzyl bromide (1.2 mL, 90 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), benzyltricyclodecadienone **13h** (0.145 g, 0.61 mmol) was obtained as a colorless oil in 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 3H, $CH_2C_6H_5$), 7.22 (d, $^3J_{5,4}$=5.7 Hz, 1H, H_5), 7.12 (d, ^3J=7.0 Hz, 2H, $CH_2C_6H_5$), 5.92 (br s, 2H, H_8 and H_9), 5.84 (d, $^3J_{4,5}$=5.7 Hz, 1H, H_4), 3.25 (br s, 1H, H_1), 3.16 (d, ^3J=13.6 Hz, 1H, $CH_2C_6H_5$), 3.04 (d, ^3J=13.6 Hz, 1H, $CH_2C_6H_5$), 2.81 (br s, 1H, H_7), 2.59 (d, $^3J_{2,1}$=4.6 Hz, 1H, H_2), 2.07 (d, $^2J_{10s,10a}$=8.8 Hz, 1H, H_{10s}), 1.83 (d, $^2J_{10a,10s}$=8.8 Hz, 1H, H_{10a}) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.2 (quat.), 167.4 (tert), 137,8 (quat.), 135.5, 135.1, 133.3, 130.1 (2×), 128.3 (2×), 126.6 (tert), 59.0 (quat.), 56.4 (tert), 50.8 (sec), 48.1, 46.6 (tert), 43.7 (sec) ppm. IR (CCl_4): ν 3086 (C–H_{unsat}), 3065 (C–H_{unsat}), 3030 (C–H_{unsat}), 2984 (C–H), 2968 (C–H), 2874 (C–H), 2854 (C–H), 1707 (C=O) cm^{-1}. MS (EI): *m/z* (%) 236 (32, M^+), 170 (20, $M^+-C_5H_6$), 145 (46, $M^+-CH_2C_6H_5$), 117 (38, $C_9H_9^+$), 91 (47, $CH_2C_6H_5^+$), 66 (100, $C_5H_6^+$). HRMS (EI): *m/z* 236.1201 [calcd for $C_{17}H_{16}O$ (M^+) 236.1201].

4.12. 6-(2′-Oxo-2′-phenylethyl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13i

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.226 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.220 g, 0.98 mmol) and the reaction mixture was quenched with 2-bromoacetophenone (2.0 g, 120 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), product **13i** (0.129 g, 0.49 mmol) was obtained as a colorless oil in 50% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, $^3J_{3,4}$=5.7 Hz, 1H, H_3), 7.35 (br s, 5H, C_6H_5), 5.99 (br s, 2H, H_8 and H_9), 5.98 (d, $^3J_{4,3}$=5.7 Hz, 1H, H_4), 3.25 (br s, 1H, H_7), 2.19 (d, $^3J_{2,1}$=4.9 Hz, 1H, H_2), 3.16 (br s, 1H, H_1), 2.88 (d, ^2J=16.1 Hz, 1H, $CH_2COC_5H_6$), 2.80 (d, ^2J=16.1 Hz, 1H, $CH_2COC_5H_6$), 1.96 (d, $^2J_{10s,10a}$=8.8 Hz, 1H, H_{10s}), 1.76 (d, $^2J_{10a,10s}$=8.8 Hz, 1H, H_{10a}) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 209.5, 208.0 (quat.), 164.4 (tert), 138.4 (quat.), 136.2, 135.2, 135.0,

128.2 (2×), 128.1 (2×), 127.5 (tert), 62.3 (quat.), 54.5, 53.0 (tert), 52.5, 52.3 (sec), 45.6 (tert) ppm. IR (CCl_4): ν 3080 (C–H_{unsat}), 3060 (C–H_{unsat}), 3030 (C–H_{unsat}), 2990 (C–H), 2950 (C–H), 2880 (C–H), 1733 (C=O), 1711 (C=O) cm^{-1}. GC–MS (EI): *m*/*z* (%) 264 (10, M^+), 236 (100, M^+-CO), 170 (62, $M^+-CO-C_5H_6^+$), 66 (30, $C_5H_6^+$). HRMS (EI): *m*/*z* 264.1146 [calcd for $C_{18}H_{16}O_2$ (M^+) 264.1150].

4.13. Ethyl 2-(5′-oxo-*endo*-tricyclo[5.2.1.0$^{2',6'}$]deca-3′,8′-dien-2′-yl)acetate 13j

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.230 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.225 g, 1.00 mmol) and the reaction mixture was quenched with ethyl 2-bromoacetate (1.1 mL, 120 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:12), tricyclic ethyl ester **13j** (0.095 g, 0.41 mmol) was obtained as a colorless oil in 40% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, $^3J_{3,4}$=5.7 Hz, 1H, H_3), 5.96 (br s, 2H, H_8 and H_9), 5.92 (d, $^3J_{4,3}$=5.7 Hz, 1H, H_4), 4.13 (q, ^3J=7.1 Hz, 2H, OCH_2CH_3), 3.25 (br s, 1H, H_7), 2.84 (br s, 1H, H_1), 2.82 (d, ^2J=14.8 Hz, 1H, CH_2COOEt), 2.75 (d, ^2J=14.8 Hz, 1H, CH_2COOEt), 2.71 (d, $^3J_{2,1}$=4.6 Hz, 1H, H_2), 1.90 (d, $^2J_{10s,10a}$=9.0 Hz, 1H, H_{10s}), 1.79 (d, $^2J_{10a,10s}$=9.0 Hz, 1H, H_{10a}), 1.24 (t, ^3J=7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 209.4, 171.0 (quat.), 166.1, 135.8, 134.8, 133.0 (tert), 60.7 (sec), 56.2 (tert), 55.8 (quat.), 50.8 (sec), 48.7, 46.5 (tert), 41.7 (sec), 14.2 (prim.) ppm. IR (CCl_4): ν 2982 (C–H), 2876 (C–H), 2854 (C–H), 1737 (C=O), 1709 (C=O) cm^{-1}. GC–MS (EI): *m*/*z* (%) 232 (42, M^+), 159 (62, $M^+-COOCH_2CH_3$), 66 (100, $C_5H_6^+$). HRMS (EI): *m*/*z* 232.1098 [calcd for $C_{14}H_{16}O_3$ (M^+) 232.1099].

4.14. 6-(3′-Bromopropyl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13k

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.228 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.223 g, 0.99 mmol) and the reaction mixture was quenched with 1,3-dibromopropane (1.0 mL, 120 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), bromopropyltricyclodecadienone **13k** (0.118 g, 0.44 mmol) was obtained as a colorless oil in 45% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, $^3J_{5,4}$=5.7 Hz, 1H, H_5), 5.94 (br s, 2H, H_8 and H_9), 5.92 (d, $^3J_{4,5}$=5.7 Hz, 1H, H_4), 3.22 (br s, 1H, H_1), 2.66 (br s, 1H, H_7), 2.51 (d, $^3J_{2,1}$=4.6 Hz, 1H, H_2), 1.90 (br s, 6H, $CH_2CH_2CH_2Br$), 1.61 (s, 2H, H_{10a} and H_{10s}) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 210.0 (quat.), 167.2, 135.8, 135.0, 132.8 (tert), 57.9 (quat.), 55.7 (tert), 51.1 (sec), 49.2, 46.5 (tert), 35.6, 33.6, 29.6 (sec) ppm. IR (CCl_4): ν 2967 (C–H), 2950 (C–H), 2876 (C–H), 2854 (C–H), 1708 (C=O) cm^{-1}. GC–MS (EI): *m*/*z* (%) 268 (6, M^+ (^{81}Br)), 266 (6, M^+ (^{79}Br)), 240 (19, M^+ (^{81}Br)–CO), 238 (19, M^+ (^{79}Br)–CO), 187 (16, M^+–Br), 159 (27, M^+–CO–Br), 145 (15, $M^+-C_3H_6Br$), 117 (76, $C_9H_9^+$), 66 (100, $C_5H_6^+$). HRMS (EI): *m*/*z* 266.0306 [calcd for $C_{13}H_{15}O^{79}Br$ (M^+) 266.0306].

4.15. 6-Acetyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 13l

General procedure A was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.231 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.224 g, 1.00 mmol) and the reaction mixture was quenched with acetyl chloride (0.7 mL, 15 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), acetyltricyclodecadienone **13l** (0.150 g, 0.80 mmol) was obtained as a colorless oil in 80% yield.

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.229 g, 1.2 mmol), bromotricyclodecadienone **6a** (0.226 g, 1.00 mmol) and the reaction mixture was quenched with acetyl chloride (0.7 mL, 15 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:10), acetyltricyclodecadienone **13l** (0.095 g, 0.51 mmol) was obtained as a colorless oil in 50% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, $^3J_{5,4}$=5.7 Hz, 1H, H_5), 6.04 (br s, 1H, H_8), 6.02 (d, $^3J_{4,5}$=5.7 Hz, 1H, H_4), 5.96 (br s, 1H, H_9), 3.28 (br s, 1H, H_1), 3.26 (d, $^3J_{2,1}$=4.7 Hz, 1H, H_2), 3.21 (br s, 1H, H_7), 2.31 (s, 3H, CH_3), 1.73 (s, 2H, H_{10}) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 208.7, 205.7 (quat.), 161.1, 137.1, 134.9, 133.7 (tert), 72.1 (quat.), 53.4 (tert), 51.0 (sec), 47.8, 45.8 (tert), 27.9 (prim.) ppm. IR (CCl_4): ν 2978 (C–H), 2927 (C–H), 2859 (C–H), 1712 (C=O), 1707 (C=O) cm^{-1}. GC–MS (EI): *m*/*z* (%) 188 (7, M^+), 145 (40, M^+-COCH_3), 117 (68, $C_9H_9^+$), 66 (50, $C_5H_6^+$), 43 (100, $COCH_3^+$). HRMS (EI): *m*/*z* 188.0834 [calcd for $C_{12}H_{12}O_2$ (M^+) 188.0837].

4.16. 6-Bromo-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one 14

The synthesis of 6-bromotricyclo[5.2.1.0^{2,6}]dec-8-en-3-one **14** (0.550 g, 2.42 mmol) was performed according to the literature procedure[5] and bromotricyclodecenone **14** was obtained as a colorless oil in 87% yield starting from 5-oxo-*endo*-tricyclo[5.2.1.0^{2,6}]deca-8-ene-2-carboxylic acid (0.534 g, 2.78 mmol). Spectral data of **14** were in agreement with those reported.[5]

4.17. Tricyclo[5.2.1.0^{2,6}]deca-2(6),8-dien-3-one 16

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.230 g, 1.2 mmol), bromotricyclodecenone **14** (0.230 g, 1.01 mmol) and the reaction mixture was quenched with water (0.2 mL, 5 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:5), tricyclodecadienone **16** (0.141 g, 0.97 mmol) was obtained as a colorless oil in 95% yield. Spectral data were in agreement with those reported.[5]

4.18. 4-*exo*-Methyltricyclo[5.2.1.0^{2,6}]deca-2(6),8-dien-3-one 17

General procedure B was followed using 1.6 M MeLi (1.5 mL, 2.4 mmol), CuI (0.235 g, 1.2 mmol), bromotricyclodecenone **14** (0.228 g, 1.01 mmol) and the reaction mixture was quenched with methyl iodide (0.7 mL, 30 min). After work-up and purification by column chromatography on silica-gel (EtOAc/hexane=1:6), 4-methyltricyclodecadienone **17** (0.143 g, 0.89 mmol) was obtained as a colorless oil in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (br s, 1H, H_8), 6.78 (br s, 1H, H_9), 3.76 (br s, 1H, H_1), 3.58 (br s, 1H, H_7), 2.79 (dd, $^2J_{5n,5x}$=19.3 Hz, $^3J_{5n,4n}$=5.9 Hz, 1H, H_{5n}), 2.67 (m, 1H, H_{4n}), 2.47 (d, $^2J_{10s,10a}$=6.7 Hz, 1H, H_{10s}), 2.39 (d, $^2J_{10a,10s}$=6.7 Hz, 1H, H_{10a}), 2.38 (d, $^2J_{5x,5n}$=19.3 Hz, 1H, H_{5x}), 1.24 (d, ^3J=7.5 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, H-dec, $CDCl_3$): δ 191.5, 158.1, 150.1 (quat.), 144.7, 141.5 (tert), 74.6 (sec), 51.0, 47.5, 45.0 (tert), 35.2 (sec), 17.2 (prim.) ppm. IR (CCl_4): ν 2980 (C–H), 2940 (C–H), 2860 (C–H), 1675 (C=O) cm^{-1}. GC–MS (EI): *m*/*z* (%) 160 (39, M^+), 145 (32, M^+-CH_3), 132 (21, M^+–CO), 117 (100, $C_9H_9^+$), 66 (39, $C_5H_6^+$). HRMS (EI): *m*/*z* 160.0887 [calcd for $C_{11}H_{12}O$ (M^+) 160.0888].

References and notes

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