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# An expeditious asymmetric formal synthesis of the antibiotic platensimycin

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ABSTRACT

A short enantioselective and protecting group free access to the novel antibiotic platensimycin is reported. The crucial stereogenic information is provided by iridium catalyzed asymmetric hydrogenation.



## 1. Introduction

The rise of multiresistant bacteria is a serious and urgent threat, especially in hospitals, where antibiotics are permanently used and bacteria strains easily evolve that withstand multiple antibiotic classes. Infections by Gram-positive pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and penicillin-resistant *Streptococcus pneumonia* (PRSP) are especially worrying.[1] From these observations the urgency to develop new antibiotics is obvious. Since novel antibiotics usually address well-known targets just at different binding sites or through new binding modes, the discovery of platensimycin[2] (**1**) and platencin[3] (**2**, Fig. 1), is a breakthrough in antibiotics research.

This is due to the fact that compounds **1** and **2** address an apparently ideal biological target. They are the first potent inhibitors of bacterial fatty acid biosynthesis (Fab), which is essential to the survival of the pathogens, distinct from the mammalian pathway and generally highly conserved among bacteria. While platensimycin is blocking the fatty acid condensing enzyme FabF selectively, platencin is inhibiting the enzymes FabF and FabH. These compounds thus display a broad-spectrum of antibiotic activity against many drug-resistant pathogens like methycillin-, macrolide- and linezolid-resistant *S. aureus*, vancomycin intermediate-resistant *S. aureus*, vancomycin-resistant *enterococci*, and

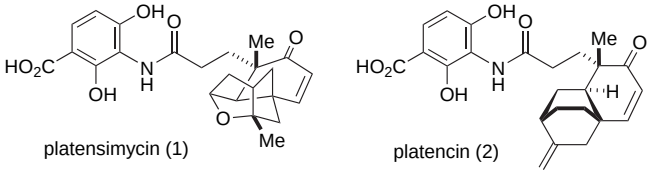


**Figure 1.** Structures of platensimycin (**1**) and platencin (**2**).

*S. pneumoniae*.[3] Meanwhile platensimycin $B_1$–$B_3$, platensimide A, homoplatensimide A as well as platensic acid and its methyl ester, much less biologically active or even inactive natural derivatives of platensimycin, have been discovered.[4]

Owing to the unique mode of action, no cross-resistances to existing drugs have been observed so far. In addition the toxicity profile seems to be good. However the in vivo efficacy is low, due to the limited metabolic stability, so that suitable synthetic derivatives will have to be prepared and investigated to find more promising drug candidates.[1]

Not surprisingly the unusual structure and the promising biological activity have attracted great interest from the scientific community, leading to three total and eleven formal syntheses[5] of **1** during the last three years.

Some time ago we completed a facile synthesis of racemic **1**.[5h] We now report our efforts to develop an enantioselective route (Scheme 1) and to overcome the diastereoselectivity issues during the conversion of dienone **7** to ketone **9**. Specifically the enantioselective hydrogenation of unsaturated acid/ester **4a**/**b** and the diastereoselective hydrogenation of dienone **7** were investigated.

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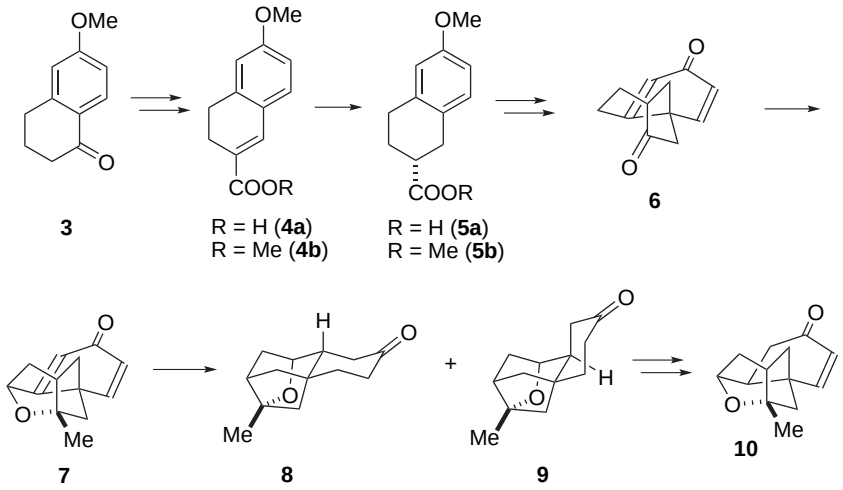
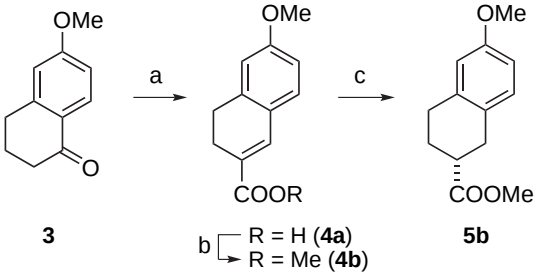



**Scheme 1.** Overview of the formal synthesis of platensimycin.[5h]

The aim of our synthesis was enone **10**, which has been converted into **1** by the Nicolaou group.[5a]

## 2. Results and discussion

Carboxylic acid **4a** is easily available from inexpensive 6-methoxy-1-tetralone (**3**) in three steps[6] (Scheme 2; $NaBH_4$-reduction, one pot elimination–vinylogous Vilsmeier reaction, oxidation with $Ag_2O$) in multigram quantities and excellent overall yield (83%). Initial attempts to reduce acid **4a** in an enantioselective fashion with Noyori catalyst[7] $RuCl_2(BINAP)(DMF)_n$ under a variety of conditions failed. We therefore explored an iridium-catalyzed asymmetric hydrogenation of methyl ester **4b** (Table 1).




**Scheme 2.** Synthesis of the optically active ester **5b**. Reagents and conditions: (a) (i) $NaBH_4$, MeOH; (ii) $POCl_3$, DMF, 0–100 °C; (iii) $AgNO_3$, NaOH, EtOH, water (83%, three steps) (Ref. 6: 54%); (b) DBU, MeI, MeCN (94%) (c) 0.2 mol % Ir-cat-1, 50 bar $H_2$, DCM, 20 h.

Iridium complexes with chiral N,P ligands are efficient catalysts for the asymmetric hydrogenation of unfunctionalized olefins.[8]

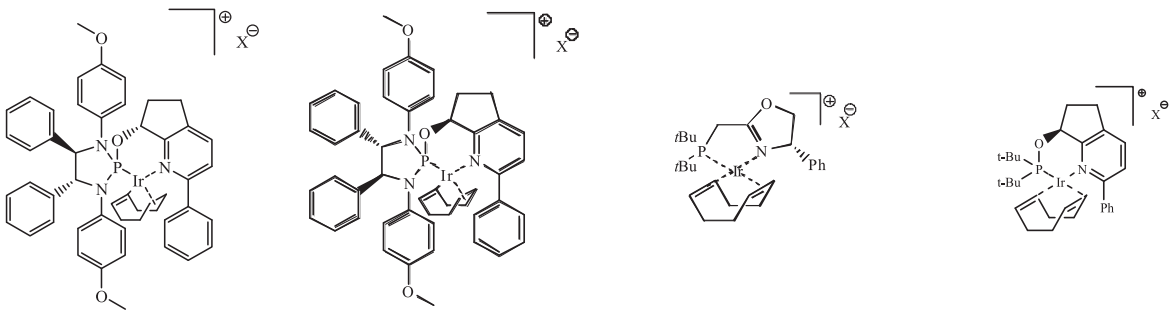
**Table 1**
Hydrogenation of ester **4b**

| Entry | Catalyst[a] | Conversion[b] [%] | ee[c] [%] | Configuration |
|---|---|---|---|---|
| 1. | Ir-cat-1 | >99 | 99.1 | *R* |
| 2. | Ir-cat-2 | >99 | 99.2 | *S* |
| 3. | Ir-cat-3 | >99 | 86 | *R* |
| 4. | Ir-cat-4 | >99 | 93 | *S* |

[a] The counterion is $BAr_F^-$ (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).
[b] Conversion was determined by GC (see Experimental section).
[c] Determined by HPLC (see Experimental section).

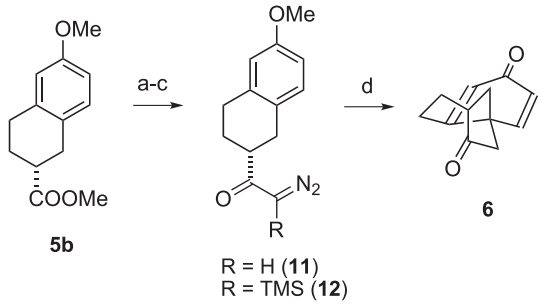
They were also successfully applied for the asymmetric hydrogenation of α,β-unsaturated carboxylic esters, a substrate class that has usually given unsatisfactory results with Ru and Rh catalysts. The ester **4b** was hydrogenated under standard conditions using a range of iridium complexes under 50 bar of $H_2$ in $CH_2Cl_2$ and a catalyst loading of 1 mol %. A brief catalyst screening showed that the two enantiomeric catalysts Ir-cat-1 and Ir-cat-2 gave excellent enantiomeric excess and full conversion (Table 1, entries 1 and 2). The phosphinooxazoline complex Ir-cat-3 (entry 3)[9] and the pyridine–phosphinite Ir-complex Ir-cat-4 (entry 4)[10] also showed full conversion but lower enantiomeric excess. The optimal catalyst, Ir-cat-1,[11] which afforded the desired (*R*)-enantiomer of the saturated ester **5b** in essentially perfect enantiomeric purity and 99% yield, was then chosen for the actual synthesis. In a preparative reaction on a multigram-scale the catalyst loading could be reduced to 0.2 mol % without affecting the enantioselectivity and yield.

Optically active ester **5b** was hydrolyzed to the carboxylic acid **5a** with $K_2CO_3$ in ethanol/water at reflux. To rule out partial racemization, a sample was re-esterified with diazomethane and the



optical rotation of the ester ($[\alpha]_D^{20}$ +52.6 (*c* 0.90, $CHCl_3$)) was compared to that of the parent material **5b** ($[\alpha]_D^{20}$ +52.7 (*c* 1.16, $CHCl_3$)). With optically active acid in hand, the synthesis was continued by the formation of the acid chloride and reaction with TMS-diazomethane in THF/$Et_2O$. The initially formed mixture (~1:1) of diazoketone **11** and TMS-diazoketone **12** was cleanly converted to pure **11** during a regular TLC-run. Therefore these conditions were mimicked (silica gel in hexane/ethylacetate=12:1) to convert the mixture to pure **11** on a multigram-scale. Diazoketone **11** was dissolved in TFA[12] and stirred for 1 h at −15 °C to furnish the optically active tricyclic dienyl-dione **6** in 59% yield over three steps (Scheme 3).

Regio- and stereoselective addition of the required methyl group to the more hindered ketone in the presence of the double-enone moiety proved difficult. Various conditions involving MeLi, MeMgCl, MeMgBr, $Me_2Mg$,[13] $AlMe_3$ in different solvents (THF, $Et_2O$, toluene)



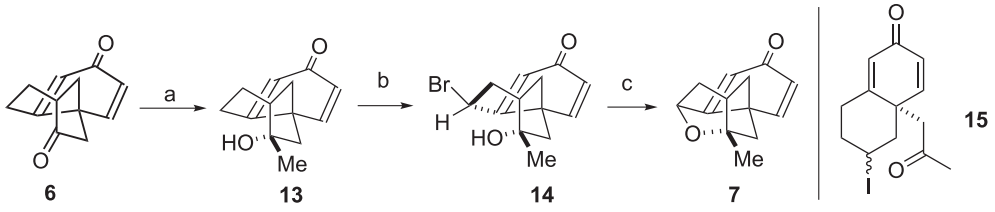

**Scheme 3.** Synthesis of the optically active tricycle **6**. Reagents and conditions: (a) $K_2CO_3$, EtOH, water, reflux (98%) (b) $SOCl_2$, DMF, toluene, rt, 3 h; (c) $TMSCHN_2$, THF; then hexane/EtOAc (10:1), $SiO_2$, rt, 12 h; (d) TFA, −15 °C, 1 h (three steps, 59%). DMF=*N*,*N*-dimethylformamide, TMS=trimethylsilyl, THF=tetrahydrofuran, TFA=trifluoroacetic acid.

chosen, which generated bromide **14** diastereoselectively. Without purification, **14** was cyclized to tetrahydrofuran **7** under basic conditions.[14] The allylic bromination of tricycle **6** on the other hand gave a 1:1-mixture of diastereomeric allylic bromides, which gives us a hint that the OH-group exerts a directing effect. Attempts to form tetrahydrofuran **7** directly from compound **13** by C–H-activation via radical 1,5-*H*-transfer of the alkoxyl radical[15] ($PhI(OAc)_2$, CyH, PhH, $I_2$, ultrasound) failed, because the tertiary alcohol underwent fragmentation to ketone **15** (Scheme 4).

A selective mono-hydrogenation of **7** to **10** could not be achieved. The twofold 1,4-reduction of **7** to **9** was also problematic. Several reaction conditions (Birch conditions, sodium borohydride in methanol and triethylsilane/trifluoroacetic acid) failed. Under optimized hydrogenation conditions ($H_2$, Pd/C, KOH, EtOH) a 1:1.9 diastereomeric mixture of **9** and **8** was obtained (Scheme 5). A higher selectivity was achieved with Crabtree's catalyst,[16] which furnished a separable 1.3:1 diastereomeric mixture of **9** and **8** but suffered from low conversion. Although Corey[5i] later developed a solution to the problem by using Rh-$(COD)_2BF_4$–(*R*,*R*)-DIOP as the catalyst, we again explored chiral iridium complexes for this diastereoselective hydrogenation. Among various catalysts tested, the iridium complex Ir-cat-1 (Table 1)[11] also proved to be the best catalyst for this step, affording the diastereomeric ketones **9** and **8** in 84% yield with an improved ratio of ca. 40:1 (via NMR spectroscopy).

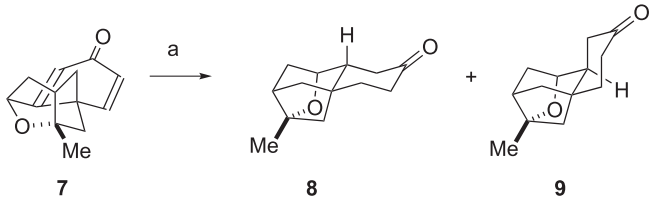
The analytical data of **9** matched those reported in literature.[5i,j] The conversion into intermediate **10**[5h,i,j] as well as the completion of the total synthesis have been reported.[5a–c]

In conclusion we have developed a short enantioselective and protecting group free[17] access to **9**, which is thus obtained from the easily available intermediate **6** in four steps. All analytical data ($^1H$ and $^{13}C$ and IR spectra and optical rotations) of our compounds **7** and **9** fully matched those reported in the literature.[5c,i]




**Scheme 4.** Synthesis of the optically active tetracycle **7**. Reagents and conditions: (a) MeMgI, THF, $Et_2O$, −78 °C (41%, 66% brsm); (b) NBS, $(BzO)_2$, $CCl_4$, reflux (67%); (c) NaOMe, THF, 0 °C, (89%).

and temperatures and additives ($CeCl_3$, LiCl) led to product mixtures. Finally methylmagnesium iodide under optimized conditions (3 equiv, THF, −78 °C) selectively delivered the desired tertiary alcohol **13**, along with recovered starting material. On a multigram-scale, the resubmission of the crude product mixture to the reaction conditions proved necessary due to a lower conversion (ca. 62%). For the activation of the allylic position a free radical bromination was




**Scheme 5.** Synthesis of key intermediate (**9**). Reagents and conditions: (a) cat. [Ir(COD)Py($PCy_3$)]$PF_6$, $H_2$ (1 bar), $CH_2Cl_2$, over night, (78% brsm), **9**:**8**=1.3:1; alternatively: Pd/C (5%), KOH, EtOH, $H_2$ (1 bar), 3 h (90%), **9**:**8**=1:2; or Ir-cat-1 (2 mol %), $H_2$ (50 bar), $CH_2Cl_2$, 65 h, (84%), **9**:**8**=ca. 40:1. brsm=based on recovered starting material, COD=cyclooctadiene, Py=pyridine, Cy=cyclohexane.

## 3. Experimental

### 3.1. General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous toluene was distilled from sodium/benzophenone under argon. Anhydrous $CH_2Cl_2$ and DMF (*N*,*N*-dimethylformamide) were distilled from $CaH_2$ under argon or reduced pressure, respectively. Anhydrous THF (tetrahydrofuran) was purchased from Acros (99.85%, water <50 ppm). The hydrogenation reactions were carried out in $CH_2Cl_2$ from FLUKA (puriss.; absolute; over molecular sieve). All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-$F_{254}$ plates. Flash column chromatography was performed with silica gel (0.04–0.063 mm, 240–400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on either a 400 or 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal ($^1H$, $\delta$=7.26 ppm; $^{13}C$, $\delta$=77.00 ppm). All

$^1$H and $^{13}$C shifts are given in parts per million (s=singlet; d=doublet; t=triplet; q=quadruplet; m=multiplet; b=broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy. High resolution mass spectra (HRMS) were performed with a resolution of 10,000.

*3.1.1. 6-Methoxy-3,4-dihydro-naphthalene-2-carboxylic acid (**4a**).* Compound **4a** was prepared via a modification of the known procedure:[6a] to a solution of 6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol[6b] (15.3 g, 85.8 mmol) in DMF (61 mL) was added $POCl_3$ (18.4 mL, 197 mmol) dropwise over 15 min at 0 °C. Afterward the reaction mixture was heated in an oil bath (100 °C) for 3.3 h. Saturated aqueous NaOAc-solution (60 mL) was added to the solid residue at 0 °C. After stirring for 5 min, the solution was neutralized with 2 M NaOH and extracted with $Et_2O$ (3×). The combined organic phases were washed with saturated $NaHCO_3$, dried over magnesium sulfate, filtered, and the solvent was carefully removed under vacuum to leave 15.9 g of aldehyde **16** (98%). The crude aldehyde was directly converted to acid **4a** via the known protocol.[1a] Analytical data (Mp, IR, NMR) matched those reported.

*3.1.2. 6-Methoxy-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (**4b**).* To a solution of 6-methoxy-3,4-dihydro-naphthalene-2-carboxylic acid (**4a**) (12.0 g, 58.8 mmol) in MeCN (170 mL) was added DBU (10.7 g, 70.5 mmol) at 0 °C within 5 min. 30 min after the slow addition of MeI (4.0 mL, 64.6 mmol), the cooling bath was removed and stirring continued for 15 h. Additional DBU (1.8 g, 11.8 mmol) and MeI (0.7 mL, 11.2 mmol) was added and after 4 h, all volatiles were removed under vacuum. Water (360 mL) was added to the brown residue and extraction 3× with $CH_2Cl_2$. The combined organic phases were dried over magnesium sulfate, filtered, silica gel was added and the solvent was carefully removed under vacuum. Purification of the adsorbed material by column chromatography (120 g silica gel) using hexane/ethylacetate=5:1 as an eluent yielded ester **4b** (12.0 g, 94%) as a colorless oil.

$R_f$=0.37 (silica gel, hexane/EtOAc 5:1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=7.48 (s, 1H), 7.12–7.08 (m, 1H), 6.72–6.68 (m, 2H), 3.78 (s, 6H), 2.81 (t, $J$=8.2 Hz, 2H), 2.60–2.54 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=167.8 (C), 160.5 (C), 138.8 (C), 136.2 (CH), 129.7 (CH), 126.2 (C), 125.5 (C), 113.6 (CH), 111.4 (CH), 55.1 ($CH_3$), 51.4 ($CH_3$), 28.0 ($CH_2$), 21.9 ($CH_2$). IR [cm$^{-1}$]: 2948, 1701, 1604, 1566, 1434, 1276, 1249, 1208. HRMS (EI) calcd for $C_{13}H_{14}O_3$: 218.0943, found: 218.0945. Mp: 48–50 °C.

*3.1.3. (R)-6-Methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (**5b**).* 6-Methoxy-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (**4b**) (6.0 g, 27.5 mmol) and iridium complex Ir-cat-1 (100.5 mg, 0.055 mmol) were placed in a high pressure steel autoclave (120 mL) with a mechanical stirrer and dissolved in $CH_2Cl_2$ (60 mL). The autoclave was attached to a high pressure hydrogen line and purged three times prior to pressurizing the reaction vessel with $H_2$. The reaction mixture was stirred for 20 h at 50 bar $H_2$ and room temperature (rt). After 20 h the residual hydrogen gas was released and the solvent was removed. The crude residue was diluted with *n*-hexane/EtOAc 20:1 and filtered through silica gel ($h$=8 cm, $d$=5 cm). After concentration the product **5b** was obtained as a slightly yellowish oil (6.02 g, 99% yield, 99% ee).

The conversion was determined by GC: Restek Rtx-1701, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min, 60 kPa, $t_{R1}$=24.0 min (product), $t_{R2}$=26.1 min (starting material).

The enantiomeric excess was determined by HPLC: Daicel Chiralcel OD-H, *n*-heptane/$^i$PrOH 99:1, 20 °C, 0.5 mL/min, 220 nm, $t_{R1}$=17.0 min ((*R*)-enantiomer), $t_{R2}$=23.3 min ((*S*)-enantiomer).

$R_f$=0.44 (silica gel, hexane/EtOAc 3:1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=7.01 (d, $J$=8.5 Hz, 1H), 6.70 (dd, $J$=8.5, 2.6 Hz, 1H), 6.62 (d, $J$=2.6 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.02–2.80 (m, 4H), 2.77–2.67 (m, 1H), 2.24–2.15 (m, 1H), 1.91–1.79 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=175.9 (C); 157.8 (C), 136.8 (C), 129.9 (CH), 127.0 (C), 113.4 (CH), 112.2 (CH), 55.2 ($CH_3$), 51.7 ($CH_3$), 40.2 (CH), 30.9 ($CH_2$), 28.8 ($CH_2$), 25.8 ($CH_2$). IR [cm$^{-1}$]: 2950, 1734, 1503, 1268, 1235. HRMS (EI) calcd for $C_{13}H_{16}O_3$: 220.1099, found: 220.1107. $[\alpha]_D^{20}$ +52.7 ($c$ 1.16, $CHCl_3$).

*3.1.4. (R)-6-Methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**5a**).* A mixture of carboxylic ester **5** (6.0 g, 27.2 mmol), ethanol (650 mL), water (130 mL), and $K_2CO_3$ (13.9 g, 101 mmol) was refluxed for 3.5 h. Ethanol was removed under vacuum (down to 100 mbar), water (640 mL) was added and the solution was acidified to pH ~2 via the addition of 3 M HCl. After extraction with $CH_2Cl_2$ (4×), the combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under vacuum to give acid **5a** (5.53 g, 98%) as colorless needles.

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$=7.02 (d, $J$=8.3 Hz, 1H), 6.71 (dd, $J$=8.3, 2.8 Hz, 1H), 6.63 (d, $J$=2.8 Hz, 1H), 3.78 (s, 3H), 3.05–2.82 (m, 4H), 2.82–2.73 (m, 1H), 2.27–2.19 (m, 1H), 1.95–1.82 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=179.9 (C), 157.8 (C), 136.7 (C), 129.9 (CH), 126.7 (C), 113.4 (CH), 112.3 (CH), 55.3 ($CH_3$), 39.8 (CH), 30.6 ($CH_2$), 28.7 ($CH_2$), 25.6 ($CH_2$). IR [cm$^{-1}$]: 2934, 2838, 1688, 1264, 1241. HRMS (EI) calcd for $C_{12}H_{14}O_3$: 206.0943, found: 206.0939. $[\alpha]_D^{20}$ +56.0 ($c$ 0.50, $CHCl_3$). Mp: 126–128 °C.

*3.1.5. (1S,9R)-Tricyclo[7.2.1.0$^{1,6}$]dodeca-2,5-diene-4,10-dione (**6**).* To a suspension of acid (**5a**) (2.00 g, 9.70 mmol) in dry toluene (90 mL) was added $SOCl_2$ (1.41 mL, 19.4 mmol) and dry DMF (eight drops) at rt (vigorous gas formation!). After stirring for 3.5 h, all volatiles were removed under vacuum. To a solution of this grayish solid residue in THF (40 mL) was added TMS-diazomethane (2 M in $Et_2O$, 14.6 mL, 29.1 mmol) at rt. After stirring for 30 min, all volatiles were removed under vacuum and the residue dissolved in hexane/EtOAc 12:1 (120 mL). Silica gel (25 g) was added and the suspension stirred for 16 h. The suspension was filtered under vacuum and washed thoroughly with EtOAc. After the solvents were removed under vacuum, a yellow oil (2.58 g) was obtained. To this crude diazoketone was added TFA (80 mL) at −15 °C (vigorous gas formation!) and stirred for 1.5 h at this temperature. After the addition of EtOAc (600 mL), the organic phase was washed with 2 M NaOH (4×160 mL) and brine. The combined aqueous phases were extracted three times with $CH_2Cl_2$. The organic phases were combined and the solvents removed under vacuum. Purification by column chromatography (40 g silica gel) using hexane/ethylacetate=1:2 as an eluent yielded ketone **6** (1.08 g, 59% over three steps) as a yellow solid.

$R_f$=0.32 (silica gel, hexane/EtOAc 1:2). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=6.78 (d, $J$=9.9 Hz, 1H), 6.31 (dd, $J$=9.9, 1.8 Hz, 1H), 6.11–6.08 (m, 1H), 2.74–2.68 (m, 1H), 2.57 (dd, $J$=15.9, 6.5 Hz, 1H), 2.51–2.39 (m, 2H), 2.32 (ddd, $J$=12.0, 5.1, 2.3 Hz, 1H), 2.24 (dd, $J$=18.4, 3.6 Hz, 1H), 2.11–2.02 (m, 1H), 1.76–1.65 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=216.1 (C), 186.3 (C), 162.6 (C), 151.7 (CH), 130.0 (CH), 124.3 (CH), 48.9 ($CH_2$), 46.5 (C), 46.3 (CH), 42.2 ($CH_2$), 29.2 ($CH_2$), 28.6 ($CH_2$). IR [cm$^{-1}$]: 2954, 1745, 1661, 1623, 1405, 1270, 1042, 888. HRMS (EI) calcd for $C_{12}H_{12}O_2$: 188.0837, found: 188.0835. $[\alpha]_D^{20}$ +77.8 ($c$ 0.83, $CHCl_3$). Mp: 125–127 °C.

*3.1.6. (1S,9R,10S)-10-Hydroxy-10-methyltricyclo[7.2.1.0$^{1,6}$]dodeca-2,5-dien-4-one (**13**).* To a solution of ketone **6** (1.98 g, 10.5 mmol) in THF (145 mL) was added dropwise methylmagnesium iodide (3 M in $Et_2O$, 10.5 mL, 31.5 mmol) at −78 °C. After stirring at this temperature for 3 h, the reaction was quenched by the addition of satd aq $NH_4Cl$ (50 mL) and water (50 mL). The aqueous phase was extracted three times with $CH_2Cl_2$. The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under vacuum.

The reaction was repeated with the crude material due to low conversion.

Purification by column chromatography (100 g silica gel) using hexane/ethylacetate=1:1→1:2 as an eluent yielded alcohol **13** (890 mg, 41%, 66% brsm) and recovered ketone **6** (750 mg).

$R_f$=0.20 (silica gel, hexane/EtOAc 1:1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=6.65 (d, $J$=9.8 Hz, 1H), 6.21 (dd, $J$=9.8, 1.8 Hz, 1H), 6.01 (br t, $J$=2.0 Hz, 1H), 3.00–2.89 (m, 1H), 2.42 (dd, $J$=15.5, 6.4 Hz, 1H), 2.26–2.10 (m, 3H), 1.98 (d, $J$=14.4 Hz, 1H), 1.87 (dd, $J$=14.3, 2.4 Hz, 1H), 1.61–1.54 (m, 1H), 1.53 (s, 3H), 1.49 (dd, $J$=11.1, 2.5 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=187.1 (C), 167.8 (C), 154.2 (CH), 129.0 (CH), 122.1 (CH), 80.0 (C), 51.2 ($CH_2$), 49.2 (C), 46.7 (CH), 44.6 ($CH_2$), 33.0 ($CH_3$), 30.1 ($CH_2$), 27.9 ($CH_2$). IR [$cm^{-1}$]: 3401, .2938, 1654, 1616, 1123, 884. HRMS (EI) calcd for $C_{13}H_{16}O_2$: 204.1150, found: 204.1152. $[\alpha]_D^{20}$ +20.7 (*c* 0.70, $CHCl_3$). Mp: 117–119 °C.

*3.1.7. (1S,7R,9S,10S)-7-Bromo-10-hydroxy-10-methyltricyclo [7.2.1.0$^{1,6}$]dodeca-2,5-dien-4-one (**14**).* A mixture of alcohol **13** (890 mg, 4.36 mmol), *N*-bromosuccinimide (1.24 g, 6.97 mmol), and benzoyl peroxide (42 mg, 0.17 mmol) in $CCl_4$ (53 mL) was heated at reflux for 2 h. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL) and washed once with water. The organic phase was dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. Purification by column chromatography (50 g silica gel) using hexane/ethylacetate=1:1 as an eluent yielded bromide **14** (0.82 g, 67%) as a slightly yellow solid.

Traces of succinimide are hard to separate by chromatography at this stage but can easily be removed after the next step.

$R_f$=0.27 (silica gel, hexane/EtOAc 1:1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=6.64–6.59 (m, 2H), 6.25 (dd, $J$=9.8, 1.8 Hz, 1H), 5.42 (ddd, $J$=11.6, 7.2, 2.1 Hz, 1H), 2.92–2.84 (m, 1H), 2.23–2.12 (m, 2H), 2.05–1.96 (m, 2H), 1.88 (dd, $J$=14.6, 2.7 Hz, 1H), 1.61 (dd, $J$=11.9, 2.7 Hz, 1H), 1.54 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=187.2 (C), 162.9 (C), 153.8 (CH), 129.0 (CH), 125.5 (CH), 79.5 (C), 52.0 ($CH_2$), 50.2 (C), 48.6 (CH), 48.2 (CH), 44.5 ($CH_2$), 41.2 ($CH_2$), 32.6 ($CH_3$). IR [$cm^{-1}$]: 3423, 2959, 1658, 1617, 1158, 1117, 888. HRMS (EI) calcd for $C_{13}H_{15}O_2Br$+$Na^+$+MeCN: 346.0419, found: 346.0415. $[\alpha]_D^{20}$ −39.5 (*c* 0.76, $CHCl_3$). Mp: 122–124 °C.

*3.1.8. (1S,7S,9S,12S)-9-Methyl-8-oxatetracyclo[5.3.3.0$^{1,6}$0$^{9,11}$]trideca-2,5-dien-4-one (**7**).* To a solution of bromide **14** (820 mg, 2.90 mmol) in THF (50 mL) was added NaH (209 mg, 8.69 mmol) and methanol (1 mL) at 0 °C. After stirring at this temperature for 30 min, the reaction was quenched by the addition of water (50 mL) and extracted 3× with $CH_2Cl_2$. The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. Purification by column chromatography (40 g silica gel) using hexane/ethylacetate=3:2 as an eluent yielded tetrahydrofuran **7** (524 mg, 89%) as a colorless solid.

$R_f$=0.40 (silica gel, hexane/EtOAc 1:1). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=6.66 (d, $J$=10.0 Hz, 1H), 6.32 (dd, $J$=10.0, 1.7 Hz, 1H), 6.12 (d, $J$=1.7 Hz, 1H), 4.71 (d, $J$=4.3 Hz, 1H), 2.59 (t, $J$=6.2 Hz, 1H), 2.28–2.14 (m, 2H,), 2.01–1.92 (m, 2H), 1.78 (d, $J$=11.4 Hz, 1H), 1.56–1.50 (m, 1H), 1.50 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=187.1 (C), 160.4 (C), 150.9 (CH), 130.1 (CH), 121.9 (CH), 87.1 (C), 80.0 (CH), 54.9 ($CH_2$), 49.9 (C), 48.7 ($CH_2$), 44.4 (CH), 42.6 ($CH_2$), 22.2 ($CH_3$). IR [$cm^{-1}$]: 2966, 1661, 1628, 1149, 943, 888. HRMS (EI) calcd for $C_{13}H_{14}O_2$: 202.0994, found: 202.0991. $[\alpha]_D^{20}$ +36.6 (*c* 0.70, $CHCl_3$); (Ref. 5i +33.7 (*c* 1.25, $CHCl_3$)). Mp: 99–101 °C.

*3.1.9. (1S,6S,7S,9S,12S)-9-Methyl-8-oxatetracyclo[5.3.3.0$^{1,6}$0$^{9,11}$]trideca-4-one (**9**).* (1S,7S,9S,12S)-9-Methyl-8-oxatetracyclo [5.3.3.0$^{1,6}$0$^{9,11}$]trideca-2,5-dien-4-one (**7**) (33.6 mg, 0.166 mmol) and iridium complex Ir-cat-1 (6.07 mg, 3.32 μmol) were placed in a dry glass vial with a magnetic stirring bar and dissolved in $CH_2Cl_2$ (0.8 mL). The vial was placed in an autoclave, which was attached to a high pressure hydrogen line and purged three times prior to pressurizing the reaction vessel with $H_2$. The reaction was stirred for 65 h at 50 bar $H_2$ and 40 °C. After 65 h the autoclave was cooled to room temperature and the residual hydrogen gas was released. The solvent was removed and the crude residue diluted with hexane/EtOAc 1:1 and filtered through silica gel ($h$=5 cm, $d$=0.5 cm). After removal of the solvent the product mixture **8** and **9** was isolated as a brownish oil (28.7 mg, 84%). The product was analyzed for conversion by GC analysis (Restek Rtx-1701, 100 °C, 2 min, 7 °C/min, 250 °C, 10 min; 60 kPa He, $t_{R1}$=22.28 min *cis*-dec (**8**), $t_{R2}$=22.63 min *trans*-dec (**9**)). No starting material (**7**) ($t_R$=25.20 min) was detected in the chromatogram. The dr could not be determined accurately, because of overlapping minor peaks between $t_R$=22.2–22.8 min. According to analysis by $^1$H NMR only traces of compound **8** could be detected (dr 40:1 according to integral of signals at 4.08 ppm and 2.75 ppm, respectively).

*3.1.9.1. Analytical data of **9**.* $R_f$=0.54 (silica gel, hexane/EtOAc 1:1). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$=4.08 (t, $J$=3.6 Hz, 1H), 2.37–2.29 (m, 3H), 2.27–2.23 (m, 2H), 2.11–2.07 (m, 1H), 2.06–2.02 (m, 1H), 1.91–1.85 (m, 2H), 1.82 (td, $J$=13.3, 5.8 Hz, 1H), 1.70 (dd, $J$=11.3, 3.4 Hz, 1H), 1.65–1.60 (m, 1H), 1.53 (d, $J$=11.3 Hz, 1H), 1.45–1.42 (m, 1H), 1.41 (s, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$=210.6 (C), 86.1 (C), 79.3 (CH), 52.8 ($CH_2$), 45.2 (CH), 45.0 (CH), 44.4 (C), 41.6 ($CH_2$), 40.0 ($CH_2$), 39.2 ($CH_2$), 37.1 ($CH_2$), 35.1 ($CH_2$), 23.1 ($CH_3$). IR [$cm^{-1}$]: 2951, 1705, 1040. HRMS (EI) calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1303. $[\alpha]_D^{20}$ −12.1 (*c* 0.95, $CHCl_3$); (Ref.5i −10.8 (*c* 0.84, $CHCl_3$)).

*3.1.9.2. Analytical data of **8**.* $R_f$=0.57 (silica gel, hexane/EtOAc 1:1). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$=3.97 (d, $J$=4.5 Hz, 1H), 2.75 (t, $J$=14.1 Hz, 1H), 2.34–2.27 (m, 4H), 2.22 (ddd, $J$=14.7, 4.4, 1.6 Hz, 1H), 2.03–1.99 (m, 1H), 1.83–1.68 (m, 4H), 1.63–1.60 (m, 1H), 1.42 (s, 3H), 1.40 (dd, $J$=11.5, 3.7 Hz, 1H), 1.23 (d, $J$=11.5 Hz, 1H). $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$=212.0 (C), 87.3 (C), 79.8 (CH), 47.6 ($CH_2$), 45.4 ($CH_2$), 44.9 (C), 44.7 (CH), 44.4 (CH), 42.7 ($CH_2$), 41.5 ($CH_2$), 39.4 ($CH_2$), 35.0 ($CH_2$), 23.3 ($CH_3$). HRMS (EI) calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1304.

## Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.098.

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