Intramolecular cycloaddition in 6,6-spiroepoxycyclohexa-2,4-dienone: simple aromatics to (±)-Platencin†

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A formal total synthesis of platencin from a simple aromatic precursor is described. Transformation of the aromatic compound into reactive spiroepoxycyclohexa-2,4-dienone and intramolecular cycloaddition are the key features of our methodology.
2-Hydroxymethyl-6-(3-hydroxy-hex-5-enyl)-phenol was oxidized with $NaIO_4$ to give a dimer that, upon a retro-Diels–Alder reaction, generated the spiroepoxycyclohexa-2,4-dienone that underwent intramolecular Diels–Alder reaction to give a tricyclic adduct having a core structure of platencin and appropriately disposed functional groups in a single step. Reduction of the double bond present in the ethano-bridge, manipulation of the oxirane ring and introduction of a double bond in the six-membered ring furnished a tricyclic intermediate which has already been converted into platencin.

Introduction

Rapid generation of complex molecular structures is one of the important aspects of synthesis design and development of methodology.[1,2] This objective is often accomplished by employing a cascade of reactions,[1,3] or multi-component reactions[4] and reactive species generated from aromatics.[5-7] Recently, a group from Merck reported the isolation and structural elucidation of platensimycin **1**[8] and platencin **2**[9] (Fig. 1) which are metabolites of *Streptomyces platensis*. Both of these compounds exhibit potent antibacterial properties.

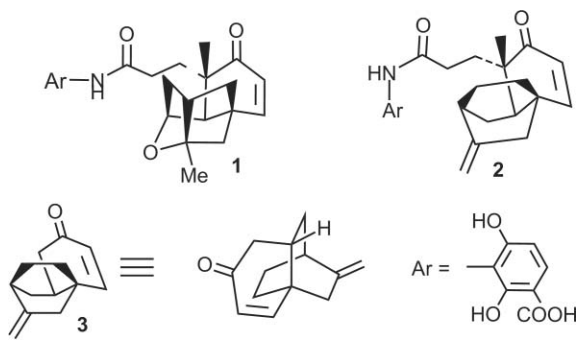

Fig. 1 Structures of platensimycin, platencin and tricyclic core of platencin.

Platensimycin is active against *Staphylococcus aureus* by blocking fatty acid biosynthesis *via* inhibition of the enzyme FabF. Interestingly, platencin inhibits action of both the enzymes FabH and FabF and therefore exhibits a broad range antibacterial activity. Remarkably, platensimycin and platencin have different carbocyclic networks but the same side chain. Platensimycin has a tetracyclic structure containing a cyclic ether whereas platencin has a tricyclic core of type **3** comprised of a bridged bicyclo[2.2.2]octane framework annulated with a six-membered ring in spiro fashion. The novel molecular architecture and promising therapeutic potential of platensimycin and platencin has stimulated considerable interest in their synthesis. Platensimycin received relatively greater attention since it was isolated earlier and several elegant syntheses have appeared.[10,11]

The unique molecular structure and promising antibiotic properties of platencin have also stimulated a high level of interest and several elegant synthetic routes were developed[12,13] soon after the reports by Nicolaou *et al.*[12a] and Rawal's group.[12b] Various types of strategies have been designed for the synthesis of the tricyclic framework of platencin. However, the majority of the approaches have employed radical-induced reactions to create the bridged structure and generate the tricyclic framework of platencin in a stepwise manner. Intramolecular Diels–Alder reaction of α,α dialkoxycyclohexadienone and a *cis*-1,2-functionalized cyclohexa-1,3-diene have been employed by Nicolaou *et al.*[13c] and Banwell and co-workers[13d], respectively, to generate the tricyclic framework of platencin in a single step. Intermolecular Diels–Alder reaction of (*S*)-(−)-perillaldehyde has also been utilized for efficient enantioselective synthesis of platencin.[12c,13b,h]

We have a long standing and continued interest in the development of new methodology involving *in situ* generation of spiroepoxycyclohexa-2,4-dienones, cycloaddition and rearrangements in excited states.[6] In view of the above we considered developing a synthesis of platencin from a simple aromatic precursor in order to further demonstrate the versatility and synthetic potential of our methodology.

Our plan for the synthesis of platencin is outlined in Scheme 1. We also focused on the synthesis of the tricyclic dienone **3** which has already been elaborated to platencin.[12a,b] It was contemplated that the tricyclic dienone **3** may be easily obtained from the enone **4**, which may be derived from the keto-epoxide **5**.

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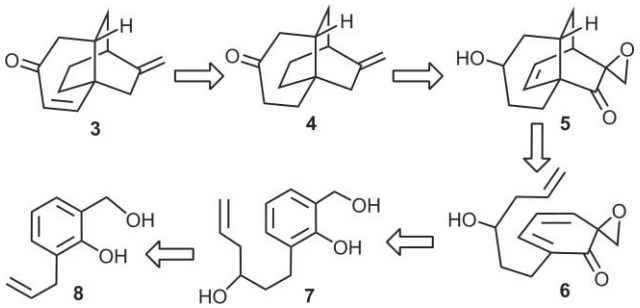
† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR spectra of compounds **10**, **11**,**7**,**12**,**13**, **5a**,**5b**, **14**–**21**, **4**, **3** and **22** and CIF data of **5b** and **18**. CCDC reference numbers 770204–770205. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c004316h



Scheme 1

The keto-epoxide **5**, in turn, was thought to be amenable from the aromatic precursor **7** by its oxidative dearomatization to spiroepoxycyclohexa-2,4-dienone **6** and subsequent intramolecular π4s + π2s cycloaddition *via* an *endo* transition state. The precursor **7** was thought to be prepared from readily available 2-allyl-(6-hydroxymethyl)phenol **8** (Scheme 1).

Some of the salient features of our strategy are as follows. The tricyclic ring system of platencin is efficiently assembled with correct relative stereochemistry and functional group disposition from a simple aromatic precursor in the very beginning of the synthetic route. Further, the juxtaposition of the functional group in the ketoepoxide **5** provides a unique opportunity for selective manipulation and transformation of the oxirane ring into an exocyclic olefin moiety of the key precursor. Remarkably, all the thirteen carbon atoms of the platencin core **3**, the unique tricyclic framework, and the requisite functionalities are present in the aromatic precursor **7** in a latent fashion.

Results and discussion

Conceptually, the tricyclic compound **4** may be prepared by intramolecular cycloaddition in the species of type **9a** and **9b** (Fig. 2). However, there are no methods for the preparation of compound of type **9a** as it is a keto-tautomer of the corresponding phenol and the compound **9b** also does not appear to be easily accessible.

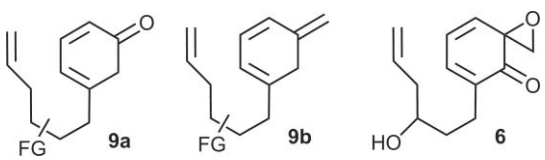
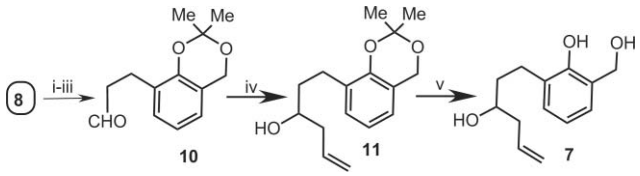


Fig. 2 Potential precursors for intramolecular Diels–Alder reaction.

We, therefore, considered employing intramolecular cycloaddition in 6,6-spiroepoxycyclohexa-2,4-dienone **6** for the synthesis of tricyclo[6.2.2.0.^{2,6}]dodecane framework of platencin, especially since cyclohexa-2,4-dienones of type **6** can be generated by oxidative dearomatization of the corresponding *o*-hydroxymethyl phenol.[14] Further, it was anticipated that the cyclohexa-2,4-dienone **6** would undergo intramolecular π4s + π2s cycloaddition. At the outset, however, we were aware that spiroepoxycyclohexa-2,4-dienones have fleeting existence and readily dimerize in the absence of a reactive 2π-partner.[6,14]

Towards the above objective, the aromatic precursor **7** was easily prepared from readily available[6c] 3-allylsaligenin **8** as shown in Scheme 2. Thus, protection of the 1,3-diol moiety in compound **8** followed by hydroboration-oxidation[15] and subsequent oxidation of the resulting alcohol furnished the aldehyde **10**. Reaction of allylmagnesium bromide on **10** gave the addition product **11** which upon removal of the acetonide readily furnished the required aromatic precursor **7** (Scheme 2).



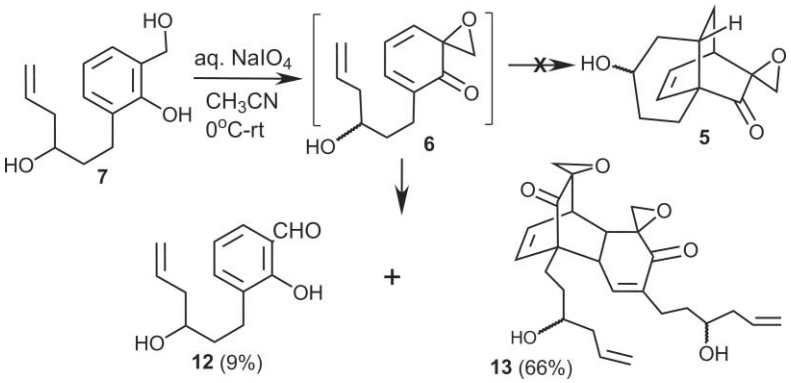
Scheme 2 **Reagents and conditions:** i, 2,2-Dimethoxypropane, *p*-TSA, acetone, 87%; ii, $NaBH_4$–I_2, H_2O_2, NaOH, 96%; iii, IBX, ethyl acetate, reflux 92%; iv, allylmagnesium bromide, THF, 96%; v, HCl, aq. acetone, 92%.

The hydroxymethyl phenol **7** was subjected to oxidative dearomatization with a view to generate the spiroepoxycyclohexa-2,4-dienone **6** and explore the possibility of intramolecular cycloaddition. Thus, a solution of **7** in acetonitrile was treated with aq. $NaIO_4$ following a procedure developed in our laboratory.[16] However, the reaction did not lead to desired cycloadduct **5**, instead the dimer **13** was obtained due to intermolecular cycloaddition as a major product along with a minor amount of the aldehyde **12** (Scheme 3).

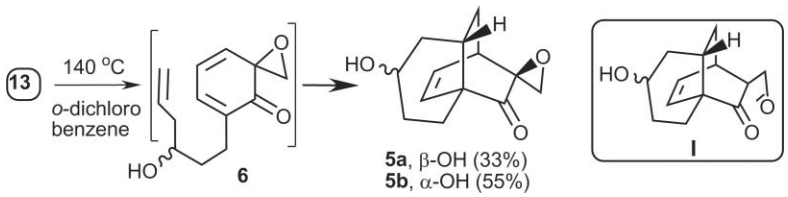
It appeared that under the aforementioned reaction conditions the dienophilic reactivity of the π-bond of the tether was not sufficient to compete with the reactivity of the γ,δ-C=C bond of the cyclohexadienone moiety towards cycloaddition. Therefore, we considered generating the cyclohexa-2,4-dienone **6** by a thermal retro-Diels–Alder reaction of the dimer **13** with anticipation that the dienone **6** generated under thermal activation may undergo intramolecular cycloaddition to give the desired tricyclic keto-epoxide **5**. Hence, the dimer **13** was heated in *o*-dichlorobenzene at 140 °C for 6 h. Indeed, it was gratifying to obtain the *endo* adducts **5a** and **5b** in high yield, the latter being the major product (Scheme 4).

It may be interesting to note that the aforementioned cycloaddition occurred with π-facial selectivity so as to give only one stereoisomer at the spiro-oxirane centre and adducts of type **I** were not observed.

The structure of both adducts was deduced from their spectral features. Thus, the minor adduct exhibited the following spectral features. The IR spectrum of the cycloadduct **5a** showed absorption bands at 3442 and 1731 cm^{-1} for the hydroxyl and carbonyl groups, respectively. The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum displayed highly characteristic signals at δ 6.59 (superimposed dd, $J_1 = J_2 = 8.0$ Hz, 1H) for the γ- proton of the β,γ-enone moiety and at δ 5.98 (d, $J = 8.0$ Hz, 1H) for the β-proton of the β,γ-enone moiety. The difference in the chemical shifts of these protons is a manifestation of the homo-conjugation of the olefinic moiety with the carbonyl group. This clearly indicated that the intramolecular cycloaddition had indeed occurred. It further exhibited highly characteristic AB patterns for methylene protons of the oxirane ring at δ 3.14 (part of an AB system, $J_{AB} = 6.4$ Hz, 1H) and 2.83



Scheme 3



Scheme 4

(part of an AB system, J_{AB} = 6.4 Hz, 1H). In addition, signals were observed at δ 4.08–4.04 (m, 1H) for the methine proton attached to the carbon bearing hydroxyl group, 2.54–2.48 (m, 1H), 2.44–2.32 (m, 2H), 2.30–2.18 (m, 1H), 1.92–1.60 (m, 5H), 1.42–1.32 (m, 1H), 1.14–1.04 (m, 1H). The structure of the adduct **5a** was also supported by the ^{13}C NMR spectrum that exhibited characteristic signals at δ 206.6 for the carbonyl carbon and δ 134.5, 130.6 for the olefinic carbons. It further exhibited signals at δ 65.2, 57.8, 53.1, 52.7, 37.8, 37.5, 30.0, 29.3, 28.2 and 20.1 for other carbons.

The IR spectrum of the cycloadduct **5b** showed absorption bands at 3373 and 1728 cm^{-1} for the hydroxyl and carbonyl groups, respectively. The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum displayed diagnostic signals at δ 6.59 (dd, J_1 = 8.0 Hz, J_2 = 7.3 Hz, 1H) and 5.96 (d, J = 8.0 Hz, 1H) for the γ- and β-proton of the β,γ-enone moiety, respectively. It further exhibited highly characteristic AB patterns for the methylene protons of the oxirane ring at δ 3.13 (part of an AB system, J_{AB} = 6.1 Hz, 1H), 2.84 (part of an AB system, J_{AB} = 6.1 Hz, 1H). In addition, signals were observed at δ 3.63–3.53 (m, 1H), 2.56–2.48 (m, 1H), 2.43–2.35 (m, 1H), 2.10–1.70 (complex m, 6H), 1.46–1.34 (m, 1H), 1.24–1.12 (m, 2H) for other protons. The ^{13}C NMR spectrum of **5b** exhibited characteristic resonances at δ 206.4 and 134.3, 130.9 for the carbonyl carbon and olefinic carbons, respectively. It further exhibited signals at δ 69.3, 57.8, 53.1, 52.2, 40.3, 37.7, 35.9, 31.1, 29.5 and 24.7 for other carbons.

The aforementioned spectral features clearly suggested the gross structure of adducts; however, it was difficult to ascertain the stereochemistry of the hydroxyl group and the oxirane moiety (though both these stereocentres are inconsequential as it would be manipulated later). Hence, a single crystal X-ray structure determination of **5b** was undertaken which confirmed its structure (Fig. 3).

The molecular structure of **5b** consists of a tricyclic ring system containing a six-membered ring (C1-C6) fused to a bridged

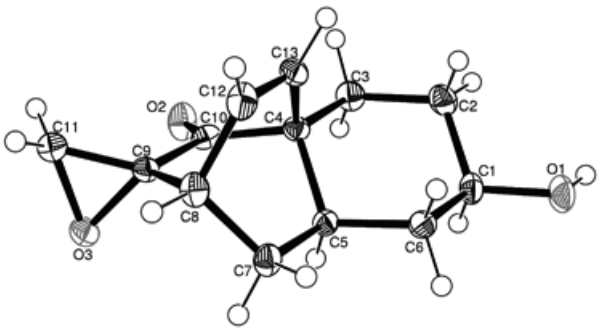
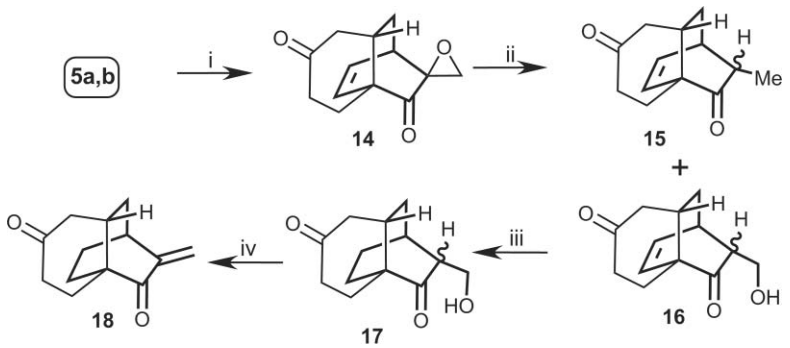


Fig. 3 ORTEP diagram of compound **5b** showing thermal ellipsoid at 50% probability. One of the disordered hydrogen atoms over O1 is omitted for clarity.

bicyclo[2.2.2]octane framework which also contains an oxirane ring (C9, C11 and O3). It also clearly reveals the expected relative stereochemical disposition of the hydroxyl group, oxirane ring and six-membered ring (C1-C6) annulated to the bridged bicyclo[2.2.2]octane framework.

The adducts **5a**,**b** contain all the structural and stereochemical features required in the desired tricyclic intermediate **3**. The elaboration of **5a**,**b** to the compound **3** required some functional group manipulation, such as reduction of the double bond and deoxygenation of the oxirane ring into exocyclic olefin and reduction of the carbonyl group present in the ethano bridge. The unique functional group disposition in the adducts readily permitted these transformations as presented below.

Both adducts **5a** and **5b** were oxidized with PDC to give the same oxidation product **14** in good yield (Scheme 5). Reduction of the epoxy-ketone **14** with Zn and NH_4Cl in aqueous methanol following a method developed in our laboratory[17] furnished the β-keto-alcohol **16** as a major product (62%) as a *syn* : *anti* mixture



Scheme 5 **Reagents and conditions:** i, PDC, CH_2Cl_2 (75% from **5a**, 85% from **5b**); ii, Zn, NH_4Cl, MeOH–H_2O (6 : 1) [**15** (15%), **16** (62%)]; iii, Pd/C (5%), H_2, ethanol (84%); iv, (a) tosyl chloride, pyridine, RT, 12 h, (69%), (b) pyridine, 100 °C, 8 h (83%).

(^{1}H NMR spectrum) in addition to the ketone **15** (as a *syn* : *anti* mixture) as a minor product. The β-keto-alcohol **16** was readily hydrogenated in the presence of Pd/C to give the alcohol **17**. Treatment of the β-keto-alcohol **17** with tosyl chloride–pyridine followed by heating readily furnished the ene-dione **18** (Scheme 5).

The structure of compound **18** was deduced from the following spectral features. The IR spectrum showed the absorption band at 1707 cm^{-1} for the carbonyl groups. The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18** displayed resonances at δ 6.01 (d, J = 1.4 Hz, 1H) and 5.26 (d, J = 1.4 Hz, 1H) for olefinic protons. Other protons appeared at δ 2.82–2.76 (m, 1H), 2.50–2.34 (m, 5H), 2.20–2.04 (m, 3H), 1.95–1.76 (m, 3H), 1.58–1.46 (m, 1H), 1.34–1.28 (m, 1H). The ^{13}C NMR spectrum displayed signals at δ 210.2, 202.7 for two carbonyl groups and at δ 146.8 and 117.8 for two olefinic carbons. Other signals were observed at δ 44.9, 44.2, 36.9, 35.7, 35.1, 34.6, 28.4, 26.0 and 21.3. The structure of the ene-dione **18** was further confirmed by a single crystal structure determination (Fig. 4).

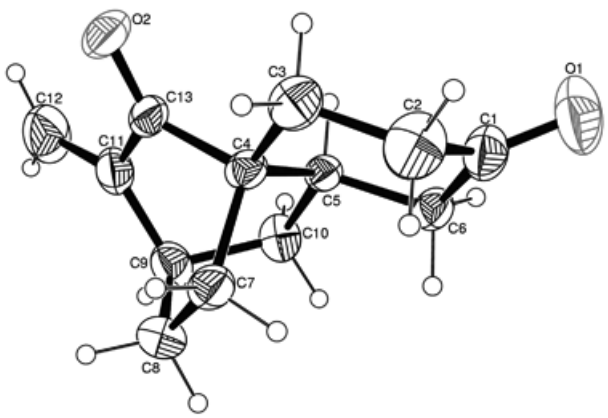
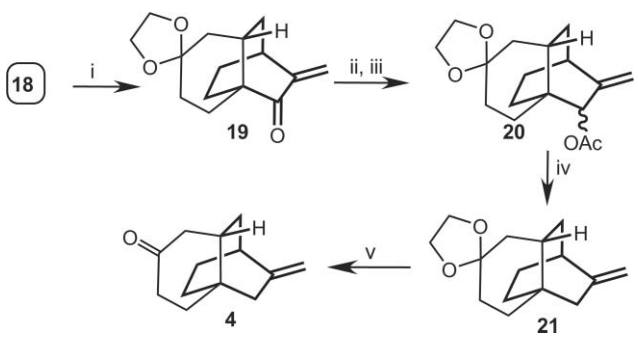


Fig. 4 ORTEP diagram of compound **18** showing thermal ellipsoid at 30% probability

The X-ray structure of **18** depicts the tricyclic ring system and clearly reveals the disposition of exocyclic methylene group (C9–C12) and the carbonyl group (C13–O2) on the bridged bicyclo[2.2.2]octane framework. It also clearly shows the desired stereochemical orientation of the cyclohexanone ring (C1–C6), especially its fusion with the bicyclo[2.2.2]octane framework at C4 and C5.

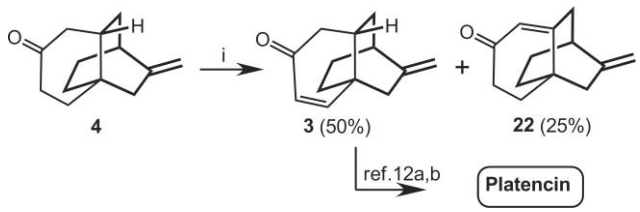
After synthesizing the tricyclic compound **18**, selective deoxygenation of the keto group of the α,β-enone moiety was required. Thus, the dienone **18** was converted into the keto acetal **19** in quantitative yield (Scheme 6). Reduction of **19** with sodium borohydride in the presence of $CeCl_3 \cdot 7H_2O$[18] at 0 °C followed by acylation gave the allylic acetate **20** in good yield. The acetate **20** was subjected to palladium-mediated reduction as developed by Tsuji *et al.*[19] Thus, treatment of **20** with $[Pd_2(dba)_3]$[13b,19] and PBu_3 in the presence of Et_3N/HCOOH gave compound **21**, which upon hydrolysis readily furnished the ketone **4** in excellent yield (Scheme 6). The structure of ketone **4** is fully consistent with its spectral features which are in excellent agreement with those reported.[13d]



Scheme 6 **Reagents and conditions:** i, ethylene glycol, *p*-TSA, benzene, reflux (95%); ii, $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH (98%); iii, acetic anhydride, DMAP, pyridine–CH_2Cl_2, (86%); iv, $Pd_2(dba)_3$, PBu_3, HCOOH, Et_3N, THF, reflux, 18 h (56%); v, aq. HCl, acetone, (92%).

Completion of the synthesis of the key intermediate **3** for platencin required introduction of a double bond in the precursor **4**. Thus, the compound **4** was treated with triethylamine and trimethylsilyl triflate and the resulting silyl enol ether was oxidized with IBX employing a slightly modified procedure,[13d] which gave the desired compound **3** in 50% yield along with the isomeric dienone **22** (25%) in minor amounts (Scheme 7).

The structure of the enone **3** was deduced from its spectral data which are in excellent agreement with those reported in the literature.[12b,13c,d] The tricyclic dienone **3** has already been converted into platencin.[12a,b] Thus, with the synthesis of the intermediate **3** as described above, a formal synthesis of platencin was complete.



Scheme 7 **Reagents and conditions:** i, (a) TMSOTf, Et_3N, CH_2Cl_2; (b) IBX, MPO, DMSO

Conclusion

A formal total synthesis of platencin from a simple aromatic precursor **7** has been reported. 2-Hydroxymethyl-6-(3-hydroxy-hex-5-enyl)-phenol, readily prepared from 2-hydroxymethyl-6-allylphenol, in a few simple steps and straightforward manner was oxidized to give the dimer **13**. *In situ* generation of 6,6-spiroepoxycyclohexa-2,4-dienone by thermal activation of **13** and a tandem intramolecular Diels–Alder reaction led to the formation of adducts **5a**,**b** endowed with the tricyclic framework of platencin and requisite functionalities. Functional group manipulation of **5a**,**b** provided the intermediate **3**, which is a known precursor of platencin. The present synthesis demonstrates the versatility and synthetic potential of spiroepoxycyclohexa-2,4-dienones, and constitutes a nice example of the creation of molecular complexity from aromatics.

Experimental section

3-(2,2-Dimethyl-4*H*-1,3-benzodioxin-8-yl)propanal (10)

To a solution of compound **8** (11.00 g, 67.07 mmol) in acetone (100 mL) and 2,2-dimethoxypropane (25 mL) was added *p*-TsOH (400 mg) and the reaction mixture was stirred at room temperature. After completion of reaction (TLC, 6 h) the reaction mixture was neutralized by the addition of excess solid sodium bicarbonate. The mixture was concentrated under reduced pressure and the residue was diluted with water (100 mL) and extracted with diethyl ether (2 × 100 mL), washed with brine (50 mL), dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed on silica gel. Elution with petroleum ether–EtOAc (96 : 4) gave acetonide (12.00 g, 87%) [IR (film) ν_{max}: 1639, 1597,1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.04-6.99 (m, 1H); 6.86- 6.81 (m, 2H); 6.02-5.90 (m, 1H); 5.09-5.00 (m, 2H); 4.84 (s, 2H); 3.33 (d, J = 6.1 Hz, 2H); 1.55 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 136.9, 128.39, 128.34, 122.7, 120.1, 119.2, 115.5, 99.5, 61.1, 33.8, 25.0]. The acetonide thus obtained was subjected to hydroboration as described below.

To a suspension of sodium borohydride (5.00 g, 131.57 mmol) in dry THF (100 mL) was slowly added a dilute solution of iodine (13.36 g, 52.59 mmol) in dry THF (100 mL) under nitrogen atmosphere at 0 °C. The addition was complete in 2 h. It was further stirred for 30 min. A solution of acetonide (10.00 g, 49.01 mmol) in THF (15 mL) was then added and the reaction mixture was stirred for 2 h at ambient temperature. The reaction mixture was cooled to 0 °C and water (20 mL) followed by a solution of NaOH (3 N, 100 mL) was added to the reaction mixture at 0 °C. Subsequently, H_2O_2 (30%, 100 mL) was added to the reaction mixture slowly and stirred for one hour. The organic layer was separated and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extract was washed with brine and dried on anhydrous sodium sulfate and concentrated *in vacuo*. Removal of solvent followed by chromatography [petroleum ether–EtOAc (85 : 15)] gave an alcohol (10.50 g, 96%) [IR (film) ν_{max}: 3408, 1596, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.06-7.01 (m, 1H), 6.89-6.81 (m, 2H), 4.85 (s, 2H); 3.59 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 6.9 Hz, 2H), 1.88-1.80 (m, 2H), 1.55 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 129.5, 128.5, 122.3, 120.1, 118.9, 99.5, 61.5 60.9, 32.7, 25.0, 24.6] which was oxidized with IBX as described below.

To a solution of the above alcohol (9.00 g, 40.54 mmol) in ethyl acetate (300 mL) was added IBX (13.62 g, 48.64 mmol) and refluxed for 6 h. The reaction mixture was filtered through a sintered funnel and washed with EtOAc. The combined filtrate was concentrated under reduced pressure and the product was purified by column chromatography on silica gel. Elution with petroleum ether–EtOAc (92 : 8) provided the compound **10** (8.22 g, 92%). IR (film) ν_{max}: 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.81 (t, J = 1.3 Hz), 7.04-7.00 (m, 1H), 6.88-6.80 (m, 2H), 4.84 (s, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.75-2.70 (m, 2H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 148.9, 128.3, 128.1, 122.8, 119.9, 119.1, 99.5, 60.8, 43.6, 24.7, 22.7. HRMS (ESI) (m/z): found 221.1173 $[M+H]^+$; calcd for $C_{13}H_{17}O_3$ 221.1178.

1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-8-yl)hex-5-ene-3-ol (11)

To a suspension of magnesium (freshly activated, 3.27 g, 136.25 mmol) in dry THF (150 mL), a crystal of iodine was added and it was cooled to 0 °C. After which a dilute solution of allyl bromide (5.9 mL, 8.26 g, 68.26 mmol) in THF (250 mL) was added very slowly over 4 h with vigorous stirring at 0 °C. It was further stirred for 2 h at ambient temperature. A solution of the aldehyde **10** (5.00 g, 22.72 mmol) in dry THF (20 mL) was added to the reaction mixture at 0 °C. The reaction mixture was further stirred for 2 h at ambient temperature. After which it was cooled in an ice bath and a saturated solution of ammonium chloride (50 mL) was added and the reaction mixture was further stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 75 mL) and the combined organic extracts were dried on sodium sulfate and the solvent was removed *in vacuo*, and the product was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (90 : 10) gave the compound **11** (5.71 g, 96%) as a colorless liquid. IR (film) ν_{max}: 3435 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.04-7.00 (m, 1H), 6.86-6.79 (m, 2H), 5.89-5.75 (m, 1H), 5.13-5.06 (m, 2H), 4.83 (s, 2H), 3.57 (brs, 1H), 2.76-2.61 (m, 2H), 2.32-2.15 (m, 3H), 1.75-1.68 (m, 2H), 1.54 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 135.1, 129.9, 128.7, 122.5, 120.3, 119.1, 117.7, 99.7, 69.7, 69.6, 61.1, 41.7, 37.2, 25.4, 24.9. HRMS (ESI) (m/z): found 285.1465 $[M+Na]^+$; calcd for $C_{16}H_{22}O_3Na$ 285.1467.

2-Hydroxymethyl-6-(3-hydroxy-hex-5-enyl)-phenol (7)

To a solution of the acetal alcohol **11** (10.00 g, 38.16 mmol) in acetone–water (1 : 1, 200 mL) was added conc. HCl (10 mL

35%) at ~10 °C. and the reaction mixture was stirred at ambient temperature for 8 h. After which more HCl (2 mL 35%) was added and the reaction mixture was further stirred for 6 h. After completion of the reaction (TLC), the reaction mixture was cooled to 0 °C and neutralized by the addition of excess solid $NaHCO_3$. The organic solvent was removed under reduced pressure and the aqueous solution was extracted with ethyl acetate (3 × 100 mL). The combined organic extract was washed with brine (30 mL) and dried on Na_2SO_4. Removal of solvent and chromatography on silica gel [petroleum ether–EtOAc (75 : 25)] gave the compound **7** (7.80 g, 92%). IR (film) ν_{max}: 3391, 1641, 1594, 1465 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (brs, 1H), 7.04-7.02 (m, 1H), 6.92-6.79 (m, 1H), 6.75 (superimposed dd, $J_1 = J_2 = 8$ Hz, 1H), 5.80-5.73 (m, 1H), 5.18-5.09 (m, 2H), 4.73 (brs, 1H), 3.80 (brs, 1H), 3.59-3.55 (m, 1H), 3.20 (brs, 1H), 2.84-2.75 (m, 1H), 2.70-2.60 (m, 1H), 2.30-2.10 (m, 2H), 1.77-1.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 134.6, 130.2, 128.6, 126.2, 125.7, 120.1, 118.1, 69.6, 63.9, 41.8, 37.0, 25.5. HRMS (ESI) (*m*/*z*): found 245.1146 $[M+Na]^+$; calcd for $C_{13}H_{18}O_3Na$ 245.1154.

5,8-Bis(3-hydroxy-hex-5-enyl)-3,10-bis(spiroepoxy)*endo*-tricyclo [6.2.2.0^{2,7}]dodec-5,11-dien-4,9-dione (13) and the aldehyde (12)

To a solution of compound **7** (9.00 g, 40.54 mmol) in acetonitrile (150 mL) was added a solution of $NaIO_4$ (17.00 g, 79.47 mmol) in water (150 mL) dropwise at 10 °C (~2 h). The reaction mixture was then stirred for 3 h at ambient temperature. After which it was filtered on a Celite bed to remove inorganic salts. The organic layer was separated from the filtrate and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The organic extracts were combined and washed with brine (50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (90 : 10) first gave the aldehyde **12** (0.800 g, 9%) as a colorless thick liquid. Further elution with petroleum ether–ethyl acetate (60 : 40) gave the dimer **13** (5.95 g, 66%, a mixture of diastereoisomers) as a colorless thick liquid.

Data for **12**: IR (film) ν_{max}: 3401, 1649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 9.88 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 6.97 (superimposed dd, $J_1 = J_2 = 8.4$ Hz, 1H), 5.89-5.76 (m, 1H), 5.16-5.09 (m, 2H), 3.67-3.59 (m, 1H), 2.81 (t, J = 8 Hz, 2H), 2.36-2.06 (cluster of m, 3H), 1.84-1.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 159.7, 137.6, 134.9, 131.9, 130.7, 120.4, 119.9, 118.1, 69.8, 42.0, 36.7, 25.3. HRMS (ESI) (*m*/*z*): found 243.0999 $[M+Na]^+$; calcd for $C_{13}H_{16}O_3Na$ 243.0997.

Data for **13**: IR (film) ν_{max}: 3487, 1731, 1693, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.60-6.50 (m, 1H), 6.40-6.28 (m, 1H), 5.86-5.64 (m, 3H), 5.20-4.90 (m, 4H), 4.15-3.92 (m, 1H), 3.58-3.38 (m, 2H), 3.28 (s, 1H), 3.26 (d of part of an AB pattern, J = 5.5 Hz, 1H), 2.82-2.70 (m, merged with d of part of an AB pattern, J = 5.5 Hz, 3H), 2.62-2.42 (m, 2H), 2.34-1.84 (m, 9H), 1.76-1.66 (m, 1H), 1.60-1.40 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 194.1, 143.6, 141.7, 137.5, 134.9, 134.7, 129.2, 118.2, 116.8, 92.9, 69.9, 69.1, 66.2, 59.2, 58.6, 54.2, 48.0, 41.9, 41.3, 40.7, 38.5, 36.7, 26.5, 26.1 (major signals).

HRMS (ESI) (*m*/*z*): found 441.2275 $[M+H]^+$; calcd for $C_{26}H_{33}O_6$ 441.2277.

9-Spiroepoxy-4-hydroxy-tricyclo[6.2.2.0^{1,6}]dodec-11-ene-10-one (5a and 5b)

A solution of epoxy dimer **13** (4.20 g, 9.54 mmol) in *o*-dichlorobenzene (30 mL) was heated at 140 °C for 6 h. The reaction mixture was charged as such on silica gel. Dichlorobenzene was eluted out in petroleum ether. Elution with petroleum ether–EtOAc (60 : 40) first gave the less polar adduct **5a** (1.40 g, 33%) as a colorless liquid. IR (film) ν_{max}: 3442, 1731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.59 (superimposed dd, $J_1 = J_2 = 8.0$ Hz, 1H), 5.98 (d, J = 8.0 Hz, 1H), 4.08-4.04 (m, 1H), 3.14 (part of an AB system, J_{AB} = 6.4 Hz, 1H), 2.83 (part of an AB system, J_{AB} = 6.4 Hz, 1H), 2.54-2.48 (m, 1H), 2.44-2.32 (m, 2H), 2.30-2.18 (m, 1H), 1.92-1.60 (m, 5H), 1.42-1.32 (m, 1H), 1.14-1.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 134.5, 130.6, 65.2, 57.8, 53.1, 52.7, 37.8, 37.5, 30.0, 29.3, 28.2, 20.1.

HRMS (ESI) (*m*/*z*): found 243.0998 $[M+Na]^+$; calcd for $C_{13}H_{16}O_3Na$ 243.0997.

Further elution with petroleum ether–EtOAc (50 : 50) furnished the more polar adduct **5b** (2.31 g, 55%) as a solid, mp. 123–125 °C. IR (film) ν_{max}: 3373, 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.59 (dd, J_1 = 8.0 Hz, J_2 = 7.3 Hz 1H), 5.96 (d, J = 8.0 Hz, 1H), 3.63-3.53 (m, 1H), 3.13 (part of an AB system, J_{AB} = 6.1 Hz, 1H), 2.84 (part of an AB system, J_{AB} = 6.1 Hz, 1H), 2.56-2.48 (m, 1H), 2.43-2.35 (m, 1H), 2.10-1.70 (complex m, 6H), 1.46-1.34 (m, 1H), 1.24-1.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 134.3, 130.9, 69.3, 57.8, 53.1, 52.2, 40.3, 37.7, 35.9, 31.1, 29.5, 24.7. HRMS (ESI)(*m*/*z*): found 243.0996 $[M+Na]^+$; calcd for $C_{13}H_{16}O_3Na$ 243.0997.

Selected X-ray data for **5b**: C_{13} H_{16} O_3, M = 220.26, Monoclinic, space group $P2_1/c$, a = 12.448(3) Å, b = 6.840(3) Å, c = 13.210(4) Å, $\alpha = \gamma = 90°$, β = 110.22(3)°, V = 1055.5(6) Å^3, D_c = 1.386 Mg m^{-3}, Z = 4, F(000) = 472, Size: 0.32 × 0.28 × 0.23 mm^3, λ = 0.71073 Å, GoF = 1.053, μ = 0.097 mm^{-1}, Total/ unique reflections = 4908/ 1844 [R(int) = 0.0477], T = 150(2) K, θ range = 3.14 to 25.00°, Final R [$I > 2\sigma(I)$]: R_1 = 0.0546, wR_2 = 0.0835, R (all data): R_1 = 0.0978, wR_2 = 0.0932.

9-Spiroepoxy-tricyclo[6.2.2.0^{1,6}]dodec-11-ene-4,10-dione (14)

To a solution of the compound **5a** (1.40 g, 6.36 mmol) in CH_2Cl_2 (30 mL) was added PDC (4.78 g, 12.71 mmol) and the reaction mixture was stirred at ambient temperature for 10 h. It was filtered through a Celite bed, the filtrate was concentrated in *vacuo* and the resulting product was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate, (60 : 40) furnished the diketone **14** (1.05 g, 75%) as a solid, mp. 130–132 °C. IR (film) ν_{max}: 1732, 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (dd, J_1 = 8.2 Hz, J_2 = 6.7 Hz, 1H), 6.2 (d, J = 8.2 Hz, 1H), 3.19 (part of an AB system, J_{AB} = 6.2 Hz, 1H), 2.90 (part of an AB system, J_{AB} = 6.2 Hz, 1H), 2.66-2.62 (m, 1H), 2.54-2.34 (complex m, 5H), 2.27-1.94 (m, 3H), 1.25-1.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0, 205.3, 136.1, 129.9, 57.9, 53.4, 52.2, 45.9, 38.1, 37.8, 37.3, 30.0, 26.4. HRMS (ESI) (*m*/*z*): found 241.0846 $[M+Na]^+$; calcd for $C_{13}H_{14}O_3Na$ 241.0841.

Similarly, the compound **5b** (2.32 g, 10.54 mmol) was oxidized with PDC (7.93 g, 21.07 mmol) in CH_2Cl_2 (40 mL). Usual work-up and chromatography furnished the diketone **14** (1.98 g,

85%) as a solid which was identical to the compound prepared above.

9-Methyl-tricyclo-[6.2.2.0^{1,6}]dodec-11-ene-4,10-dione (15) and 9-hydroxymethyl-tricyclo[6.2.2.0^{1,6}] dodec-11-ene-4,10-dione (16)

To a solution of the compound **14** (0.90 g, 4.12 mmol) in MeOH–H_2O (5 : 1, 50 mL) was added zinc (activated 5.00 g, 79.36 mmol, excess) and NH_4Cl (1.00 g, 18.69 mmol, excess). The reaction mixture was stirred at ambient temperature. After completion of the reaction (TLC, 6 h), it was filtered on a Celite bed and washed with methanol (30 mL). The filtrate was concentrated under vacuum; the residue was diluted with water (50 mL) and extracted with ethyl acetate (4 × 30 mL). The combined extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by column chromatography. Elution with petroleum ether–ethyl acetate (85 : 15) first gave the compound **15** as a liquid (*syn*/*anti* mixture, 0.135 g, 15%). IR (film) ν_{max}: 1718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 and 6.63 (each as superimposed dd, $J_1 = J_2 = 8.0$ Hz, total 1H), 6.08 and 6.03 (each as d, J = 8.0 Hz, total 1H), 2.84-2.75 (m, 1H), 2.48-2.39 (m, 2H), 2.34-2. 00 (m, 7H), 1.10 (d, J = 5.8 Hz, 3H), 1.00 - 0.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.2, 209.8, 139.6, 128.2, 51.8, 46.2, 42.0, 37.7, 37.5, 37.3, 28.1, 26.9, 14.6. HRMS (ESI) (*m*/*z*): found 205.1228 [M+H]$^+$; calcd for $C_{13}H_{17}O_2$ 205.1229.

Further elution with petroleum ether–ethyl acetate (30 : 70) furnished β-keto alcohol **16** as a liquid (*syn*/*anti* mixture, 0.560 g, 62%). IR (film) ν_{max}: 3500, 1712 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 and 6.68 (each of these superimposed dd, $J_1 = J_2$ = 6.6 Hz, total 1H); 6.13 and 6.05 (each as d, J = 6.6 Hz, total 1H), 3.88-3.78 (m, 1H), 3.74-3.50 (m, 2H), 3.10-2.94 (m, 1H), 2.78-2.64 (m, 1H), 2.38-2.00 (m, 8H), 1.22-0.98 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.1, 209.2, 139.2, 128.2, 61.6, 51.9, 51.2, 49.3, 45.8, 37.7, 33.6, 28.5, 26.3 (major signals). HRMS (ESI)(*m*/*z*): found 243.0998 [M+Na]$^+$; calcd for $C_{13}H_{16}O_3Na$ 243.0997.

9-Hydroxymethyl-tricyclo[6.2.2.0^{1,6}]dodec-4,10-dione (17)

To a solution of alcohol **16** (0.500 g, 2.272 mmol) in EtOH (25 mL) was added Pd on carbon (5% wt/wt, 0.150 g) at room temperature. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 1 h. The reaction mixture was filtered on a pad of silica gel and the filtrate was concentrated *in vacuo*. The resulting product was purified by column chromatography on silica gel. Elution with petroleum ether–ethyl acetate (30 : 70) gave the title compound **17** as a colorless liquid (0.420 g, 84%). IR (film) ν_{max}: 3425, 1710 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10-3.86 (m, 1H), 3.78-3.62 (m, 1H), 2.96-2.80 (m, 1H), 2.60-2.30 (m, 6H), 2.28-1.64 (m, 7 H), 1.60-1.40 (m, 1H), 1.39-1.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.3, 210.0, 62.2, 53.9, 44.8, 44.5, 36.9, 35.8, 30.2, 29.7, 28.4, 26.3, 21.8 (major signals). HRMS (ESI)(*m*/*z*): found 223.1329 [M+H]$^+$; calcd for $C_{13}H_{19}O_3$ 223.1334.

9-Methylene-tricyclo[6.2.2.0^{1,6}]dodec-4,10-dione (18)

To a solution of alcohol **17** (0.42 g, 1.89 mmol) in pyridine (10 mL) was added tosyl chloride (0.54 g, 2.83 mmol) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured onto cold water (300 mL) and conc. HCl (5 mL). The resulting mixture was extracted with ether (3 × 80 mL) and the organic layer was washed with aq. $NaHCO_3$ (50 mL), H_2O (50 mL), aq. $CuSO_4$ (2 × 50 mL) and brine (50 mL). The organic layer was dried and concentrated under vacuum. The product was purified by column chromatography on silica gel. Elution with petroleum ether–ethyl acetate (75 : 25) gave tosylate (0.49 g, 69%) as a colorless liquid [IR (film) ν_{max}: 1715, 1597, 1452 cm^{-1}] which was subjected to elimination reaction as described below.

A solution of the above tosylate (0.49 g, 1.30 mmol) in pyridine (10 mL) was heated at 100 °C for 8 h, after which the reaction mixture was poured onto cold water (300 mL) and conc. HCl (5 mL). The resulting mixture was extracted with ether (3 × 80 mL) and the organic layer was washed with $NaHCO_3$ (50 mL) solution, H_2O (50 mL), aq. $CuSO_4$ (2 × 50 mL) and brine (50 mL). The organic layer was dried and the solvent was removed under vacuum. The product was purified by column chromatography on silica gel. Elution with petroleum ether–ethyl acetate (80 : 20) gave the compound **18** (0.22 g, 83%) as a solid, mp. 70–72 °C. IR (film) ν_{max}: 1707 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (d, J = 1.4 Hz, 1H), 5.26 (d, J = 1.4 Hz, 1H), 2.82-2.76 (m, 1H), 2.50-2.34 (m, 5H), 2.20-2.04 (m, 3H), 1.95-1.76 (m, 3H), 1.58-1.46 (m, 1H), 1.34-1.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 202.7, 146.8, 117.8, 44.9, 44.2, 36.9, 35.7, 35.1, 34.6, 28.4, 26.0, 21.3. HRMS (ESI)(*m*/*z*): found 227.1041 [M+Na]$^+$; calcd for $C_{13}H_{16}O_2Na$ 227.1048.

Selected X-ray data for **18**: $C_{13}H_{16}O_2$, M = 204.26, Orthorhombic, space group *Pbc*, a = 6.5326(19) Å, b = 16.022(7) Å, c = 21.032(6) Å, $\alpha = \beta = \gamma = 90°$, V = 2201.3(13) Å^3, D_c = 1.233 Mg m^{-3}, Z = 8, $F(000)$ = 880, Size: 0.28 × 0.23 × 0.18 mm^3, λ = 0.71073 Å, GoF = 0.827, μ = 0.082 mm^{-1}, Total/unique reflections = 9349/1932 [R(int) = 0.0376], T = 293(2) K, θ range = 3.20 to 25.00°, Final R [$I > 2\sigma(I)$]: R_1 = 0.0357, wR_2 = 0.0793, R (all data): R_1 = 0.0834, wR_2 = 0.0871.

9-Methylenetricyclo[6.2.2.0^{1,6}]dodecanespiro[4.2′]-1,3-dioxalan-10-one (19)

To a mixture of ethylene glycol (0.5 mL), *p*-toluene sulfonic acid (0.010 g, catalytic amount), and benzene (20 mL) dried in a Dean–Stark apparatus was added a solution of the ene-dione **18** (0.30 g, 1.47 mmol) in dry benzene (10 mL). The reaction mixture was refluxed for 4 h. It was cooled, and a saturated solution of sodium bicarbonate (20 mL) was slowly added. The benzene layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under vacuum, and the resulting product was chromatographed on silica gel [petroleum ether–ethyl acetate (80 : 20)] to give the keto-ketal **19** (0.346 g, 95%) as a solid, mp. 120–122 °C. IR (film) ν_{max}: 1706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (d, J = 1.8 Hz, 1H), 5.18 (d, J = 1.8 Hz, 1H), 3.98-3.88 (m, 4H), 2.72-2.66 (m, 1H), 2.34-2.22 (m, 1H), 2.08-1.90 (m, 3H), 1.84-1.60 (m, merged with signal due to H_2O in $CDCl_3$, 6H), 1.56-1.46 (m, 1H), 1.34-1.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0, 147.5, 116.7, 108.3, 64.4, 64.3, 44.0, 39.0, 35.8, 34.2, 32.0, 30.0, 26.35, 26.31, 21.0. HRMS (ESI)(*m*/*z*): found 249.1494 [M+H]$^+$; calcd for $C_{15}H_{21}O_3$ 249.1491.

9-Methylenetricyclo[6.2.2.0^{1,6}]dodecanespiro[4.2′]-1,3-dioxalan-10-yl acetate (20)

To a solution of compound **19** (0.100 g, 0.403 mmol) in methanol (16 mL) was added $CeCl_3 \cdot 7H_2O$ (0.9 g) at 0 °C. Sodium borohydride (0.012 g, 0.315 mmol) was then slowly added at 0 °C and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with water (5 mL) and extracted with diethyl ether (6 × 20 mL). The combined extract was washed with brine and dried on sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether–ethyl acetate] (75 : 25) gave an alcohol (0.098 g, 98%) as a colourless liquid (as a mixture of diastereoisomers) [IR (film) ν_{max}: 3452 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 and 5.05 (each of these superimposed dd, J_1 = J_2 = 1.6 Hz, total 1H), 5.02-4.98 (m, 1H), 3.93 (s, 4H), 3.85 and 3.76 (each of these brs, total 1H); 2.30-2.22 (m, 1H), 2.14-1.96 (m, 2H); 1.94-1.32 (m, 8H), 1.30-1.24 (m, 1H), 1.20-0.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 116.1, 108.9, 75.0, 64.2, 64.1, 39.5, 36.7, 35.6, 35.4, 34.3, 30.9, 28.7, 22.8, 16.9 (major signals). HRMS (ESI) (m/z): found 273.1454 [M+Na]$^+$; calcd for $C_{15}H_{22}O_3Na$ 273.1467]. The alcohol thus obtained was subjected to acetylation as described below.

To a solution of the above alcohol (0.100 g, 0.400 mmol) and DMAP (0.004 g, 0.032 mmol) in CH_2Cl_2-pyridine (10 mL, 20 : 1) at 0 °C was added acetic anhydride (0.20 g, 1.96 mmol). After stirring for 5 min the reaction was stirred at ambient temperature for 1 h. The reaction mixture was cooled to 0 °C and quenched with saturated aq. $NaHCO_3$ solution and the it was stirred vigorously at room temperature for 30 min after which the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with aq. HCl (0.1 M, 20 mL), water (20 mL) and brine (30 mL), and dried on Na_2SO_4. The solvent was removed under vacuum and the resulting product was purified by column chromatography on silica gel. Elution with petroleum ether–ethyl acetate (84 : 16) gave the acetate **20** as a colourless liquid (as a mixture of diasteroisomers) (0.100 g, 86%). IR (film) ν_{max}: 1736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 and 5.22 (each of these brm, total 1H), 4.99-4.88 (brm, 2H), 3.90 (s, 4H), 2.32-2.24 (m, 2H), 2.20-2.04 (m merged with two singlets, total 5H), 2.00-1.80 (m, 2H), 1.78-1.40 (m merged with signal due to H_2O, 6H), 1.20-1.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 151.4, 110.1, 108.6, 75.6, 64.4, 64.2, 39.7, 36.0, 35.6, 35.0, 30, 2, 28.8, 28.2, 25.8, 22.4, 21.4 (major signals). HRMS (ESI) (m/z): found 315.1580 [M+Na]$^+$; calcd for $C_{17}H_{24}O_4Na$ 315.1572.

9-Methylenetricyclo[6.2.2.0^{1,6}]dodecane spiro[4.2′]-1,3-dioxalane (21)

To a solution of **20** (0.100 g, 0.342 mmol) in THF (5 mL) was added a pre-mixed solution of Pd_2dba_3 (0.062 g, 0.067 mmol), PBu_3 (0.800 g, ~0.05 mL, 3.960 mmol), Et_3N (0.400 g, 0.6 mL, 3.960 mmol) and formic acid (0.180 g, ~0.15 mL, 3.913 mmol) in THF (2 mL) and the reaction mixture was refluxed. After 20 h the reaction mixture was cooled to room temperature, diluted with ether and the ether solution was washed with water (20 mL), aq. HCl (2 M, 2 × 20 mL), saturated aq. $NaHCO_3$ (2 × 30 mL) and brine (30 mL). The organic layer was dried on Na_2SO_4, the solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel. Elution with petroleum ether removed some impurities. Continued elution with petroleum ether–ethyl acetate (98 : 2) gave the compound **21** (0.045 g, 56%) as a solid, mp. 59–61 °C. IR (film) ν_{max}: 2923, 1648 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75-4.71 (m, 1H), 4.60-4.58 (m, 1H), 3.97-3.88 (m, 4H), 2.24-2.12 (m, 2H), 2.06-1.94 (m, 2H), 1.92-1.82 (m, 1H), 1.78-1.28 (m, 9H), 1.08-0.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 109.0, 104.7, 64.2, 64.0, 43.7, 39.6, 35.7, 35.3, 35.1, 34.5, 31.9, 30.5, 26.8, 23.8. HRMS (ESI) (m/z): found 235.1707 [M+H]$^+$; calcd for $C_{15}H_{23}O_2$ 235.1698.

9-Methylene-tricyclo[6.2.2.0^{1,6}]dodec-4-one (4)

To a solution of **21** (0.040 g, 0.170 mmol) in acetone–water (10 mL, 4 : 1) was added aq. HCl (10%, 0.5 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 10 h. The reaction mixture was neutralized with solid $NaHCO_3$ and the organic solvent was removed. The aqueous residue was extracted with diethyl ether (3 × 20 mL). The combined extract was washed with brine (20 mL) and dried on anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether–ethyl acetate 96 : 4] gave **4** (0.030 g, 92%) as a thick colorless liquid. IR (film) ν_{max}: 1713 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (q, J = 2.1 Hz, 1H), 4.63 (q, J_1 = 1.8 Hz, 1H), 2.50-2.10 (complex m, 7H), 2.06-1.92 (complex m, 2H), 1.90-1.78 (m, 1H); 1.78-1.64 (m, 3H), 1.53 (superimposed ddd, J_1 = J_2 = 13.5 Hz, J_3 = 5.4 Hz, 1H), 1.32-1.21 (m, 1H), 1.14 (ddd, J_1 = 12.5 Hz, J_2 = 5.7 Hz, J_3 = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.7, 150.8, 105.5, 46.2, 43.1, 38.8, 37.5, 36.7, 35.5, 35.4, 32.3, 26.5, 23.9. HRMS (ESI) (m/z): found 191.1445 [M+H]$^+$; calcd for $C_{13}H_{19}O$ 191.1436. The above data are in excellent agreement with those reported.[13d]

9-Methylene-tricyclo[6.2.2.0^{1,6}]dodec-2,3-diene-4-one (22) and 9-methylene-tricyclo[6.2.2.0^{1,6}]dodec-5,6-diene-4-one (3)

To a solution of ketone **4** (0.020 g, 0.105 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added triethyl amine (0.350 g, 3.465 mmol) and TMSOTf (0.380 g, 1.711 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, and further stirred at ambient temperature for 2 h. It was then diluted with pentane (50 mL). The resulting organic layer was separated and washed with saturated solution of $NaHCO_3$ (20 mL), brine (20 mL) and dried on Na_2SO_4 and concentrated under reduced pressure to give a light-yellow oil. This crude mixture of silyl enol ethers was dissolved in DMSO (0.5 mL), then a solution of IBX (0.420 g, 1.500 mmol) and 4-methoxypyridine *N*-oxide (MPO) (0.190 g, 1.520 mmol) in DMSO (0.5 mL) was added. The resulting mixture was protected from light and allowed to stir at ambient temperature for 18 h. The reaction mixture was then poured into aq. $NaHCO_3$ (5 mL) and extracted with ethyl acetate (6 × 10 mL). The combined organic extract was washed with brine (20 mL) and dried on Na_2SO_4 and concentrated under reduced pressure to give a yellow liquid. The product was purified by column chromatography on silica gel. Elution with petroleum ether–ethyl acetate (95 : 5) gave the desired compound **3** as a colorless liquid (0.010 g, 50%). Further elution with petroleum ether–ethyl acetate (92 : 8) gave the isomeric compound **22** as a liquid (0.005 g, 25%).

Data for compound **3**: IR (film) ν_{max}: 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.57 (d, J = 9.8 Hz, 1H), 5.87 (dd, J_1 = 9.8 Hz, J_2 = 0.9 Hz,1H), 4.83 (dt, J_1 = 3.0 Hz, J_2 = 1.8 Hz,1H), 4.69 (dd, J_1 = 3.7 Hz, J_2 = 1.6 Hz,1H), 2.50-2.39 (m, 2H), 2.38-2.28 (m, 2H), 2.22-2.07 (m, 2H), 2.06-1.96 (m, 1H),1.82-1.66 (m, 3H), 1.56-1.48 (m, 1H),1.22 (ddd, J_1 = 12.5 Hz, J_2 = 8.0 Hz, J_3 = 1.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 156.7, 148.8, 127.7, 106.8, 41.6, 40.8, 35.9, 35.5, 35.4, 34.8, 26.3, 24.4. HRMS (ESI) (m/z): found 211.1090 $[M+Na]^+$; calcd for $C_{13}H_{16}ONa$ 211.1099. These spectral features are in excellent agreement with the literature.[12b,13c,d]

Data for compound **22**: IR (film) ν_{max}: 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (t, J = 2.0 Hz, 1H), 4.86 (dd, J_1 = 3.5 Hz, J_2 = 1.7 Hz, 1H), 4.69 (dd, J_1 = 3.5 Hz, J_2 = 1.7 Hz, 1H), 2.80-2.24 (m, 7H), 1.84-1.65 (m, 5H), 1.56-1.48 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 170.0, 148.6, 124.1, 106.8, 39.7, 36.6, 36.3, 33.9, 32.1, 30.3, 29.6, 26.3. HRMS (ESI) (m/z): found 211.1109 $[M+Na]^+$; calcd for $C_{13}H_{16}ONa$ 211.1099. These features are in agreement with those reported.[13d]

Crystal structure determination

Single crystal X-ray structural studies of **5b** and **18** were performed on a CCD Oxford Diffraction XCALIBUR-S diffractometer equipped with an Oxford Instruments low-temperature attachment. Data were collected at 150(2) K and 293(2) K for **5b** and **18**, respectively, using graphite-monochromoated Mo-Kα radiation (λ_α = 0.71073 Å). The strategy for the data collection was evaluated by using the CrysAlisPro CCD software. The data were collected by the standard phi-omega scan techniques, and were scaled and reduced using CrysAlisPro RED software. The structures were solved by direct methods using SHELXS-97[20] and refined by full matrix least squares with SHELXL-97, refining on F^2. The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in geometrically constrained positions and refined isotropically. The hydrogen atom of the hydroxyl group [(H101 and H102) over O1] in the structure of compound **5b** was found to be disordered and was refined by assigning 0.5 partial occupancy. However, one of the disordered hydrogen atoms has been removed for clarity in the ORTEP diagram (Fig. 3).

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