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Cycloaddition of annulated cyclohexa-2,4-dienones and novel reduction of halogen at bridgehead: an expedient route to tetracyclo[6.5.2.0^{2,7}.0^{9,13}]-pentadec-2(7),11-dien-14-one and framework of conidiogenol and conidiogenone

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ABSTRACT

An expedient route to tetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2(7),11-dien-14-one and tetracyclic framework of conidiogenol have been reported. Cycloaddition of annulated cyclohexa-2,4-dienone with cyclopentadiene, photochemical oxa-di-π-methane reaction and a highly unusual dehalogenation of bridgehead halogen are the key features of our methodology.

1. Introduction

Recently, Sterner and co-workers isolated two new diterpenes from the extracts of fermentation broth of *Penicillium cyclopium*, which were found to induce conidiogenesis in the producing organism.[1a] These diterpenoids were identified as conidiogenol **1** and conidiogenone **2** (Fig. 1), which have a unique tetracyclic molecular architecture containing a linear triquinane annulated with a six-membered ring in angular fashion. Most recently, several analogues of **2** were isolated from marine microorganism *Penicillium* sp.[1b] It seems, there are no synthetic approaches to conidiogenol **1** and the ketone **2** despite their potent conidiation inducing activity, though there are a few routes to the tetracyclic systems related to **1** and **2**, which were developed earlier in context of synthesis of megallanane family of alkaloids.[2]

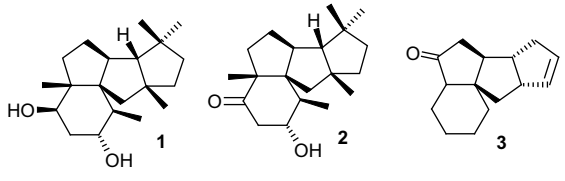

Figure 1.

In continuation of our studies[3] on development of new methods from simple aromatics based on the chemistry of cyclohexa-2,4-dienones, their cycloaddition and photochemical reaction we considered developing a route to the tetracyclic compound such as **3**, which contains carbocyclic network of conidiogenol and conidiogenone and wish to report our results herein.

Initially, we envisioned that the tetracyclic system of type **3** could be derived from **4** by a regioselective cleavage of the cyclopropane ring and that the intermediate **4** would be obtained from the bridged tricyclic compound **5** via oxa-di-π-methane rearrangement or photochemical 1,2-acyl shift. The chromophoric system **5** was thought to be derived from the ketoepoxide **6** and that the ketoepoxide itself would be amenable from the hydroxymethyltetrahydronaphthol **8** via its oxidation to annulated cyclohexa-2,4-dienone **7** and $\pi^{4s}+\pi^{2s}$ cycloaddition with cyclopentadiene (Scheme 1).

It is interesting to note that the pentacyclic system **4** would be generated in a single stereoselective step. Further, all the carbon atoms, which form the basic tetracyclic network of **3** are assembled in a single step with correct connectivity and relative stereochemical orientation, from a simple precursor **8**. Moreover, the

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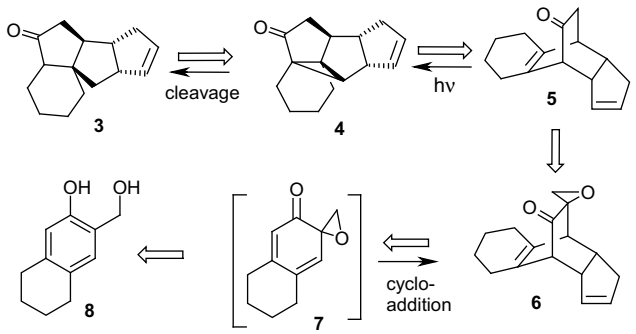
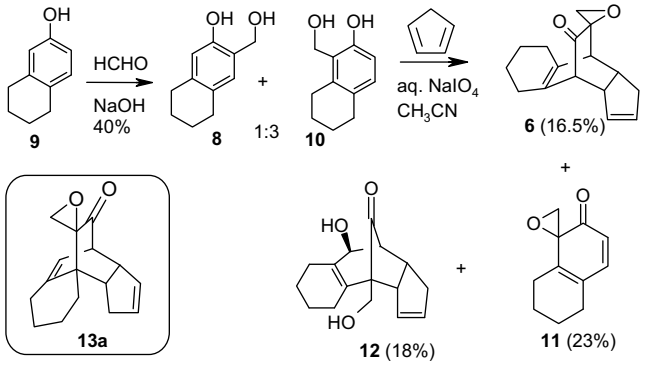


Scheme 1.

β,γ-enone moiety that is required for the transformation of bridged structure into a ring fused structure is also generated in the very first step of the synthetic sequence.

2. Results and discussion

In order to prepare the aromatic precursor **8**, tetrahydronaphthol **9** was hydroxymethylated, which gave a mixture of **8** and **10** that was inseparable by chromatography.[4] Therefore, we thought to use the same mixture for the generation of cyclohexadienones and interception with cyclopentadiene with a hope that the resulting adducts would be easily separable. Thus, the mixture of **8** and **10** was oxidized with sodium metaperiodate[5] in the presence of cyclopentadiene following a procedure developed in our laboratory.[6] Work-up gave a mixture of products from which the unreacted cyclohexadienone **11**[3b] (derived from **10**), a highly unusual product **12**, and the desired adduct **6** were isolated by a careful chromatography (Scheme 2).



Scheme 2.

While, the structure of **6** was easily deduced from its spectral data and comparison,[3] structure of the unusual product **12** was deduced as follows. The IR spectrum of compound **12** showed absorption bands at 3453, 3333, 1727 cm^{-1} for hydroxyl and carbonyl groups. Its ^1H NMR (300 MHz) spectrum exhibited signals at δ 5.88–5.84 (ddd, J_1=6 Hz, J_2=3.3 Hz, J_3=2.5 Hz, 1H), 5.59–5.55 (ddd, J_1=6 Hz, J_2=4.2 Hz, J_3=2.5 Hz, 1H) for two olefinic protons. Further signals were observed at δ 4.42 (d, J=3.3 Hz, 1H), 3.94 (part of an AB system, J_{AB}=12 Hz, 1H), 3.85 (part of an AB system, J_{AB}=12 Hz, 1H), 3.18–3.12 (m, 1H), 2.99–2.88 (m, 1H), 2.73 (dd, J_1=8 Hz, J_2=3.3 Hz, 1H), 2.49–2.22 (m, 6H), 2.20–2.05 (m, 1H), 1.90–1.60 (m, 3H), 1.53–1.24 (m, 2H). Its ^{13}C NMR (100 MHz) spectrum displayed signals at δ 218.8, 137.0, 134.3, 133.4, 127.2 for carbonyl group and four olefinic carbons. Further signals are observed at δ 78.9, 61.2, 58.1, 54.0, 51.8, 34.0, 32.5, 27.2, 26.8, 22.15, 22.11 for other carbons. These spectral features suggested that it is not the expected adduct **13a**, which may arise by the cycloaddition of **11** (formed as a result of oxidation of **10**). Moreover, HRMS suggested the presence of three oxygens in its molecular structure. The above spectral features clearly indicated that a major structural reorganization had occurred during the above reaction. However, it was very difficult to ascertain the structure of the product from the spectral data alone. Hence, X-ray structure was undertaken, which established its formulation as **12** (Fig. 2).

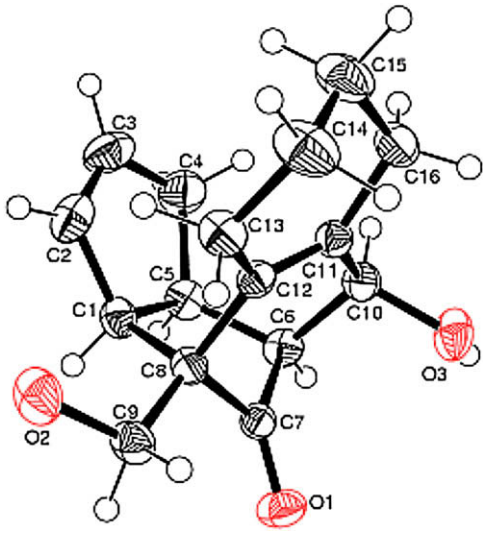
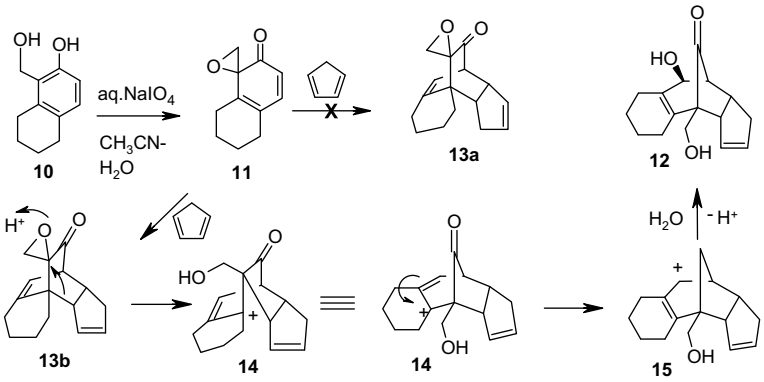


Figure 2. ORTEP diagram of compound **12**.

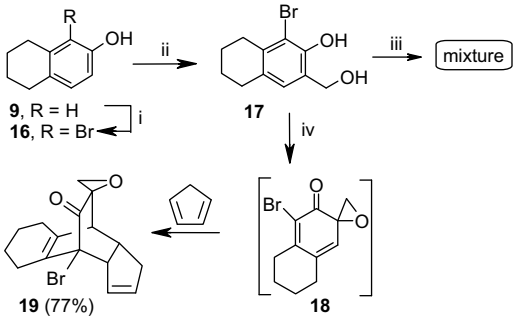
A probable mechanism of formation of **12** is shown below (Scheme 3). It appears that the reaction of cyclohexadienone **11** arising from the oxidation of **10**, with cyclopentadiene did not give adduct of type **13a**, instead it led to the formation of unusual regioisomer **13b**. It may be mentioned that in general cycloaddition of spiroepoxycyclohexa-2,4-dienones with cyclopentadiene gives the adducts of type **13a** (wherein the double bond of the cyclopentane ring is closer to the carbonyl group).[3] Presumably the steric interaction between six-membered ring and methylene of the cyclopentene ring in **13a** led to the alternate mode of addition and formation of **13b**. The adduct **13b** subsequently undergoes opening of the oxirane ring under the reaction conditions (acidic) and a 1,2-shift to give the allyl cation **14**. Migration of the double bond in **14** gives the more stable carbocation **15** whose interception with water gives the final product **12** (Scheme 3).

While we could prepare the desired tetracyclic ketoepoxide **6** as described above, we considered developing an alternate preparation of **8** (and hence **6**). It was thought that tetrahydronaphthol **9** may be converted into bromo derivative **16**, which upon hydroxymethylation would give **17** and removal of bromine would furnish the desired precursor **8**.

Thus, regioselective bromination of **9** with NBS as described[7] gave **16** in excellent yield (92%). Hydroxymethylation of **16** also proceeded well and gave compound **17** in good yield (78%). However, reduction of bromine in **17** proved to be difficult, as the treatment of bromo compound **17** with Raney Ni gave an inseparable mixture of products containing **8** in variable yields (Scheme 4). Therefore, we considered preparing tricyclic compound **19** with a hope to remove the halogen at later stages of the sequence. Thus, a solution of compound **17** in acetonitrile containing a freshly cracked cyclopentadiene was oxidized with $NaIO_4$,



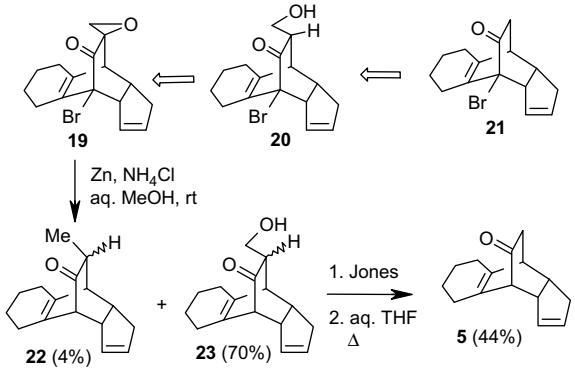
Scheme 3.



Scheme 4. Reagents and conditions: (i) NBS, DMF, 92%; (ii) HCHO, NaOH, 78%; (iii) Raney Ni, H_2, KOH; (iv) aq $NaIO_4$, CH_3CN.

which furnished the adduct **19** in very good yield (77%) (Scheme 4). The structure of adduct was revealed from its spectral data and comparison with the structural features of the related compound prepared earlier.

It was thought that the reduction of oxirane ring in **19** with zinc would give the β-hydroxymethyl ketone **20**, which upon oxidation and decarboxylation would provide the bromoketone **21**. Subsequent reductive dehalogenation in **21** would then give desired tetracyclic chromophoric system **5** (Scheme 5). Thus, the ketoepoxide **19** was subjected to reduction with activated zinc and ammonium chloride in aq methanol according to the procedure developed in our laboratory.[3a] Surprisingly, chromatography of the product mixture gave the β-keto alcohol **23** as major product [*syn*:*anti* mixture] along with minor amounts of **22**, *which were devoid of bromine* (Scheme 5).

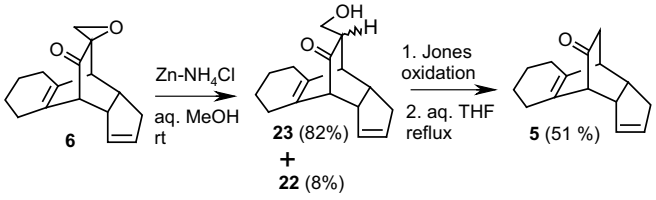


Scheme 5.

The spectral features (^{1}H NMR and ^{13}C NMR), and especially the HRMS data of compounds **22** and **23** suggested that these compounds do not contain bromine. The HRMS of keto alcohol **23** showed a peak at *m*/*z* 267.1371 $(M+Na)^+$ corresponding to molecular formula $C_{16}H_{20}O_2$. It also exhibited a peak at *m*/*z* 245.1537 $[(M+Na)^+-H_2O]$, a characteristic of primary alcoholic functional group. Similarly, the mass spectrum of compound **22** also showed peak at *m*/*z* 229.1581 $(M+H)^+$ corresponding to the molecular formula $C_{16}H_{20}O$.

The β-hydroxymethyl ketone **23** thus obtained was oxidized with Jones reagent and the resulting β-keto-acid was decarboxylated to give the desired tetracyclic compound **5** whose structure was deduced from the following spectral features. The IR spectrum of **5** showed band at 1717 cm^{-1} for carbonyl group. Its ^{1}H NMR (300 MHz) spectrum showed characteristic signals at δ 5.66–5.62 (m, 1H), 5.38–5.34 (m, 1H) for two olefinic protons. Other protons exhibited signals at δ 3.22–3.15 (m, 1H), 2.85 (d, J=2.6 Hz, 1H), 2.65–2.48 (m, 3H), 2.18–1.88 (m, 6H), 1.82–1.72 (m, 1H), 1.62–1.55 (m, merged with signal due to water in $CDCl_3$, 4H). The ^{13}C NMR (75 MHz) spectrum showed signals at δ 213.5 for carbonyl carbon and δ 136.5, 132.4, 129.6, 129.1 for four olefinic carbons. Other carbons showed signals at δ 57.6, 48.8, 42.0, 41.1, 40.0, 38.3, 30.0, 28.5, 22.9, 22.8 (all the 15 carbons). The HRMS showed a peak at (*m*/*z*): 237.1262 $(M+Na)^+$ corresponding to its molecular formula $C_{15}H_{18}O$. This also confirmed the structure of the β-hydroxymethyl ketone and that dehalogenation had occurred during reduction of the bromoketoepoxide **19** with zinc–NH_4Cl.

In order to further confirm the structures of **22**, **23** and **5**, compound **5** was also prepared from adduct **6**. Thus, the adduct **6** was treated with zinc–NH_4Cl to give a β-keto alcohol, which was identical with **23** and the ketone **22**. Oxidation of the β-keto alcohol **23** and subsequent decarboxylation gave compound **5**, which was prepared earlier from the adduct **19** (Scheme 6).



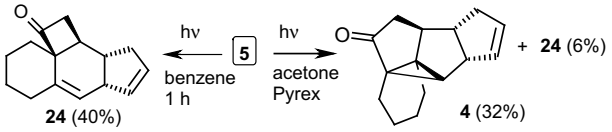
Scheme 6.

These studies further confirmed that reductive dehalogenation had occurred during the reaction of adduct **19** with zinc–NH_4Cl in addition to the reduction of the oxirane group. The aforementioned dehalogenation though fortuitous was indeed highly surprising. While reduction of halogens α- to a carbonyl group by zinc is well known,[8] reduction of bridgehead halogen is generally not observed.

Having prepared the chromophoric system **5**, its photochemical reaction was explored. Photoreaction of β,γ-enones have

stimulated interest for long time,[9] which has enhanced recently by virtue of its synthetic potential.[10,11] In general, β,γ-enones undergo a 1,2-acyl shift or the oxa-di-π-methane rearrangement, upon triplet excitation and 1,3-acyl shift on singlet excitation, respectively. However, it also depends upon the structure of the chromophoric system and functional group in a subtle fashion.

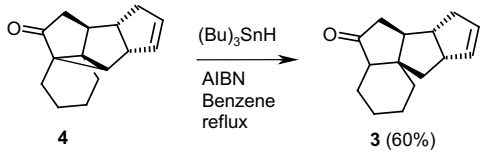
Thus, a solution of the tetracyclic compound **5** in acetone (both solvent and sensitizer) was irradiated with medium pressure mercury vapour lamp (125 W) in a Pyrex immersion well. Removal of solvent followed by chromatography of the photolysate gave the desired photoproduct **4** in moderate yield (32%) as a result of oxa-di-π-methane reaction, along with a minor amount of **24** (6%) arising via a 1,3-acyl shift (Scheme 7).



Scheme 7.

The 1,3-acyl shift product **24** formed during sensitized irradiation apparently arise from the excited singlet state, which may be generated by direct absorption. In some cases, 1,3-acyl shift is also known to occur from T2 state. Direct irradiation of a solution of **5** in dry benzene gave the 1,3-acyl shift product **24** as a major product, as expected (Scheme 7). However, the formation of compound **4** was not observed during direct irradiation (1S). Though, the efficiency of oxa-di-π-methane reaction is only moderate, it provides a stereoselective avenue to the pentacyclic product **4**, which is not readily accessible otherwise.

In order to prepare the tetracyclic system **3**, compound **4** was treated with tributyltin hydride–AIBN[12] in refluxing benzene to give the tetracyclic compound **3** in good yield (Scheme 8) whose structure was clearly revealed from its spectral features.



Scheme 8.

3. Conclusion

In summary, we have described an efficient stereoselective approach to a tetracyclic framework of conodiogenol from a simple aromatic precursor. Our methodology involves transformation of annulated *o*-hydroxymethylphenol into cyclohexadienone and its cycloaddition with cyclopentadiene to give tetracyclic adduct containing a β,γ-enone chromophore. Further manipulation of adduct followed by photochemical rearrangement and cleavage of the peripheral cyclopropane bond furnished the tetracyclic network of conidiogenol in stereoselective manner. In addition, unusual rearrangement and a novel dehalogenation with zinc have also been described. The present methodology provides a nice example of creating molecular complexity from simple precursors, a desirable aspect of the development of new methods.[13,14]

4. Experimental section

4.1. General remarks

IR spectra were recorded on Nicolet Impact 400 FT-IR Instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian VXR 300 instrument. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on Mercury Varian 400 MHz instrument. The samples were dissolved in $CDCl_3$ as solvent and $SiMe_4$ as internal standard. The high resolution mass spectra were recorded on Q-Tof micro (YA-105) Mass Spectrometer. Melting points were determined on a Veego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous sodium sulfate. Reactions were monitored with thin layer chromatography and spots were visualized with iodine vapour. Column chromatography was performed using SRL/Thomas Baker silica gel (60–120 and 100–200 mesh). The elution was done with petroleum ether (60–80 °C) and ethyl acetate mixture.

*4.1.1. 15-Spiroepoxytetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2(7),11-dien-14-one (**6**), cyclohexa-2,4-dienone (**11**) and 8-hydroxy-1-hydroxymethyltetracyclo[7.5.1.0^{2,7}.0^{10,14}] pentadec-2(7),12-diene-15-one (**12**).* To a solution of compounds **8** and **10** (0.890 g, 5 mmol) in acetonitrile (30 mL) was added freshly cracked cyclopentadiene (5 mL, excess) followed by the addition of a saturated solution of sodium *meta*periodate (2.4 g, 11.2 mmol) drop wise (~15 min) at ~0 °C. After stirring the reaction mixture in ice bath for additional two and half hours, the reaction mixture was further stirred at room temperature (~30 °C) overnight. After which the reaction mixture was saturated with sodium chloride and the organic layer was separated and aqueous layer was extracted with ethyl acetate (4×10 mL). The organic extract was combined and dried on anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was chromatographed on silica gel. Elution with petroleum ether gave some impurities and unreacted cyclopentadiene. Further elution with petroleum ether–ethyl acetate (95:5) afforded adduct **6** (0.200 g, 16.5%). Continued elution with petroleum ether–ethyl acetate (90:10) furnished known[3b] cyclohexadienone **11** (0.200 g, 23%). Further elution with petroleum ether–ethyl acetate (60:40) furnished compound **12** (0.234 g, 18%) as a solid that was recrystallised from petroleum ether–ethyl acetate.

*Data for **6**.* Mp 100–102 °C. R_f (20% EtOAc–petroleum ether) 0.6; IR (KBr) ν_{max}: 1736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.74–5.68 (ddd, J_1=5.4 Hz, J_2=4.8 Hz, J_3=2.0 Hz, 1H), 5.42–5.37 (m of d, J=5.4 Hz, 1H), 3.38–3.32 (m, 1H), 3.12 (part of an AB system, J_{AB}=6 Hz, 1H), 3.05 (d, J=2.7 Hz, 1H), 3.02–2.93 (m, 1H), 2.86 (part of an AB system, J_{AB}=6 Hz, 1H), 2.66–2.53 (m, 1H), 2.24 (d, J=2.7 Hz, 1H), 2.20–2.11 (m, 1H), 2.11–1.94 (m, 3H), 1.89–1.78 (m, 1H), 1.68–1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.3, 134.6, 133.1, 130.3, 129.0, 58.6, 57.0, 52.3, 49.6, 48.0, 37.9, 36.0, 30.1, 28.4, 22.6, 22.5. HRMS (ESI) (*m*/*z*): found 265.1208 [M+Na]$^+$. $C_{16}H_{18}O_2Na$ requires 265.1204.

*Data for **12**.* Mp 174–178 °C. R_f (50% EtOAc–petroleum ether) 0.4; IR (KBr) ν_{max}: 3453, 3333, 1727 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88–5.84 (ddd, J_1=6 Hz, J_2=3.3 Hz, J_3=2.5 Hz, 1H), 5.59–5.55 (ddd, J_1=6 Hz, J_2=4.2 Hz, J_3=2.5 Hz, 1H, olefinic proton), 4.42 (d, J=3.3 Hz, 1H), 3.94 (part of an AB system, J_{AB}=12 Hz, 1H), 3.85 (part of an AB system, J_{AB}=12 Hz, 1H), 3.18–3.12 (m, 1H), 2.99–2.88 (m, 1H), 2.73 (dd, J_1=8 Hz, J_2=3.3 Hz, 1H), 2.49–2.22 (m, 6H), 2.20–2.05 (m, 1H), 1.90–1.60 (m, 3H), 1.53–1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.8, 137.0, 134.3, 133.4, 127.2, 78.9, 61.2, 58.1, 54.0, 51.8, 34.0, 32.5, 27.2, 26.8, 22.15, 22.11. HRMS (ESI) (*m*/*z*): found 283.1309 [M+Na]$^+$. $C_{16}H_{20}O_3Na$ requires 283.1310.

*Crystal data of **12**.* $C_{16}H_{20}O_3$, M=260.32, triclinic, space group P-1, a=7.6060(16) Å, b=7.8830(9) Å, c=12.5260(17) Å, α=90.604(10)°, β=107.024(14)°, γ=115.530(15)°, U=639.82(18) Å^3, D_c=1.346 mg/m^3, Z=2, F(0,0,0)=278, λ=0.71073 Å, μ=0.092 mm^{-1}, total/unique reflections=2409/2225 [R(int)=0.0174], T=293(2) K, θ range=1.72–24.97°, final $R[I>2\sigma(I)]$, $R1$=0.0462, $wR2$=0.1142, R (all data): $R1$=0.0847, $wR2$=0.1288. The complete crystal data can be obtained

free of charge from The Cambridge Crystallographic data Centre via www.ccdc.cam.ac.uk/data_request/cif quoting the CCDC number 695219.

*4.1.2. 1-Bromo-5,6,7,8-tetrahydro-3-hydroxymethyl-2-naphthol (**17**).* To a solution of compound **16** (10.54 g, 46.4 mmol) in aq NaOH (3.7 g, 92 mmol, in 100 mL), formaldehyde (37–40%, excess) was added at ~0–5 °C. After 5 min ice bath was removed and reaction mixture was stirred for 24 h at room temperature. After completion of the reaction (TLC) the reaction mixture was neutralized with ammonium chloride and the resulting solution was extracted with ethyl acetate (4×50 mL). Combined organic extracts were dried (anhydrous Na_2SO_4), evaporated under reduced pressure and residue was chromatographed. Elution with petroleum ether–ethyl acetate (85:15) gave compound **17** (9.4 g, 78%). Mp 84–86 °C. R_f (20% EtOAc–petroleum ether) 0.6; IR (KBr) ν_{max}: 3543, 3478 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 4.71 (s, 2H), 2.71–2.67 (m, 4H), 1.82–1.69 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 136.4, 130.7, 128.0, 124.4, 113.7, 62.6, 30.4, 29.3, 23.2, 22.8. HRMS (ESI) (*m*/*z*): found 278.9999 $[M+Na]^+$. $C_{11}H_{13}BrO_2Na$ requires 278.9997.

*4.1.3. 1-Bromo-15-spiroepoxytetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2(7),11-dien-14-one (**19**).* A solution of compounds **17** (1.3 g, 5.07 mmol) in acetonitrile (30 mL) was cooled at ~0–5 °C. To this were added freshly cracked cyclopentadiene (5 mL, excess) and a saturated aq solution of sodium *meta*periodate (2.4 g, 11.2 mmol, 50 mL H_2O) drop wise. After stirring the reaction mixture in ice bath for additional two and half hours, the reaction mixture was stirred at room temperature overnight. The reaction mixture was saturated with sodium chloride and the organic layer was separated and aqueous layer was extracted with ethyl acetate (4×20 mL). The combined extract was dried, solvent was removed and residue was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (90:10) afforded adduct **19** (1.25 g, 77%). Mp 106–108 °C. R_f (20% EtOAc–petroleum ether) 0.6; IR (film) ν_{max}: 1743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.85–5.80 (m, 1H), 5.69–5.63 (m, 1H), 3.57–3.53 (m, 1H), 3.22 (part of an AB system, J_{AB}=6.4 Hz, 1H), 3.07–3.00 (m, 1H), 2.95 (part of an AB system, J_{AB}=6.4 Hz, 1H), 2.72–2.62 (m, 1H), 2.28 (d, *J*=2.8 Hz, 1H), 2.23–2.0 (m, 5H), 1.64–1.58 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 135.3, 134.7, 130.4, 128.6, 77.5, 59.1, 57.8, 53.0, 47.3, 39.0, 37.5, 30.9, 28.8, 23.1, 22.3. HRMS (ESI) (*m*/*z*): Found 343.0323 $[M+Na]^+$. $C_{16}H_{17}BrO_2Na$ requires 343.0310.

*4.1.4. 15-Hydroxymethyltetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2(7),11-dien-14-one (**23**) and 15-methyltetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2(7),11-dien-14-one (**22**).* To a solution of epoxy ketone **19** (0.950 g, ~3 mmol) in methanol–water (6:1, 84 mL) were added zinc (activated, 6.0 g, excess) and ammonium chloride (1 g, 18.7 mmol). The reaction mixture was stirred at ambient temperature for 8 h. The reaction mixture was then filtered through a Celite bed and washed with ethyl acetate (4×5 mL). The filtrate was combined and solvent was removed in vacuo. Water was added to the residue and extracted with ethyl acetate (4×25 mL). The combined extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography. Elution with petroleum ether–ethyl acetate (95:5) gave compound **22** (0.030 g, ~4%), elution with petroleum ether–ethyl acetate (80:20) gave β-keto alcohol **23** (0.510 g, 70%) as a mixture of *syn*–*anti* isomers.

*Data for **23**.* R_f (20% EtOAc–petroleum ether) 0.3; IR (neat) ν_{max}: 3429, 1715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.67–5.62 (m, 1H), 5.37–5.35 (m, 1H), 3.87–3.82 (m, 1H), 3.69–3.58 (m, 1H), 3.23–3.11 (m, 1H), 2.87 (d, *J*=2.4 Hz, 1H), 2.78–2.62 (m, 1H), 2.61–2.58 (m, 1H), 2.58–2.40 (m, 1H), 2.27–2.14 (m, 2H), 2.07–1.77 (m, 3H), 1.80–1.60 (m, 2H), 1.6–1.4 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.0, 137.4, 132.8, 129.3, 62.3, 57.7, 50.9, 49.7, 44.1, 38.1, 34.8, 29.9, 28.4, 22.89, 22.82 (signals due to major isomer). HRMS (*m*/*z*): found 267.1371 $[M+Na]^+$. $C_{16}H_{20}O_2Na$ requires 267.1361.

*Data for **22**.* Mp 50–52 °C. R_f (20% EtOAc–petroleum ether) 0.8; IR (film) ν_{max}: 1721 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.67–5.63 (m, 1H, olefinic proton), 5.37–5.33 (m, 1H, olefinic proton), 3.11–3.04 (m, 1H), 2.83–2.75 (m, 2H), 2.56–2.45 (m, 1H), 2.41–2.31 (m, 1H), 2.20–1.90 (m, 5H), 1.82–1.73 (m, 1H), 1.72–1.50 (m, 4H), 1.12, 1.05 (two d, *J*=7.3 Hz, total 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.3, 137.4, 132.4, 129.4, 128.8, 57.3, 49.1, 47.6, 43.3, 37.8, 33.6, 29.8, 28.1, 22.7, 22.6, 14.1. HRMS (ESI) (*m*/*z*): found 229.1581 $[M+H]^+$. $C_{16}H_{21}O$ requires 229.1592.

*4.1.5. Tetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2(7),11-dien-14-one (**5**).* To a solution of β-keto alcohol **23** (0.532 g, 2.18 mmol) in acetone (30 mL) was added freshly prepared Jones reagent drop wise at ~5 °C. After completion of the reaction (TLC) acetone was removed under vacuum. The residue was diluted with water (10 mL) and extracted with ethyl acetate (4×10 mL). The extract was combined, dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give the β-keto-acid, which was dissolved in the THF–H_2O mixture (1:1, 10 mL) and refluxed for 12 h. The reaction mixture was saturated with NaCl and organic layer was separated. The aqueous layer was extracted with ether (3×20 mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by column chromatography. Elution with petroleum ether–ethyl acetate (90:10) gave compound **5** (0.204 g, 44%) as a colourless solid. Mp 112–114 °C. R_f (20% EtOAc–petroleum ether) 0.8; IR (KBr) ν_{max}: 1717 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.66–5.62 (m, 1H, olefinic proton), 5.38–5.34 (m, 1H, olefinic proton), 3.22–3.15 (m, 1H), 2.85 (d, *J*=2.7 Hz, 1H), 2.65–2.48 (m, 3H), 2.18–1.88 (m, 6H), 1.82–1.72 (m, 1H), 1.62–1.55 (m, merged with signal due to water present in $CDCl_3$, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.5, 136.5, 132.4, 129.6, 129.1, 57.6, 48.8, 42.0, 41.1, 40.0, 38.3, 30.0, 28.5, 22.9, 22.8. HRMS (ESI) (*m*/*z*): found 237.1262 $[M+Na]^+$. $C_{15}H_{18}ONa$ requires 237.1255.

*4.1.6. Tetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2(**7**),11-dien-14-one (**5**) prepared via adduct **6**.* To a solution of epoxy ketone **6** (0.650 g, 2.7 mmol) in methanol–water (6:1, 28 mL) were added zinc (activated, 6.0 g, excess) and ammonium chloride (1 g, 18.7 mmol). The reaction mixture was stirred at ambient temperature for 8 h. The reaction mixture was then filtered through a Celite bed and washed with ethyl acetate (4×5 mL). The combined filtrate was concentrated in vacuo and water was added to the residue and extracted with ethyl acetate (4×25 mL). The combined extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography. Elution with petroleum ether–ethyl acetate (95:5) gave compound **22** (0.049 g, 8%), continued elution with petroleum ether–ethyl acetate (80:20) gave β-keto alcohol **23** (0.536 g, 82%), which were identical with those obtained earlier.

To a solution of β-keto alcohol **23** thus obtained (0.552 g, 2.3 mmol) in acetone (30 mL) at 5 °C was added freshly prepared Jones reagent drop wise. After completion of the reaction (TLC) acetone was removed under vacuum. The residue was diluted with water (10 mL) and extracted with ethyl acetate (4×10 mL). The extract was combined, dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give the β-keto-acid, which was dissolved in the THF–H_2O mixture (1:1, 10 mL) and refluxed for ~12 h. The reaction mixture was saturated with NaCl and the organic layer was separated. The aqueous layer was further extracted with ether (3×20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude

product was purified by column chromatography. Elution with petroleum ether–ethyl acetate (90:10) gave compound **5** (0.248 g, 51%) as a colourless solid, which was found identical in all respect to the compound prepared earlier.

*4.1.7. Pentacyclo[7.6.0.0^{1,6}.0^{6,15}.0^{10,14}]pentadec-12-en-7-one (**4**).* A solution of the enone **5** (0.074 g, 3.21 mmol) in degassed acetone (100 mL, solvent as well as sensitizer) was irradiated with mercury vapour lamp (125 W) in a Pyrex immersion well for 1.25 h under nitrogen. Acetone was removed under vacuum and the residue was chromatographed. Elution with petroleum ether–ethyl acetate (95:5) first gave the minor compound **24** (0.004 g, 6%), which was found to be identical with the compound prepared by direct irradiation as described below.

Continued elution with the same solvent furnished the desired product **4** (0.024 g, 32%) as a colourless solid, mp 60 °C. R_f (10% EtOAc–petroleum ether) 0.5; IR (KBr) ν_{max}: 1703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76–5.70 (m, 2H), 3.08–3.06 (m, 1H), 2.77–2.20 (m, 6H), 2.00–1.88 (m, 2H), 1.70–1.50 (m merged with signal due to H_2O present in $CDCl_3$, 2H), 1.40–1.19 (m, 3H), 1.10–0.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.9, 133.4, 131.8, 56.4, 51.3, 48.7, 48.2, 47.2, 46.8, 44.2, 38.2, 25.9, 25.7, 22.3, 21.2. HRMS (ESI) (m/z): found 237.1254 $[M+Na]^+$. $C_{15}H_{18}ONa$ requires 237.1255.

*4.1.8. Tetracyclo[9.4.0.0^{1,4}.0^{5,9}]pentadeca-7,10-dien-2-one (**24**).* A solution of enone **5** (0.1 g, 0.43 mmol) in dry benzene (100 mL) was irradiated for 1 h under nitrogen atmosphere in a Pyrex immersion well. Removal of solvent followed by chromatography of the photolysate gave 1,3-acyl shift product **24** (0.04 g, 40%). R_f (10% EtOAc–petroleum ether) 0.8; IR (neat) ν_{max}: 1765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84–5.82 (m, 1H), 5.70–5.67 (m, 1H), 5.30 (br s, 1H), 3.15 (d, J=8.1 Hz, 1H), 2. 94 (d of part of an AB system, J_{AB}=16.5 Hz, J_2=12 Hz, 1H), 2.84 (d of part of an AB system, J_{AB}=16.5 Hz, J_2=12 Hz, 1H), 2.59–2.50 (m, 1H), 2.42–2.28 (m, 2H), 2.17–1.86 (m, 4H), 1.84–1.60 (m, merged with signal due to water, 2H), 1.44–1.21(m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.6, 133.3, 130.6, 130.1, 120.6, 65.4, 47.5, 41.1, 37.2, 36.6, 35.5, 33.7, 32.8, 27.0, 23.9. HRMS (ESI) (m/z): Found 215.1428 $[M+H]^+$. $C_{15}H_{19}O$ requires 215.1436.

*4.1.9. Tetracyclo[7.6.0.0^{1,6}.0^{10,14}]pentadec-12-en-7-one (**3**).* The photoproduct **4** (0.066 g, 0.3 mmol), AIBN (0.02 g) was taken in benzene (30 mL) and tributyltin hydride (0.1 mL, 0.11 g, 2 equiv) was added under nitrogen atmosphere and the reaction mixture was refluxed for 12 h. Solvent was removed under vacuum and residue was chromatographed. Tin impurities were removed by elution with petroleum ether. Further elution with petroleum ether–ethyl acetate (98:2) furnished the product **3** as a colourless liquid (0.04 g, 60%). R_f (10% EtOAc–petroleum ether) 0.45; IR (neat) ν_{max}: 1738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68–5.65 (m, 1H), 5.57–5.54 (m, 1H), 3.31–3.27 (m, 1H), 2.66–2.57 (m, 1H), 2.50–2.00 (complex m 7H), 1.84 (t, J=8.4 Hz, 1H), 1.65–0.93 (complex m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.9, 135.4, 127.5, 52.2, 52.1, 51.7, 50.1, 48.3, 41.9, 41.3, 38.8, 35.4, 23.18, 23.13, 20.7. HRMS (ESI) (m/z): found 217.1597 $[M+H]^+$. $C_{15}H_{21}O$ requires 217.1592.

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