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Molecular complexity from aromatics. Cycloaddition of spiroepoxycyclohexa-2,4-dienones and intramolecular Diels–Alder reaction: a stereoselective entry into tetracyclic core of atisane diterpenoids

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ABSTRACT

A stereoselective approach to tetracyclic core of atisane diterpenoids is described. Oxidative dearomatization, intermolecular cycloaddition of spiroepoxycyclohexa-2,4-dieone with ethyl acrylate, and intramolecular inverse demand $\pi^4s+\pi^2s$ cycloaddition are the key features of our design. Oxidation of appropriately appended *o*-hydroxymethyl phenols to corresponding 6,6-spiroepoxycyclohexadienones followed by cycloaddition with ethyl acrylate furnished bridged bicyclo[2.2.2]octanes disposed with appropriate functionality. Regioselective manipulation of functional groups led to highly embellished bicyclic systems endowed with appendages containing diene and dienophilic moieties that upon inverse electron demand intramolecular cycloaddition provide the tetracyclic framework of atisanes in stereoselective fashion. A remarkable effect of a remote functional group on intramolecular Diels–Alder reaction has also been described.

1. Introduction

Creation of structural, functional, and stereochemical complexity from simple precursors is an important aspect of contemporary design and development of synthetic methodology.[1] Cascade/tandem reactions and multi-component reactions are some of the methods to achieve this objective.[2] Recently, there has been an upsurge of interest in the chemistry of reactive species such as α,α-dialkoxycyclohexa-2,4-dienone, α-hydroxy-cyclohexa-2,4-dienone, and spiroepoxycyclohexa-2,4-dienones generated by oxidative dearomatization of arenols and reactions of these species have proved to be an important tool for efficient creation of molecular complexity.[3–8] Atisane diterpenoids have generated significant interest on account of their complex tetracyclic architecture containing spiro-fused bicyclo[2.2.2]octane ring system and important biological properties exhibited by some members of this family.[9–11] While atiserinic acid **1** and gummiferolic acid **2** (Fig. 1) are some of the older members of this family,[9c,d] recently, many other diterpenoids have been isolated from various natural sources.[10,11] For example, serofendic acid A **3** was isolated from calf serum and exhibits neuroprotective activity.[10] Similarly, several diterpenoids having highly oxygenated *ent*-atisane framework were isolated from liverwort *Lepidolaena clavigera*,[11a] *Isodon albopilosus*,[11b] and *Euphorbia nematocypha*[11c] and some of these exhibit cytotoxic activity.[11b]

Though atisane diterpenoids are known for long time, only a few synthetic routes have been developed.[12–14] Iahara and co-workers employed a novel double Michael addition methodology toward the synthesis of atisane framework.[12a] Ghatak and co-workers developed a new method for the synthesis of atisane framework by addition of diazo-ketone.[12b,c] Toyota and co-workers developed a radical cyclization method to generate bridged bicyclo[2.2.2]octane framework.[13] Recently, Abad and co-workers have also

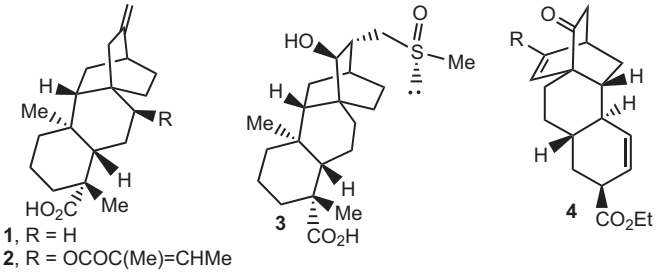

Fig. 1. Atisane diterpenoids and tetracyclic compound **4**.

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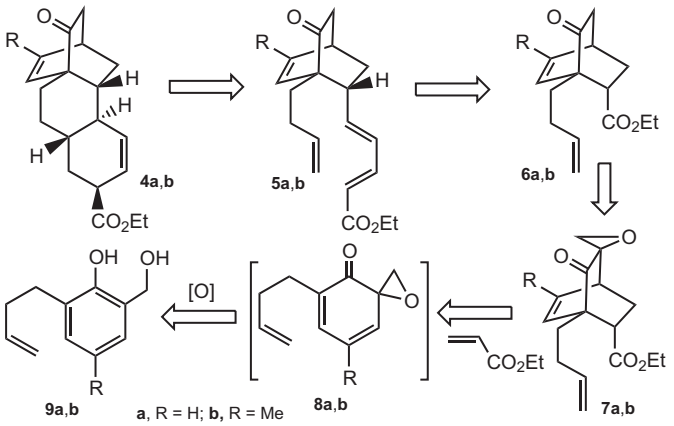
developed the synthesis of several atisane diterpenoids employing diazo-ketone addition across a C=C bond and rearrangement of the resulting cyclopropane derivative to create bridged bicyclo[2.2.2] octane framework of atisanes.[14b,c]

In view of our continuing interest in creation of molecular complexity from simple aromatics employing 6,6-spiroepoxycyclohexa-2,4-dienones,[8] and in order to expand the scope of our methodology, we considered exploring a route for the synthesis of tetracyclic network of atisanes such as **4** and wish to delineate our results herein.

Our plan toward the synthesis of tetracyclic core structure **4** is outlined in Scheme 1. We envisaged that tetracyclic compound of type **4** would be accessible in a single step through intramolecular $\pi^4s+\pi^2s$ cycloaddition in the bridged bicyclic precursor **5** endowed with appropriate tethers. The precursor of type **5** was thought to be amenable from keto-ester **6** via the manipulation of ester functionality. Keto-ester **6** would be derived from the keto-epoxide of type **7**, which in turn, was thought to be obtained from aromatic precursor **9** via oxidative dearomatization to spiroepoxycyclohexa-2,4-dienone of type **8** and intermolecular cycloaddition with ethyl acrylate (Scheme 1).



Scheme 1. Retro-synthetic strategy for tetracyclic systems **4a**,**b**.

Some interesting features of our strategy are as follows. The bicyclo[2.2.2]octane ring system of atisane is generated from an aromatic precursor in the very beginning of synthetic route. Further, the four-carbon olefinic chain required at the bridgehead in the crucial precursor **5** is derived from the aromatic precursor **9** itself, and the other olefinic tether containing diene moiety will be introduced by manipulation of the *endo* ester group thus keeping both the tethers in a cis-stereochemical disposition as required. Moreover, mutually compatible functional groups in adduct **7** permit further manipulation in a regioselective manner so as to prepare the key precursor for intramolecular inverse electron demand Diels–Alder reaction.

2. Result and discussion

In principle, bridged bicyclo[2.2.2]octanes of type **6** may be prepared by $\pi^4s+\pi^2s$ cycloaddition between cyclohexa-2,4-dienone **I** (Fig. 2) and acrylate. However, cyclohexadienone **I** is a keto-tautomer of the corresponding phenol and there are no suitable methods for its preparation. Hence, we considered employing spiroepoxycyclohexa-2,4-dienone of type **8** as a synthetic equivalent of **I**. We thought that oxidative dearomatization of *o*-hydroxymethyl phenols would generate cyclohexadienone **8** that upon interception with acrylate followed by manipulation of the resulting adduct would give a bicyclic compound of type **6**. At the outset, however, we were aware that spirocyclohexadienone of type **8** has fleeting existence and readily undergoes dimerization.

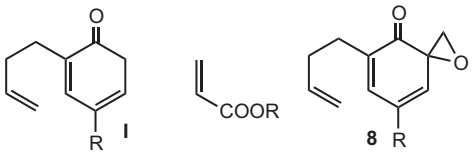
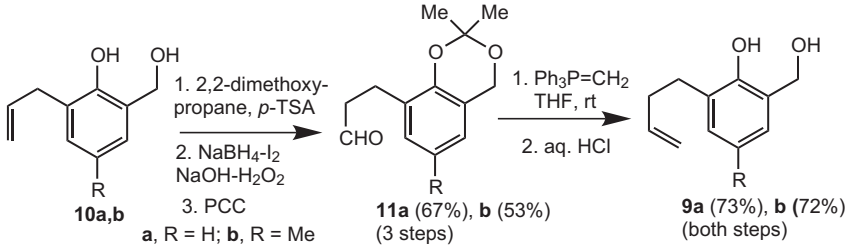


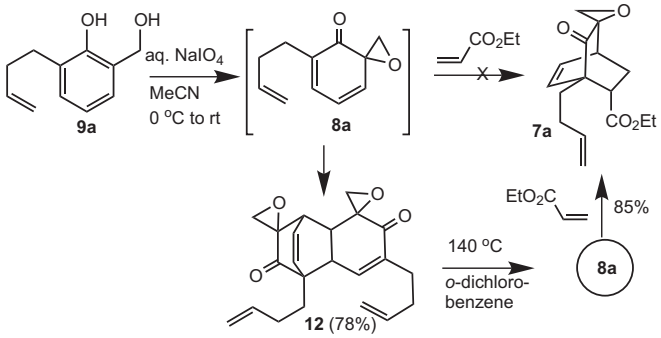
Fig. 2. Cyclohexa-2,4-dienones and potential dienophile.

In order to realize the aforementioned objective, aromatic precursors **9a**,**b** were prepared from readily available[8d,e] hydroxymethyl phenols **10a**,**b** as shown in Scheme 2. Thus, the protection of the hydroxyl groups in **10a** followed by hydroboration and subsequent oxidation gave the known[8e] aldehyde **11a**. Wittig olefination of **11a** followed by the removal of the protecting group furnished the desired aromatic precursor **9a** containing a butenyl chain. Similarly, compound **10b** was also converted into precursor **9b** (Scheme 2).

Toward the synthesis of adduct of type **7**, we first attempted oxidative dearomatization of **9a** for in situ generation of cyclohexadienone **8a** and interception with ethyl acrylate. Thus, a solution of *o*-hydroxymethyl phenol **9a** in acetonitrile was oxidized with aq $NaIO_4$ in the presence of ethyl acrylate following an earlier procedure developed in our laboratory.[15] However, it did not give adduct **7a**, instead the dimer **12** was obtained. It appeared that the failure to obtain adduct **7a** during oxidation of **9a** under ambient conditions (0 °C–rt) is presumably due to the greater propensity of cyclohexadienone **8a** toward dimerization as compared to the intermolecular cycloaddition with ethyl acrylate. Therefore, we contemplated that the generation of cyclohexadienone **8a** via retro-Diels–Alder reaction of dimer **12** at elevated temperature in the presence of ethyl acrylate may lead to the desired adduct **7a**. Indeed, pyrolysis of epoxy dimer **12** in *o*-dichlorobenzene at 140 °C in the presence of ethyl acrylate gave *endo* adduct **7a** in excellent yield as a result of retro-Diels–Alder/intermolecular Diels–Alder cascade reaction (Scheme 3).

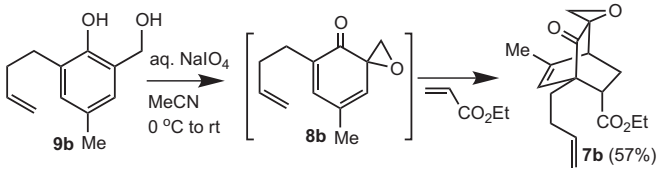


Scheme 2. Preparation of aromatic precursors **9a**,**b**.



Scheme 3. Synthesis of keto-epoxide **7a**.

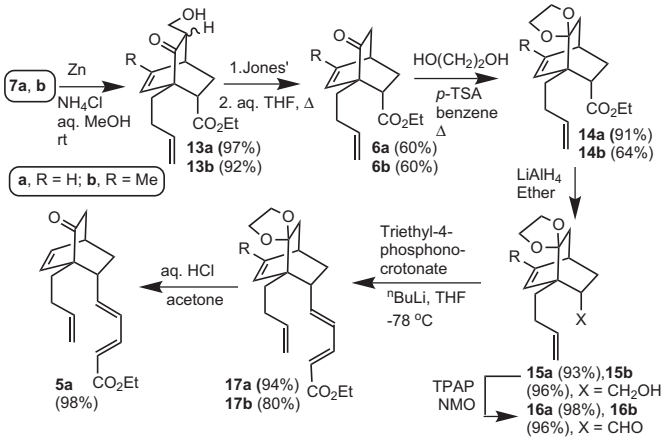
On the other hand, oxidation of a solution of aromatic precursor **9b** in acetonitrile containing ethyl acrylate directly furnished adduct **7b** in reasonably good yield (Scheme 4) as a consequence of the in situ generation of cyclohexadienone **8b** and subsequent cycloaddition with ethyl acrylate under ambient conditions. It is interesting to note the effect of C-4 methyl group on the reactivity of **8b** (compared to **8a**) toward cycloaddition with ethyl acrylate.



Scheme 4. Synthesis of keto-epoxide **7b**.

The structure of both adducts was deduced from their spectral features. The IR spectrum of the adduct **7a** showed a broad absorption band at 1733 cm^{-1} due to carbonyl groups. ^1H NMR (400 MHz) spectrum displayed characteristic signals at δ 6.61 (dd, J_1=8.2 Hz, J_2=7 Hz, 1H) and 6.06 (m of d, J=8.2 Hz, 1H) for the γ- and β-proton of β,γ-enone moiety. Olefinic protons of butenyl chain showed signals at δ 5.91–5.80 (m, 1H) and 5.08–4.94 (m, 2H). Methylene protons of the oxirane moiety appeared as AB quartet at δ 3.16 (part of an AB system, J_{AB}=6.0 Hz, 1H) and 2.87 (part of an AB system, J_{AB}=6.0 Hz, 1H). The methylene protons of the carboethoxy group were observed at δ 4.21–4.08 (m, 2H). In addition, signals were shown at δ 2.66–2.61 (m, 1H), 2.52–2.42 (m, 1H), 2.30–2.13 (m, 2H), 1.95–1.75 (m, 3H), and 1.27 (t, J=7.0 Hz, 3H) due to other protons. The ^{13}C NMR (100 MHz) spectrum exhibited signals at δ 204.0 and 173.1 for the carbonyl group of the ketone and ester moiety, respectively. Further signals were observed at δ 138.5, 134.0, 131.1, and 114.6 for four olefinic carbons. In addition, signals were observed at δ 61.0, 57.8, 54.6, 53.4, 43.5, 38.1, 29.3, 29.2, 28.6, and 14.3 for the other carbons. These spectral characteristics clearly suggested the structure of adduct **7a**. The *endo* stereochemical disposition of the carboethoxy group was confirmed through chemical transformation and crystal structure of a derivative of **7a** (vide infra). Stereochemistry of the oxirane ring, though it would be lost during further transformation, was suggested on the basis of the general tendency of the spiroepoxycyclohexa-2,4-dienones during their cycloaddition. The adduct **7b** also exhibited similar spectral characteristics.

The presence of compatible functional groups in adducts **7a**,**b** provided a unique opportunity for regioselective manipulation and synthesis of precursors for intramolecular Diels–Alder (IMDA) reaction. Thus, reduction of **7a** with Zn–NH_4Cl in aq MeOH gave β-hydroxymethyl keto-ester **13a** in excellent yield. Oxidation of **13a** with Jones reagent followed by decarboxylation readily gave keto-ester **6a** (Scheme 5). Treatment of compound **6a** with ethylene glycol in the presence of *p*-TSA gave acetal **14a** in excellent yield that upon reduction with $LiAlH_4$ gave alcohol **15a**.



Scheme 5. Synthesis of precursors for IMDA reaction.

Similarly, adduct **7b** was also converted into alcohol **15b**. Oxidation of **15a**,**b** with TPAP–NMO gave aldehydes **16a**,**b**, respectively, in excellent yield. Subsequent olefination in **16a**,**b** gave compounds **17a**,**b** having appropriate tethers in good yield. Removal of the acetal group in **17a** furnished the desired IMDA precursor **5a** (Scheme 5). The structures of all the compounds were deduced from their spectral data. The structure of keto-ester **5a** was further confirmed by single crystal X-ray structure determination (Fig. 3) that also established structure of its progenitors.

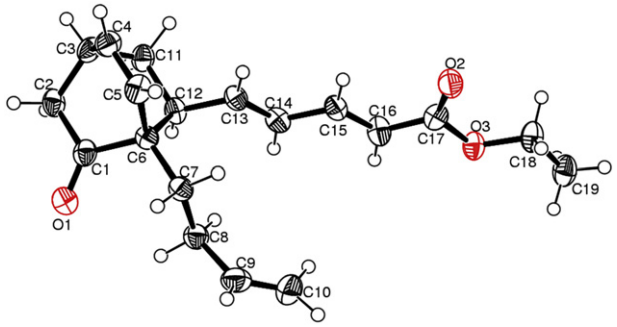
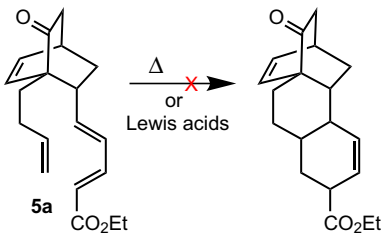


Fig. 3. X-ray crystal structure of compound **5a**.

After having developed the synthesis of embellished bridged bicyclo[2.2.2]octenones endowed with appropriate tethers, we set out to explore an intramolecular Diels–Alder reaction in **5a**. Diels–Alder reaction, both inter- and intramolecular, is a powerful tool and constitutes a versatile method for the synthesis of complex molecular structures,[16–19] the latter is often controlled by subtle structural, stereochemical, and electronic factors. There are a large number of intramolecular reactions between electron rich diene and activated dienophiles, intramolecular Diels–Alder reaction between electron deficient diene and unactivated dienophiles is rare.

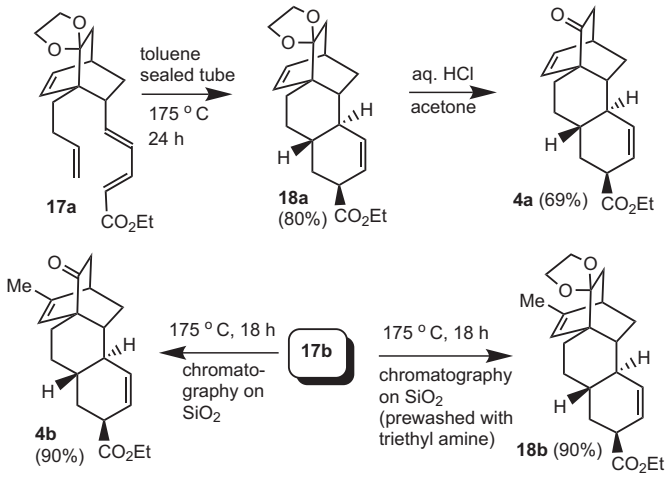
Keeping the above in mind, we attempted IMDA reaction in compound **5a**. Thus, a solution of compound **5a** in toluene was heated in a sealed tube. Unfortunately, it did not give adduct, instead a complex mixture was formed (Scheme 6). Lewis acid-mediated cycloaddition employing $Sc(OTf)_3$ and $TiCl_4$ as catalyst at low temperature was also not fruitful.



Scheme 6. Attempted IMDA reaction in compound **5a**.

It was rather difficult to understand the aforementioned failure. We surmised that the presence of carbonyl group in **5a** at the ethano-bridge, perhaps, controls the intramolecular Diels–Alder reaction in a subtle fashion (via geometrical constrains). At this juncture, therefore, we considered exploring Diels–Alder reaction in the acetal **17a** especially since it was thought that the presence of five-membered ring acetal moiety in **17a** may bring olefinic tethers in closer proximity that might facilitate the desired intramolecular Diels–Alder reaction.

Indeed, heating a solution of **17a** in toluene at 175 °C in a sealed tube followed by removal of solvent and chromatography furnished the desired adduct **18a** as a sole product in excellent yield (Scheme 7). It was delightful to observe such a rare and dramatic effect of a remote functional group on the IMDA reaction. Subsequent treatment of **17a** with aq HCl in acetone gave the tetracyclic keto-ester **4a**.



Scheme 7. Synthesis of tetracyclic compounds **4a**,**b**.

Similarly, acetal **17b** also underwent a smooth IMDA reaction upon heating to give the corresponding adduct (^{1}H NMR) that upon chromatography on silica gel gave the keto-ester **4b** as a result of hydrolysis of acetal moiety. Subsequently, the reaction mixture was chromatographed on silica gel (prewashed with triethyl amine) that furnished adduct **18b** in excellent yield (Scheme 7).

The structure of adducts and their derivative was deduced from their spectral features and comparison with the spectral features of **4b** whose structure and stereochemistry were further confirmed by single crystal structure determination (vide infra).

Thus, ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of adduct **18b** displayed signals at δ 5.81–5.69 (m, 2H) and 5.58 (br s, 1H) for the presence of only three olefinic protons, which clearly indicated that intramolecular Diels–Alder reaction had occurred. Further, signals were observed at δ 4.13 (q, J=7.0 Hz, 2H), 3.91–3.80 (m, 4H) for oxymethylene protons of ester and acetal moieties, respectively. In addition, resonances were observed at δ 3.12–3.00 (m, 1H), 2.38–2.32 (m, 1H), 2.04 (d, J=12.0 Hz, 1H), 1.91–1.71 (m overlapped with d, J=1.5 Hz, total 5H), 1.68–1.62 (m, 2H), 1.60–1.50 (m merged with signal due to H_2O present in $CDCl_3$, 3H), 1.40–1.17 (m merged with t, J=7.0 Hz, total 6H), and 1.10–1.03 (m, 1H) for other protons. The ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **18b** showed signals at δ 174.3 for the CO group of the ester moiety. The presence of only four signals at δ 143.5, 132.3, 125.7, 124.4 for olefinic carbons also suggested that cycloaddition had taken place. Other carbons displayed signals at δ 114.7, 65.2, 64.7, 60.6, 46.6, 45.9, 42.3, 40.9, 38.4, 36.7, 36.6, 31.45, 31.41, 29.3, 26.5, 20.2, and 14.4, thus accounting for all the 22 carbons.

Similarly, the keto-ester **4b** displayed signals at δ 5.82–5.72 (m, 2H) and 5.39 (br s, 1H) for three olefinic protons in its ^{1}H NMR (400 MHz, $CDCl_3$) spectrum. Further signals were shown at δ 4.14 (q, J=7.1 Hz, 2H), 3.09–3.04 (m, 1H), 2.68–2.63 (m, 1H), 2.15–1.96 (complex m, total 4H), 1.86 (s, 3H), 1.84–1.68 (m, 3H), 1.63–1.53 (m merged with the signal due to H_2O in $CDCl_3$, 1H), 1.52–1.18 (cluster of m merged with t, J=7.1 Hz, total 8H) for the other protons. The ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **4b** also corroborated with its structure as it showed signals at δ 213.3, 174.0 for CO group at the ethano-bridge and CO of ester moiety, respectively. Further signals were observed at δ 146.5, 131.3, 125.4, 122.4 due to four olefinic carbons. In addition, signals were shown at δ 60.8, 53.3, 45.6, 40.8, 40.3, 39.3, 36.8, 36.3, 31.3, 31.2, 28.8, 27.4, 20.3, 14.3 for other carbons. The compounds **18a** and **4a** also exhibited similar spectral characteristics.

The aforementioned spectral data of compounds **18b** and **4b** clearly suggested their gross tetracyclic structures, however, it was difficult to ascertain the stereochemistry of the newly generated stereogenic centers from the spectral data alone. Therefore, a single crystal X-ray analysis of compound **4b** was undertaken (Fig. 4), which confirmed its structure and stereochemistry. Hence, structure of the adduct **18b** and its precursors was also established. The structure and stereochemistry of adduct **18a** and keto-ester **4a** were suggested on the basis of spectral data and comparison with structural features of **18b** and **4b**, respectively.

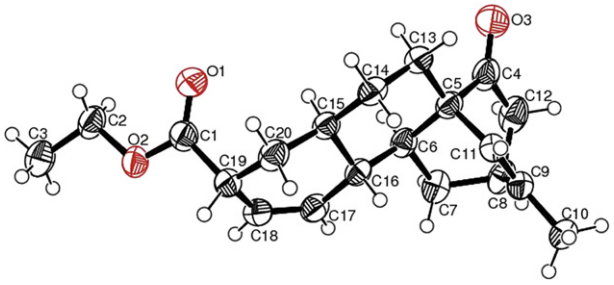


Fig. 4. X-ray crystal structure of **4b**.

3. Conclusion

In summary, we have developed a stereoselective route to tetracyclic framework of atisane diterpenoids. The methodology involves synthesis of functionalized and appended bridged bicyclo [2.2.2]octane from simple aromatic precursors employing in situ generation of spiroepoxycyclohexa-2,4-dienones and cycloaddition with ethyl acrylate. The functional groups in cycloadducts readily permitted selective manipulation that led to synthesis of advanced precursors having bridged bicyclo[2.2.2]octane ring system endowed with appropriate tethers for intramolecular Diels–Alder reaction. Heating the precursors **17a**,**b** led to a smooth and stereoselective inverse electron demand intramolecular Diels–Alder reaction to give the tetracyclic framework of atisane diterpenoids. A highly remarkable effect of a remote functionality on the intramolecular cycloaddition is observed.

The present methodology constitutes a nice example of creation of molecular complexity from simple aromatics, which is an

important aspect of synthesis design. Simplicity of the reagents and conditions employed in synthesis are additional interesting features.

4. Experimental section

4.1. 2,2,6-Trimethyl-8-(3-propanal)-1,3-benzodioxin (11b)

To a solution of dio1 **10b** (9.00 g, 50.56 mmol) in acetone (150 mL) were added 2,2-dimethoxypropane (9.2 mL, 7.88 g, 75.76 mmol) and *p*-TSA (100 mg). The reaction mixture was stirred at ambient temperature. After completion of reaction (TLC, 6 h), solid sodium bicarbonate was added and the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with diethyl ether (2×100 mL), washed with brine (50 mL), and dried on anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the product was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (96:4) gave the protected compound (9.0 g, 81%). R_f=0.5 petroleum ether/ethyl acetate (95:05) [IR (neat) ν_{max}: 2942, 1511 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.66 (s, 1H), 6.01–5.90 (complex m, 1H), 5.09–4.99 (m, 2H), 4.80 (s, 2H), 3.29 (br d, J=6.6 Hz, 2H), 2.23 (s, 3H), 1.51 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 137.0, 129.3, 129.0, 128.1, 122.9, 119.0, 115.4, 99.4, 61.1, 33.8, 24.9, 20.8]. This product was subjected to hydroboration as described below.

To a suspension of sodium borohydride (2.35 g, 61.84 mmol) in dry THF (50 mL) was slowly added a dilute solution of iodine (5.80 g, 22.83 mmol) in dry THF (70 mL) under nitrogen atmosphere at 0 °C. The addition was complete in 2 h. It was further stirred for 30 min. A solution of the above compound (5.00 g, 22.93 mmol) in THF (15 mL) was then added to the reaction mixture and it 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, 70 mL) were added to the reaction mixture at 0 °C. Subsequently, H_2O_2 (30%, 70 mL) was added to the reaction mixture slowly and stirred for 1 h. 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. The crude product was chromatographed on silica gel. Elution with petroleum ether/EtOAc (80:20) provided an alcohol (5.3 g, 98%). R_f=0.5 petroleum ether/ethyl acetate (80:20) [IR (neat) ν_{max}: 3399 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.63 (s, 1H), 4.80 (s, 2H), 3.58 (dd, J_1=6.2 Hz, J_2=2.5 Hz, 2H), 2.65 (t, J=7.5 Hz, 2H), 2.24 (s, 3H), 2.00 (br s, 1H), 1.86–1.79 (m, 2H), 1.54 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 129.6, 129.4, 122.9, 188.9, 99.6, 61.7, 61.1, 33.1, 25.1, 24.8, 20.7. HRMS (ESI) (m/z): found 237.1492 $[M+H]^+$; calcd for $C_{14}H_{21}O_3$ 237.1491]. This alcohol was then oxidized with PCC as follows.

To a stirred solution of the above alcohol (5.0 g, 21.18 mmol) in dichloromethane (100 mL) was cooled to 0 °C and PCC (11.38 g, 52.93 mmol) was added in one portion. The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was filtered through a column of dry silica gel and washed with dichloromethane. The combined filtrate was dried on Na_2SO_4, concentrated under reduced pressure, and the product was purified by column chromatography on silica gel. Elution with petroleum ether/EtOAc (95:5) provided the aldehyde **11b** (3.3 g, 67%) [R_f=0.5 petroleum ether/ethyl acetate (95:5)]. IR (neat) ν_{max}: 1720 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (t, J=3.3 Hz, 1H), 6.83 (s, 1H), 6.64 (s, 1H), 4.79 (s, 2H), 2.90–2.84 (m, 2H), 2.71–2.67 (m, 2H), 2.23 (s, 3H), 1.51 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 146.9, 129.39, 129.32, 128.1, 123.3, 119.1, 99.5, 61.0, 43.9, 24.9, 22.9, 20.7. HRMS (ESI) (m/z): found 257.1152 $[M+Na]^+$; calcd for $C_{14}H_{18}O_3Na$ 257.1154.

4.2. 2-(But-3-enyl)-6-hydroxymethyl phenol (9a)

To a stirred suspension of methyltriphenyl phosphonium iodide (8.20 g, 20.29 mmol) in dry THF (100 mL) was added *t*-BuOK (2.60 g, 23.00 mmol) at 0 °C and the reaction mixture was stirred for 1 h at ambient temperature. The resulting ylide was cooled to 0 °C and a solution of the aldehyde **11a** (3.20 g, 14.54 mmol) in dry THF (10 mL) was added dropwise. After complete addition, the reaction mixture was stirred for 4 h at ambient temperature. After completion of reaction (TLC) the reaction mixture was quenched with cold water and extracted with ether (3×30 mL). The combined extract was dried on anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product that was purified by column chromatography. Elution with petroleumether/ethyl acetate (97:3) gave the desired product (2.5 g 79%) as a clear liquid [R_f=0.5 petroleum ether/EtOAc (95:5)] [IR (neat) ν_{max}: 1638 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 7.04–6.98 (m, 1H), 6.84–6.78 (m, 2H), 5.93–5.82 (complex m, 1H), 5.02 (m of d, J=16.3 Hz, 1H), 4.95 (m of d, J=10.9 Hz, 1H), 4.83 (s, 2H), 2.68–2.64 (m, 2H), 2.37–2.30 (m, 2H), 1.54 (s, partly merged with signal due to H_2O present in $CDCl_3$, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 138.7, 129.9, 128.3, 122.3, 119.8, 119.0, 114.5, 99.3, 61.1, 33.9, 29.2, 24.9]. This product was subjected to hydrolysis as follows.

To a stirred solution of above product (2.50 g, 11.46 mmol) in THF/H_2O (1:1, 160 mL) was added concd HCl (6 mL 35%) at ~5 °C and the reaction mixture was stirred at ambient temperature for 8 h. After which, some more HCl (2 mL 35%) was added and the reaction mixture was further stirred for 2 h. After completion of reaction (~2 h, TLC), the reaction mixture was cooled to 0 °C and quenched by the addition of excess solid sodium bicarbonate. The organic solvent was removed under reduced pressure and the aqueous solution was extracted with ethyl acetate (3×100 mL). The combined organic layer was washed with brine (30 mL) and dried on anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed on silica gel. Elution with petroleum ether/EtOAc (80:20) provided compound **9a** (1.9 g, 93%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (80:20)]. IR (neat) ν_{max}: 3421, 2929 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (br s, 1H), 7.10 (dd, J_1=6.0 Hz, J_2=2.0 Hz, 1H), 6.89 (dd, J_1=6 Hz, J_2=2 Hz, 1H), 6.79 (superimposed dd, J=8 Hz, 1H), 5.96–5.84 (m, 1H), 5.06 (m of d, J=18.0 Hz, 1H), 4.98 (m of d, J=10.0 Hz, 1H), 4.86 (s, 2H), 2.77–2.71 (m, 2H), 2.42–2.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 138.7, 130.3, 129.5, 125.7, 124.2, 119.7, 114.8, 65.3, 34.0, 29.5. HRMS (ESI) (m/z): found 179.1072 $[M+H]^+$; calcd for $C_{11}H_{15}O_2$ 179.1069.

4.3. 2-(But-3-enyl)-4-methyl-6-hydroxymethylphenol (9b)

The reaction of compound **11b** (3.00 g, 12.82 mmol) with methyltriphenyl phosphonium iodide (8.20 g, 20.29 mmol) and *t*-BuOK (2.80 g, 24.77 mmol) according to the aforementioned procedure followed by work-up and chromatography (elution with petroleum ether/ethyl acetate 95:5) furnished an alkene as a clear liquid (2.4 g, 80%) [R_f=0.5 petroleum ether/EtOAc (95:5)] [IR (neat) ν_{max}: 2921, 1481 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.61 (s, 1H), 5.92–5.81 (m, 1H), 5.03 (d, J=16.3 Hz, 1H), 4.95 (d, J=10.9 Hz, 1H), 4.80 (s, 2H), 2.62 (t, J=14.8 Hz, 2H), 2.31 (dd, J_1=14.8 Hz, J_2=8.8 Hz, 2H), 2.23 (s, 3H), 1.52 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 138.9, 129.8, 129.3, 129.1, 122.7, 118.9, 114.6, 99.3, 61.2, 34.1, 29.4, 25.0, 20.8].

Hydrolysis of the above product (1.30 g, 5.60 mmol) by aq HCl as described earlier followed by work-up and column chromatography [elution with petroleum ether/ethyl acetate (85:15)] gave the desired aromatic precursor **9b** (0.970 g, 90%) as a clear liquid [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 3393, 1481 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H), 6.86 (s, 1H), 6.62 (s, 1H), 5.93–5.82 (m, 1H), 5.05 (m of d, J=17.1 Hz, 2H), 4.96 (d,

J=11.4 Hz, 1H), 4.68 (s, 2H), 2.86 (br s, 1H), 2.65 (t, J=7.5 Hz, 2H), 2.35 (dd, J_1=7.5 Hz, J_2=6.7 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 138.8, 130.7, 129.1, 128.9, 126.4, 124.3, 114.9, 64.8, 34.1, 29.5, 20.6. HRMS (ESI) (m/z): found 215.1048 $[M+Na]^+$; calcd for $C_{12}H_{16}O_2Na$ 215.1056.

4.4. 6,9-Bis-spiroepoxy-1,4-bis-(buten-3-yl)-tricyclo[6.2.2.0^{2,7}] dodec-3,11-dien-5,10-dione (12)

To a stirred solution of compound **9a** (10.00 g, 45.87 mmol) in acetonitrile (150 mL) was added a solution of $NaIO_4$ (24.54 g, 114.67 mmol) in water (150 mL) dropwise at 10 °C (2 h). The reaction mixture was then stirred for 3 h at ambient temperature. The reaction mixture 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). The solvent was evaporated under reduced pressure, dried on anhydrous Na_2SO_4 and the residue was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (75:25) gave compound **12** (7.71 g, 78%) as a thick liquid [R_f=0.5 petroleum ether/EtOAc (75:25)]. IR (neat) ν_{max}: 1733, 1689 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (dd, J_1=8.2 Hz, J_2=6.8 Hz, 1H), 6.44 (d, J=6.8 Hz, 1H), 5.96–5.81 (m, 2H), 5.78–5.67 (m, 1H), 5.11 (m of d, J=16.5 Hz, 1H), 5.05–4.97 (complex m, total 3H), 3.31 (dd, J_1=9 Hz, J_2=6.3 Hz, 1H), 3.13 (part of an AB system J_{AB}=6.3 Hz, 1H), 2.91 (part of an AB system J_{AB}=6.3 Hz, 1H), 2.88 (m of d, J=7.2 Hz, 1H), 2.83 (s, 2H), 2.73 (dd, J_1=9 Hz, J_2=1.8 Hz, 1H), 2.41–2.34 (m, 2H), 2.29–2.16 (m, 4H), 2.01–1.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 193.1, 143.0, 139.8, 138.1, 137.6, 133.8, 133.5, 115.8, 115.2, 59.1, 58.7, 58.4, 58.2, 54.0, 41.2, 40.6, 39.8, 32.4, 29.6, 28.9, 28.8. HRMS (ESI) (m/z): found 353.1756 $[M+H]^+$; calcd for $C_{22}H_{25}O_4$ 353.1753.

4.5. Ethyl-1-(but-3-enyl)-5-spirooxirane-6-oxo-bicyclo[2.2.2] oct-7-en-2-carboxylate (7a)

A mixture of the dimer **12** (8.0 g, 22.72 mmol) in *o*-dichlorobenzene (30 mL) and ethyl acrylate (15 mL, excess) was heated at 110 °C for 7 h. After which, the reaction mixture was charged on a column of silica gel. Elution with petroleum ether/ethyl acetate (96:4) removed the *o*-dichlorobenzene and unreacted ethyl acrylate. Further elution with petroleum ether/ethyl acetate (88:12) gave the epoxy ketone **7a** (10.66 g, 85%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 1733 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (dd, J_1=8.2 Hz, J_2=7 Hz, 1H), 6.06 (m of d, J=8.2 Hz, 1H), 5.91–5.80 (m, 1H), 5.08–4.94 (m, 2H), 4.21–4.08 (m, 2H), 3.16 (part of an AB system, J_{AB}=6.0 Hz, 1H), 2.92 (ddd, J_1=6.6 Hz, J_2=5.4 Hz, J_3=0.9 Hz, 1H), 2.87 (part of an AB system, J_{AB}=6.0 Hz, 1H), 2.66–2.61 (m, 1H), 2.52–2.42 (m, 1H), 2.30–2.13 (m, 2H), 1.95–1.75 (m, 3H), 1.27 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0, 173.1, 138.5, 134.0, 131.1, 114.6, 61.0, 57.8, 54.6, 53.4, 43.5, 38.1, 29.3, 29.2, 28.6, 14.3. HRMS (ESI) (m/z): found 299.1253 $[M+Na]^+$; calcd for $C_{16}H_{20}O_4Na$ 299.1259.

4.6. Ethyl-1-(but-3-enyl)-5-spirooxirane-6-oxo-bicyclo[2.2.2] oct-7-en-8-methyl-2-carboxylate (7b)

To a stirred solution of the **9b** (0.500 g, 2.60 mmol) in acetonitrile (70 mL) and ethyl acrylate (7 mL, excess) was added a solution of $NaIO_4$ (2.4 g, 11.21 mmol) in water (25 mL) dropwise at 0 °C (4 h). The reaction mixture was further stirred for 8 h at ambient temperature. NaCl was added to the reaction mixture and filtered on a Celite bed and washed with ethyl acetate. The organic layer was separated from the filtrate and the aqueous layer was extracted with ethyl acetate (3×50 mL). The organic extracts were combined and washed with brine (50 mL) and dried on anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (90:10) gave compound **7b** (0.430 g, 57%) as a clear liquid [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 3393, 1715 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89–5.79 (m, 1H), 5.61 (br s, 1H), 5.03 (m of d, J=16.9 Hz, 1H), 4.95 (m of d, J=10.7 Hz, 1H), 4.20–4.08 (m, 2H), 3.14 (part of an AB system J_{AB}=6.1 Hz, 1H), 2.92–2.87 (part of an AB system merged with another m, J_{AB}=6.1 Hz, total 2H), 2.44–2.36 (m, 2H), 2.28–2.13 (m, 2H), 1.95 (s, 3H), 1.89–1.81 (m, 2H), 1.78–1.70 (m, 1H), 1.26 (t, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 173.3, 143.9, 138.7, 123.1, 114.5, 61.0, 57.8, 54.6, 52.6, 44.0, 43.4, 29.4, 28.7, 20.8, 14.3. HRMS (ESI) (m/z): found 291.1589 $[M+H]^+$; calcd for $C_{17}H_{23}O_4$ 291.1596.

4.7. Ethyl-1-(but-3-en-yl)-6-oxo-bicyclo[2.2.2]oct-7-en-2-carboxylate (6a)

To a solution of adduct **7a** (3.9 g, 14.13 mmol) in MeOH/H_2O (6:1, 50 mL) were added zinc (activated, 32 g, excess) and NH_4Cl (4.00 g, 76.22 mmol). The reaction mixture was stirred at ambient temperature (30 °C) for 12 h. It was filtered on a Celite bed and washed with ethyl acetate. The filtrate was concentrated under vacuum, and the residue was diluted with water (15 mL) and extracted with ethyl acetate (4×25 mL). The combined extract was washed with brine and dried. The solvent was removed under reduced pressure and the product was purified by column chromatography. Elution with petroleum ether/ethyl acetate (65:35) gave a keto-alcohol **13a** (3.8 g, 97%, mixture of *syn*:*anti* isomers) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (75:35)]. IR (neat) ν_{max}: 3445, 1717 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (superimposed dd, J=7.2 Hz, 1H), 6.00 (d, J=7.2 Hz, 1H), 5.90–5.79 (m, 1H), 5.03 (m of d, J=18.1 Hz, 1H), 5.15 (m of d, J=10.9 Hz, 1H), 4.18–4.06 (m, 2H), 3.82 (dd, J_1=11.4 Hz, J_2=5.7 Hz, 1H), 3.71–3.63 (m, 1H), 2.80–2.60 (m, total 2H), 2.23–2.05 (m, 4H), 2.00–1.80 (m, 2H), 1.65–1.59 (m merged with signal due to H_2O present in $CDCl_3$, 1H), 1.30–1.20 (m, total 4H) (signals due to major isomer). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.6, 173.3, 147.1, 138.9, 121.4, 114.4, 63.0, 60.9, 54.9, 49.2, 44.8, 39.9, 29.2, 27.7, 20.3, 12.3. HRMS (ESI) (m/z): found 279.1602 $[M+H]^+$; calcd for $C_{16}H_{23}O_4$ 279.1596. The β-keto-alcohol was subjected to oxidation and decarboxylation as presented below.

To a stirred solution of **13a** (2.5 g, 8.99 mmol) in acetone (30 mL) was added freshly prepared Jones reagent dropwise at 0 °C and the reaction mixture was stirred for 15 min. After that, isopropanol was added to reaction mixture to quench excess Jones reagent. Solvent was removed under reduced pressure, the residue was diluted with water (10 mL) and aqueous layer was extracted with ethyl acetate (3×30 mL). Organic extract was combined and dried over anhydrous Na_2SO_4. Removal of solvent gave a keto-acid that was directly subjected for decarboxylation.

Thus, the carboxylic acid thus obtained was dissolved in THF/H_2O (1:1, 80 mL) and the reaction mixture was refluxed for 18 h. After that it was saturated with NaCl, organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×20 mL). Organic extract was combined and dried on anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography. Elution with petroleum ether/ethyl acetate (80:20) gave the keto-ester **6a** (1.35 g, 60%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (80:20)]. IR (neat) ν_{max}: 2937, 1723, 1640 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (dd, J_1=8.7 Hz, J_2=6.2 Hz, 1H), 5.94 (d, J=8.7 Hz, 1H), 5.91–5.80 (m, 1H), 5.03 (m of d, J=16.9 Hz, 1H), 4.95 (m of d, J=9.6 Hz, 1H), 4.16–4.05 (m, 2H), 3.05–2.99 (m, 1H), 2.78 (dd, J_1=9.2 Hz, J_2=5.1 Hz, 1H), 2.27–2.09 (m, 5H), 1.86–1.75 (m, 3H), 1.25 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.1, 173.7, 139.0, 136.7, 129.8, 114.4, 60.9, 54.3, 42.7, 40.1, 32.9, 32.1, 29.2, 28.9, 14.3. HRMS (ESI) (m/z): found 249.1486 $[M+H]^+$; calcd for $C_{15}H_{21}O_3$ 249.1491.

4.8. Ethyl-1-(but-3-en-yl)-6-oxo-bicyclo[2.2.2]oct-7-en-8-methyl-2-carboxylate (6b)

The reduction of adduct **7b** (1.40 g, 4.82 mmol) with zinc (1.5 g, excess) and NH_4Cl (0.767 g, 14.47 mmol) in MeOH/H_2O (6:1, 35 mL) at ambient temperature (30 °C) for 12 h, as described above followed by work-up and chromatography (petroleum ether/ethyl acetate 65:35) gave β-hydroxy-ketone **13b** (1.3 g, 92%, mixture of *syn*:*anti* isomers) as a clear oil [R_f=0.5 petroleum ether/EtOAc (75:25)]. IR (neat) ν_{max}: 3475, 1718, 1640 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 5.90–5.78 (m, 1H), 5.55 (s, 1H), 5.02 (m of d, J=16.8 Hz, 1H), 4.94 (d with str, J=10.5 Hz, 1H), 4.18–4.04 (m, 2H), 3.80 (dd, J_1=10.5 Hz, J_2=8.4 Hz, 1H), 3.70–3.61 (m, 1H), 2.78–2.73 (m, 1H), 2.70 (br s, 1H), 2.63 (dd, J_1=11.2 Hz, J_2=6.4 Hz, 1H), 2.27–2.06 (m, 4H), 1.94 (s, 3H), 1.91–1.78 (m, 2H), 1.67–1.58 (m, merged with signal due to H_2O present in $CDCl_3$, 1H), 1.25 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.5, 173.4, 147.1, 138.9, 121.4, 114.4, 63.0, 60.9, 54.9, 49.4, 44.8, 39.9, 29.2, 29.0, 27.6, 20.3, 14.3. HRMS (ESI) (m/z): found 293.1746 $[M+H]^+$; calcd for $C_{17}H_{25}O_4$ 293.1753.

The Jones oxidation of keto-alcohol **13b** thus obtained (0.700 g, 2.39 mmol) in acetone (20 mL) followed by decarboxylation of the resulting β-keto-acid following aforementioned procedure and chromatography (petroleum ether/ethyl acetate 80:20) gave the keto-ester **6b** (0.380 g, 60%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (80:20)]. IR (neat) ν_{max}: 1721, 1640 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 5.91–5.80 (complex m, 1H), 5.49 (br s, 1H), 5.03 (m of d, J=16.4 Hz, 1H), 4.94 (m of d, J=10.2 Hz, 1H), 4.16–4.06 (m, 2H), 2.80–2.73 (m, 2H), 2.26–2.13 (m, 2H), 2.21–2.03 (m, 3H), 1.90 (d, J=1.5 Hz, 3H), 1.81–1.72 (m, 3H), 1.25 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 173.7, 146.1, 139.1, 121.7, 114.2, 60.7, 54.2, 43.2, 39.7, 37.4, 32.2, 29.3, 28.8, 20.3, 14.3. HRMS (ESI) (m/z): found 263.1653 $[M+H]^+$; calcd for $C_{16}H_{23}O_3$ 263.1647.

4.9. Ethyl-1-(but-3-enyl)-6-spiro(1,3-dioxalane)-bicyclo[2.2.2]oct-7-en-2-carboxylate (14a)

A mixture of ethylene glycol (5 mL, excess), *p*-toluenesulphonic acid (0.020 g, catalytic amount), and benzene (30 mL) was dried in a Dean–Stark apparatus. After that, a solution of the keto-ester **6a** (1.5 g, 6.04 mmol) in dry benzene was added to the reaction mixture at ambient temperature and the reaction mixture was refluxed for 12 h. After which, it was cooled and poured into a cold solution of sodium bicarbonate (30 mL) and stirred at ambient temperature. The benzene layer was separated and the aqueous layer was extracted with ether (3×20 mL). The combined organic layer was washed with saturated sodium bicarbonate (2×20 mL) and dried on anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was chromatographed. Elution with petroleum ether/ethyl acetate (95:5) gave the ketal-ester **14a** as a colorless liquid (1.60 g, 90.90%) [R_f=0.5 petroleum ether/EtOAc (95:5)]. IR (neat) ν_{max}: 1732 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 6.42 (dd, J_1=8.4 Hz, J_2=6 Hz, 1H), 6.03 (d, J=8.4 Hz, 1H), 5.86–5.74 (m, 1H), 4.99 (m of d, J=17.0 Hz, 1H), 4.91 (m of d, J=11.0 Hz, 2H), 4.08 (q, J=7.2 Hz, 2H), 3.93–3.85 (m, 4H), 3.13 (dd, J_1=15.1 Hz, J_2=8.8 Hz, 1H), 2.75–2.68 (m, 1H), 2.32–2.14 (m, 2H), 2.20 (merged ddd, J_1=13.3 Hz, J_2=10.6 Hz, J_3=2.6 Hz, 1H), 1.89–1.74 (m, 2H), 1.72–1.64 (m, 2H), 1.58–1.50 (m, 1H), 1.23 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 139.9, 134.2, 132.9, 114.2, 113.8, 64.4, 64.3, 60.3, 46.2, 42.6, 42.0, 33.0, 30.8, 29.8, 29.6, 14.3. HRMS (ESI) (m/z): found 293.1762 $[M+H]^+$; calcd for $C_{17}H_{25}O_4$, 293.1753.

4.10. Ethyl-1-(but-3-enyl)-6-spiro(1,3-dioxalane)-bicyclo[2.2.2]oct-7-en-8-methyl-2 carboxylate (14b)

The treatment of **6b** (0.200 g, 0.76 mmol) with ethylene glycol (3 mL, excess) in the presence of *p*-TSA (0.01 g, catalytic) in benzene (50 mL) following aforementioned procedure and chromatography (elution of petroleum ether/ethyl acetate 95:5) gave compound **14b** (0.150 g, 64%) [R_f=0.5 petroleum ether/EtOAc (95:5)]. IR (neat) ν_{max}: 2927, 1695 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 5.87–5.76 (complex m, 1H), 5.61 (br s, 1H), 4.99 (m of d, J=18.0 Hz, 1H), 4.92 (m of d, J=10.0 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.94–3.86 (m, 4H), 3.13 (dd, J_1=10.2 Hz, J_2=5.2 Hz, 1H), 2.48–2.44 (br m, 1H), 2.33–2.12 (m, 2H), 2.00–1.93 (m, 1H), 1.86 (d, J=1.5 Hz, 3H), 1.84–1.72 (m, 2H), 1.69–1.66 (m, 2H), 1.60–1.52 (m, merged with signal due to H_2O present in $CDCl_3$, 1H), 1.24 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 143.2, 140.1, 124.8, 114.6, 113.7, 64.4, 60.3, 46.8, 42.7, 42.4, 36.4, 32.2, 29.8, 29.7, 20.2, 14.3. HRMS (ESI) (m/z): found 307.1915 $[M+H]^+$; calcd for $C_{18}H_{27}O_4$ 307.1909. Further elution with petroleum ether/ethyl acetate (90:10) gave some unreacted **6b** (0.020 g, 10%).

4.11. 1-(But-3-enyl)-6-spiro(1,3-dioxalane)-2-hydroxymethyl-bicyclo[2.2.2]oct-7-ene (15a)

To a stirred solution of ester **14a** (1 g, 3.42 mmol) in dry ether (50 mL) was added lithium aluminum hydride (0.195 g, 5.13 mmol) at 0 °C. After which, reaction mixture was stirred for 12 h at ambient temperature and the reaction was quenched by a careful addition of water (~4 mL) dropwise at 0 °C. It was filtered through a Celite bed and washed with ethyl acetate (3×40 mL). Organic extract was combined and dried on sodium sulfate. Removal of solvent followed by column chromatography [elution with petroleum ether/ethyl acetate (75:25)] furnished the ketal-alcohol **15a** as a colorless liquid (0.800 g 93.45%) [R_f=0.5 petroleum ether/EtOAc (75:25)]. IR (neat) ν_{max}: 3446, 1639 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 6.36 (dd J_1=8.0 Hz, J_2=6.6 Hz, 1H), 5.90–5.79 (merged m, 2H), 5.02 (m of d, J=17.3 Hz, 1H), 4.94 (m of d, J=9.3 Hz, 1H), 3.94–3.83 (m, 4H), 3.70 (dd, J_1=10.4 Hz, J_2=5.2 Hz, 1H), 3.31(dd, J_1=10.4 Hz, J_2=8.6 Hz, 1H), 2.68–2.63 (br m, 1H), 2.45–2.38 (m, 1H), 2.32–2.22 (m, 2H), 1.99–1.86 (cluster of m, 2H), 1.71–1.59 (m, 3H), 1.39–1.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 135.4, 134.0, 114.9, 113.8, 65.3, 64.1, 64.0, 45.7, 43.2, 37.8, 31.0, 30.8, 29.8, 29.4. HRMS (ESI) (m/z): found 251.1641 $[M+H]^+$; calcd for $C_{15}H_{23}O_3$ 251.1647.

4.12. 1-(But-3-enyl)-8-methyl-6-spiro(1,3-dioxalane)-2-hydroxymethyl-bicyclo[2.2.2]oct-7-ene (15b)

The reaction of **14b** (0.140 g, 0.457 mmol) with lithium aluminum hydride (0.034 g, 1.13 mmol) in dry diethyl ether (30 mL) according to above procedure followed by chromatography (elution of petroleum ether/ethyl acetate 75:25) gave the alcohol **15b** (0.114 g, 96.66%) [R_f=0.5 petroleum ether/EtOAc (75:25)]. IR (neat) ν_{max}: 3397, 1639 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 5.90–5.79 (complex m, 1H), 5.46 (br s, 1H), 5.02 (m of d, J=17.1 Hz, 1H), 4.93 (m of d, J=10.9 Hz, 1H), 3.95–3.82 (m, 4H), 3.69 (dd, J_1=10.4 Hz, J_2=4.5 Hz, 1H), 3.34 (dd, J_1=10.4 Hz, J_2=7.8 Hz, 1H), 2.45–2.38 (m, 2H), 2.31–2.19 (m, 2H), 1.97–1.83 (m, 2H), 1.80 (d, J=1.6 Hz, 3H), 1.71–1.54 (m, merged with signal due to H_2O present in $CDCl_3$, total 3H), 1.36 (m of d, J=12.5 Hz, 1H), 1.20 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 140.1, 126.0, 115.2, 113.8, 65.5, 64.2, 64.0, 46.0, 42.9, 38.4, 36.4, 30.3, 29.8, 29.6, 20.2. HRMS (ESI) (m/z): found 265.1801 $[M+H]^+$; calcd for $C_{16}H_{25}O_3$ 265.1804.

4.13. 1-(But–3-enyl)-6-spiro(1,3-dioxalane)-bicyclo[2.2.2]oct-7-en-2-carboxaldehyde (16a)

To a stirred mixture of alcohol **15a** (0.350 g, 1.4 mmol), 4-methyl-morpholine-*N*-oxide (NMO) (0.229 g, 1.95 mmol), and powdered molecular sieves (4 Å, 1.0 g) in dry dichloromethane (50 mL) was added TPAP (0.017 g, 0.09 mmol) at room temperature

under nitrogen atmosphere. The reaction mixture was further stirred for 12 h (TLC) and filtered through a small pad of silica gel. The filtrate was concentrated and the product was chromatographed on silica gel (petroleum ether/ethyl acetate, 80:20) to give the aldehyde **16a** (0.340 g, 98%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (80:20)]. IR (neat) ν_{max}: 2925, 1740 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (d, J=4.4 Hz, 1H), 6.47 (dd, J_1=8.0 Hz, J_2=6.6 Hz, 1H), 6.04 (d, J=8.0 Hz, 1H), 5.86–5.75 (m, 1H), 5.02 (m of d, J=17.3 Hz, 1H), 4.94 (m of d, J=10.6 Hz, 1H), 3.95–3.85 (m, 4H), 3.06–3.00 (m, 1H), 2.80–2.76 (m, 1H), 2.31–2.23 (m, 2H), 1.95–1.86 (m, 2H), 1.83–1.71 (m, 2H), 1.68–1.58 (m, partly merged with signal due to H_2O in $CDCl_3$, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7, 139.3, 136.3, 132.9, 114.3, 64.6, 64.5, 49.8, 45.9, 43.4, 30.8, 29.8, 29.7, 27.9. HRMS (ESI) (m/z): found 249.1485 $[M+H]^+$; calcd for $C_{15}H_{21}O_3$ 249.1491.

4.14. Ethyl-5-[(but-3-enyl)-6-spiro(1,3-dioxalane)-bicyclo [2.2.2]oct-7-en-2-yl]-penta-2,4-dienoate (17a)

To a solution of triethyl phosphonocrotonate (0.36 g, 1.44 mmol) in dry THF (5 mL) was added a solution of *n*-BuLi (0.8 mL, 1.28 mmol, 1.6 M) at −78 °C. The mixture was stirred for 30 min at −78 °C after which a solution of the aldehyde **16a** (0.2 g, 0.8 mmol) in dry THF (5 mL) was added. The mixture was then stirred for 1 h at −78 °C and then it was quenched by careful addition of water and extracted with ether (4×10 mL). The combined extract was washed with brine (20 mL) and dried on anhydrous sodium sulfate. The solvent was removed and the product was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (90:10) gave **17a** (0.26 g, 94%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 2927, 1714 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, J_1=15.5 Hz, J_2=11.1 Hz, 1H), 6.42 (dd, J_1=8.8 Hz, J_2=6.6 Hz, 1H), 6.13 (dd, J_1=15.5 Hz, J_2=11.1 Hz, 1H), 5.96 (d, J=8.8 Hz, 1H), 5.80–5.69 (m, 2H), 4.93 (m of d, J=15.5 Hz, 1H), 4.87 (m of d, J=11.1 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.94–3.83 (m, 4H), 2.93–2.85 (m, 1H), 2.68–2.60 (m, 1H), 2.25–2.16 (m, 2H), 2.04–1.94 (m, 1H), 1.77–1.53 (m, merged with signal due to H_2O present in $CDCl_3$, 4H), 1.32–1.23 (t merged with m, J=7.1 Hz, total 4H), 1.16–1.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 147.8, 144.9, 139.8, 135.5, 132.8, 127.6, 119.4, 114.3, 113.7, 64.1, 64.0, 60.2, 46.7, 43.0, 41.3, 34.3, 30.8, 30.0, 29.6. HRMS (ESI) (m/z): found 345.2057 $[M+H]^+$; calcd for $C_{21}H_{29}O_4$ 345.2066.

4.15. Ethyl-8-methyl-5-[(but-3-enyl)-6-spiro(1,3-dioxalane)-bicyclo[2.2.2]oct-7-en-2-yl]-penta-2,4-dienoate (17b)

To a solution of alcohol **15b** (0.100 g, 0.37 mmol) in CH_2Cl_2 (30 mL) was added TPAP (0.013 g, 0.0.037 mmol), NMO (0.066 g, 0.56 mmol), and crushed molecular sieves (4 Å, 0.500 g). The reaction mixture was stirred at ambient temperature for 12 h. It was filtered on Celite pad and washed with dichloroethane. The filtrate was concentrated and the product was chromatographed on silica gel (petroleum ether/ethyl acetate, 80:20) to give the aldehyde **16b** (0.95 g, 96%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (80:20)] [IR (neat) ν_{max}: 1719, 1641 cm^{-1} ^1H MNR (400 MHz, $CDCl_3$): δ 9.39 (d, J=4.5 Hz, 1H), 5.86–5.74 (m, 1H), 5.62 (br s, 1H), 5. 00 (m of d, J=16.4 Hz, 1H), 4.93 (m of d, J=9.4 Hz, 1H), 3.99–3.83 (m, 4H), 3.03–2.97 (m, 1H), 2.55–2.49 (br m, 1H), 2.32–2.18 (m, 2H), 1.92–1.82 (m, merged with the signal due to Me, total 5H), 1.79–1.58 (cluster of m merged with signal due to H_2O in $CDCl_3$, total 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 145.4, 139.4, 125.0, 114.2, 64.6, 64.4, 50.5, 46.3, 43.0, 36.3, 30.0, 29.7, 27.3, 20.3]. The aldehyde thus obtained was subjected to Wittig reaction as described below.

To a stirred solution of triethyl phosphonocrotonate (0.120 g, 0.48 mmol) in dry THF (5 mL) was added *n*-BuLi (0.204 g, 0.300 mL, 1.60 mmol) at −78 °C. The reaction mixture was stirred for 30 min after which a solution of the aldehyde **16b** (0.060 g, 0.22 mmol) in dry THF (5 mL) was added. The reaction mixture was further stirred for 1 h at −78 °C and it was quenched by careful addition of water followed by brine. The organic layer was separated and aqueous layer was extracted with ether (3×10 mL). Combined organic extract was washed with brine and dried. Removal of solvent followed by chromatography (elution with petroleum ether/ethyl acetate 90:10) gave compound **17b** (0.065 g, 80%) as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 1714, 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, J_1=14.6 Hz, J_2=10.0 Hz, 1H), 6.12 (dd, J_1=14.6, J_2=10.0 Hz, 1H), 5.81–5.69 (merged m, total 3H), 5.54 (br s, 1H), 4.93 (m of d, J=16.0 Hz, 1H), 4.87 (m of d, J=10.6 Hz, 1H), 4.18 (q, J=7.1 Hz, 2H), 3.94–3.83 (m, 4H), 2.93–2.84 (m, 1H), 2.41–2.37 (m, 1H), 2.23–2.14 (m, 2H), 2.01–1.92 (m, 1H), 1.84 (br s, 3H), 1.74–1.48 (m merged with signal due to H_2O in $CDCl_3$, 3H), 1.32–1.25 (t merged with m, 4H), 1.14–1.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 148.4, 145.1, 144.5, 140.2, 127.6, 125.1, 119.4, 114.9, 113.8, 64.3, 64.2, 60.3, 47.1, 42.9, 42.2, 36.5, 33.9, 30.4, 29.7, 20.3, 14.4. HRMS (ESI) (m/z): found 359.2225 $[M+H]^+$; calcd for $C_{22}H_{31}O_4$ 359.2222.

4.16. Ethyl-5 [1-(but-3-enyl)-6-spiro(1,3-dioxalane) bicyclo [2.2.2]oct-7-en-2-yl]penta-2,4-dienoate (5a)

To a solution of **17a** (0.100 g, 0.29 mmol) in acetone/water (20 mL, 4:1) was added dil HCl (0.2 mL) at ~10 °C. The reaction mixture was stirred at ambient temperature for 6 h. Acetone was removed and aqueous residue was extracted with ethyl acetate (3×15 mL). Combined extract was washed with sodium bicarbonate, brine, and dried on anhydrous sodium sulfate. The solvent was removed and the product was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (90:10) gave the keto-ester **5a** (0.085 g, 98%), which solidified after keeping in refrigerator, mp 64–65 °C [R_f=0.4, petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 1715 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, J_1=15.2 Hz, J_2=11.4 Hz, 1H), 6.62 (dd, J_1=9.5 Hz, J_2=7.6 Hz, 1H), 6.14 (dd, J_1=15.2 Hz, J_2=11.4 Hz, 1H), 5.89 (d, J=7.6 Hz, 1H), 5.88–5.70 (m, 3H), 5.01 (m of d, J=17.1 Hz, 1H), 4.92 (m of d, J=9.5 Hz, 1H), 4.19 (q, J=7.2 Hz, 2H), 3.00–2.92 (m, 1H), 2.62–2.52 (m, 1H), 2.24–2.00 (m, 5H), 1.70–1.60 (m, 2H), 1.40–1.35 (m, 1H), 1.28 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.8, 167.1, 144.3, 144.1, 139.1, 137.6, 129.7, 129.0, 120.7, 114.4, 60.4, 55.5, 43.4, 40.8, 34.4, 32.1, 29.6, 28.9, 14.4. HRMS (ESI) (m/z): found 301.1810 $[M+H]^+$; calcd for $C_{19}H_{25}O_3$ 301.1804.

Crystal data for **5a**: $C_{19}H_{24}O_3$, mol. wt. 300.38. Crystal size 0.33×0.23×0.18 mm. Space group: monoclinic $P2_1/c$, Z=4, a=16.541(2), b=7.4877(15), c=13. 6629(18) Å, α=90.00°, β=16.983(16)°, γ=90.00°; D_c: 1.188 mg/m^3; crystal volume 1679.6(5) $Å^3$ T=150(2) K; λ=0.71073 Å $F(000)$=648. GOF=1.093. Reflections collected/unique 7748/2947, [R_{int}=0.1045], final R indices [$I>2\sigma(I)$], R_1=0.0810, wR_2=0.2223. R indices all data=R_1=0.1614, wR_2=0.2555. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre, CCDC no. 892902. Copy of the data can be obtained, free of charge, on application to CCDC. E-mail: deposit@ccdc.cam.ac.uk.

4.17. Ethyl-14-ethylenedioxy-tetracyclo[10.2.2.$0^{1,10}$.$0^{4,9}$]hexadec-15-ene-6-carboxylate (18a)

A solution of compound **17a** (0.075 g, 0.21 mmol) in dry toluene (10 mL) was heated at 175 °C sealed tube for 24 h. After which, toluene was removed under reduced pressure and residue was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (85:15) gave compound **18a** (0.056 g, 80%) as a thick colorless liquid [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}:

2929, 1715 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 6.36 (dd, J_1=8.2 Hz, J_2=6.6 Hz, 1H), 5.95 (d, J=8.2 Hz, 1H), 5.77–5.70 (br m, 2H), 4.14 (q, J=6.6 Hz, 2H), 3.90–3.81 (m, 4H), 3.06–3.01 (m, 1H), 2.63–2.58 (m, 1H), 2.05 (d, J=11.6 Hz, 1H), 1.94–1.83 (m, 2H), 1.80–1.73 (m, 1H), 1.72–1.54 (m merged with signal due to H_2O present in $CDCl_3$, 3H), 1.40–1.16 (m merged with t, total 8H), 1.14–1.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 134.8, 133.7, 132.2, 124.5, 114.3, 65.2, 64.6, 60.7, 46.4, 46.0, 42.7, 40.9, 37.6, 36.7, 31.9, 31.4, 31.0, 29.3, 26.4, 14.4. HRMS (ESI) (m/z): found 345.2053 $[M+H]^+$; calcd for $C_{21}H_{29}O_4$ 345.2066.

4.18. Ethyl-14-oxo-tetracyclo[10.2.2.0^{1,10}.0^{4,9}]hexadec-15-ene-6-carboxylate (4a)

To a stirred solution of compound **18a** (0.042 g, 0.12 mmol) in acetone/water (4:1, 20 mL), was added 1 N HCl (0.5 mL) at 0 °C after which reaction mixture was further stirred for 2 h at ambient temperature. After completion of reaction (TLC), the reaction mixture cooled to 0 °C and $NaHCO_3$ was added to it. Acetone was evaporated under reduced pressure, water (10 mL) was added to reaction mixture, and the aqueous layer was extracted with ethyl acetate (3×30 mL). Combined organic extract was dried on anhydrous Na_2SO_4, solvent was removed, and product was chromatographed. Elution with petroleum ether/ethyl acetate (85:15) gave keto-ester **4a** (0.025 g 69%) as a colorless liquid [R_f=0.4 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 2931, 1718 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 6.52 (superimposed dd, J=6.6 Hz, 1H), 5.82 (d, J=6.6 Hz, 1H), 5.80–5.73 (m, 2H), 4.14 (q, J=7.4 Hz, 2H), 3.10–3.03 (m, 1H), 2.97–2.90 (m, 1H), 2.14–2.00 (m, 4H), 1.92–1.70 (m, 4H), 1.59–1.51 (m, 1H), 1.49–1.34 (m, 3H), 1.30–1.20 (m merged with t, J=7.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.9, 173.9, 137.2, 131.2, 130.3, 125.4, 60.7, 53.5, 45.6, 40.8, 39.7, 39.6, 36.3, 31.6, 31.4, 31.2, 28.8, 27.3, 14.3. HRMS (ESI) (m/z): found 301.1809 $[M+H]^+$; calcd for $C_{19}H_{25}O_3$ 301.1804.

4.19. Ethyl-16-methyl-14-ethylenedioxy-tetracyclo[10.2.2.0^{1,10}.0^{4,9}]hexadec-15-ene-6-carboxylate (18b)

The solution of compound **17b** (0.050 g, 0.139 mmol) in dry toluene (10 mL) was heated at 175 °C in a sealed tube for 18 h. Toluene was removed under reduced pressure and residue was chromatographed on neutral silica gel (100–200 mesh). Elution with petroleum ether/ethyl acetate (90:10) gave (0.045 g, 90%) compound **18b** as a colorless liquid [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (neat) ν_{max}: 2929, 1732 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 5.81–5.69 (m, 2H), 5.58 (br s, 1H), 4.13 (q, J=7.0 Hz, 2H), 3.91–3.80 (m, 4H), 3.12–3.00 (m, 1H), 2.38–2.32 (m, 1H), 2.04 (d, J=12.0 Hz, 1H), 1.91–1.71 (m overlapped with d, J=1.5 Hz, total 5H), 1.68–1.62 (m, 2H), 1.60–1.50 (m merged with signal due to H_2O present in $CDCl_3$, total 3H), 1.40–1.17 (m merged with t, J=7.0 Hz, total 6H), 1.10–1.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 143.5, 132.3, 125.7, 124.4, 114.7, 65.2, 64.7, 60.6, 46.6, 45.9, 42.3, 40.9, 38.4, 36.7, 36.6, 31.45, 31.41, 29.3, 26.5, 20.2,14.4. HRMS (ESI) (m/z): found 359.2233 $[M+H]^+$; calcd for $C_{22}H_{31}O_4$ 359.2222.

4.20. Ethyl-16-methyl-14-oxo-tetracyclo[10.2.2.0^{1,10}.0^{4,9}]hexadec-15-ene-6-carboxylate (4b)

A solution of compound **17b** (0.050 g, 0.139 mmol) in dry toluene (11 mL) was heated in a sealed tube at 175 °C. After 18 h, toluene was removed in vacuo and residue was chromatographed on silica gel (100–200 mesh). Elution with petroleum ether/ethyl acetate (90:10) gave compound **4b** (0.039 g, 90%) as a colorless solid, mp 63–64 °C [R_f=0.5 petroleum ether/EtOAc (90:10)]. IR (KBr) ν_{max}: 1717 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 5.82–5.72 (m, 2H), 5.39 (br s, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.09–3.04 (m, 1H), 2.68–2.63 (m, 1H), 2.15–1.96 (complex m, 4H), 1.86 (s, 3H), 1.84–1.68 (m, 3H), 1.63–1.53 (m merged with signal due to H_2O in $CDCl_3$, 1H), 1.52–1.18 (cluster of m merged with t, J=7.1 Hz, total 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.3, 174.0, 146.5, 131.3, 125.4, 122.4, 60.8, 53.3, 45.6, 40.8, 40.3, 39.3, 36.8, 36.3, 31.3, 31.2, 28.8, 27.4, 20.3, 14.3. HRMS (ESI) (m/z): found 315.1961 $[M+H]^+$; calcd for $C_{20}H_{27}O_3$ requires 315.1960.

Crystal data for **4b**: $C_{20}H_{26}O_3$, mol. wt. 314.41. Crystal size 0.33×0.26×0.21 mm. Space group: monoclinic $P2_1/n$, Z=4, a=10.8066(10), b=9.1156(6), c=17. 6322(13) Å, α=90.00°, β=94.569(7)°, γ=90.00°; D_C: 1.206 mg/m^3; Crystal volume 1731.4(2) $Å^3$; T=293(2) K; λ=0.71073 Å; F(000)=680. GOF=1.028. Reflections collected/unique 14,256/3040, [R_{int}=0.1258], final R indices [$I>2\sigma(I)$], R_1=0.0617, wR_2=0.1322. R indices all data=R_1=0.1372, wR_2=0.1740. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre, CCDC no. 893371. Copy of the data can be obtained, free of charge, on application to CCDC. E-mail: deposit@ccdc.cam.ac.uk.

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Supplementary data

^1H NMR and ^{13}C NMR spectra of all new compounds and CIF data of **5a** and **4b**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.051.

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