Synthesis of (±)-14-*epi*-hydroxydolasta-1(15),7,9-triene and (±)-7-*epi*-acetoxy-14-*epi*-hydroxydolasta-1(15),8-diene*

George Majetich and Jianhua Yu

Abstract: 1,3-Dimethyl-2-nitrobenzene was converted to the key intramolecular Friedel–Crafts intermediate **24** in ten steps. Treatment of **24** with $TiCl_4$ produced tricyclic enone **25** in 61%–75% yield, having the requisite trans relationship of the two angular methyl groups and many of the salient features of the dolastane diterpenes. The structure of enone **25** was verified by X-ray crystallography analysis. Cyclization product **25** permitted the facile synthesis of (±)-14-*epi*-hydroxydolasta-1(15),7,9-triene and (±)-7-*epi*-acetoxy-14-*epi*-hydroxydolasta-1(15),8-diene, which are detailed in this article.

Key words: dolastanes, cyclialkylation, intramolecular Friedel–Crafts reactions, conformational biasing, regiospecific reductions.

Résumé : On a effectué la transformation en dix étapes du 1,3-diméthyl-3-nitrobenzène en composé **24**, l'intermédiaire clé d'une réaction de Friedel–Crafts intramoléculaire. Le traitement du produit **24** par du $TiCl_4$ à conduit avec un rendement de 61 à 75 % à formation de l'énone tricyclique **25** comportant la relation trans requise entre les deux groupes méthyles angulaires ainsi que plusieurs des caractéristiques principales des diterpènes du dolastane. La structure de l'énone **25** par diffraction des rayons-X. La cyclisation du produit **25** a permis de réaliser facilement la synthèse du (±)-14-*épi*-hydroxydolasta-1(15),7,9-triène et du (±)-7-*épi*-acétoxy-14-*épi*-hydroxydolasta-1(15),8-diène. Veuillez noter la cyclialkylation dans le texte.

Mots-clés : dolastanes, cycloalkylation, réactions de Friedel–Crafts intramoléculaires, biais conformationnel, réductions régiospécifiques.

[Traduit par la Rédaction]

Introduction

Fifty years ago, the diterpenoids were rare components of the marine environment. However, there are now more than 1900 diterpenoids known,[1] including twenty-five dolastanes. Dolatriol (**1**), the first dolastane isolated, was obtained from extracts of the digestive gland of the poisonous Indian Ocean sea hare *Dolabella auricularia* (Scheme 1)[2–5] and was very cytotoxic. Further work, however, established that dolatriol was actually produced by a brown algae genus *Dictyota* and only concentrated by *Dolabella auricularia* through its diet. All dolastanes have a distinctive 5,7,6-linear fused tricyclic framework. Their structural diversity rests on the following features: (*i*) the number and the position(s) of the hydroxyl group and double bond(s) (cf. **3**); (*ii*) the trans configuration of the two angular methyl groups at C-5 and C-12; (*iii*) the BC-ring system is usually trans fused; and (*iv*) many of the relative stereochemical configurations have been assigned based on X-ray crystal structure analysis or NMR studies. Finally, isoamijiol (**2**) has antimicrobial activity against *Mucor mucedo* and *Staphylococcus aureus*, and several dolastanes exhibit promising biological activity.[6]

The research groups of Pattenden,[7] Piers,[8] Mehta,[9] Paquette,[10] Williams,[11] and Majetich[12] have completed total syntheses of various dolastanes. The first dolastane synthesized was (±)-amijiol (**2**) by Pattenden and co-workers in 1986.[7] Their strategy for introducing the trans angular methyl groups is shown in Chart 1. The alkylation of hydroazulenone **5**, produced in seven steps from cyclopentanone, gave exclusively the α–epimer **6** because of the steric influence of the C-16 angular methyl group. The C-ring was formed with the requisite C-14 stereochemistry, using an intramolecular reductive coupling of ketone **6** with the alkyne; an allylic oxidation of alkene **7** introduced the C-2 hydroxyl group, albeit in low yield. In their synthesis of **3** from ketone **8**, Piers and Friesen used a similar alkylation strategy to introduce the C-12 and C-5 chirality (cf. **9** → **10**).[8] Vinylstannane **10** was converted into a Grignard reagent, which added to the C-14 carbonyl group to complete the synthesis. In 1987 Mehta and Krishnamurthy used a similar A+B→AB+C→ABC strategy to prepare **10**, using Pattenden's strategy, to install the C–14 hydroxyl group and create the C-ring.[9] The synthesis of the non-natural (±)-4aβ,10β-doladiol acetate (**4**) was achieved by Paquette et. al.[10] Instead of using the C-12

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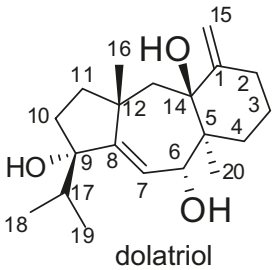
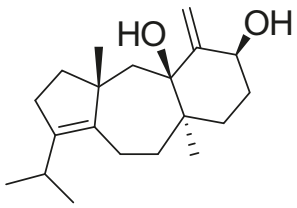
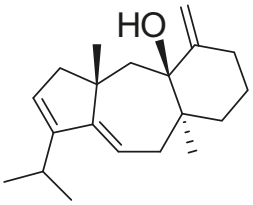
Scheme 1.



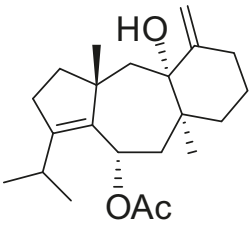
dolatriol (**1**)[2]



isoamijiol (**2**)[3]



14-hydroxydolasta-1(15),7,9-triene (**3**)[4]



7-*epi*-acetoxy-14-*epi*-hydroxydolasta-1(15),8-diene (**4**)[5]

methyl group to create the C-5 stereocenter, the alkylation of decalenone **11** produced alkylated product **12**, using the C-5 angular methyl group to create the C-12 stereochemistry. This synthesis featured a photochemical rearrangement to isomerize the 6,6,6-tricyclic α,β-epoxy ketone **13** into a 5,7,6-tricyclic dolastane skeleton. Six additional steps were needed to convert enone **14** into the 7,14-epimers of natural dolastane **4**. Williams and co-workers synthesized (–)-clavulara-1(15),17-dien-3,4-diol (**18**) from (+)-9,10-dibromocamphor **15**, which fragmented to form acid **16** upon exposure to NaOH.[11] Thirty-four transformations were required to transform **16** into macrocyclic epoxide **17**. An acid-catalyzed transannular epoxide opening of **17** created the C-ring with the required C-5 stereogenic center in 38% yield. In contrast to these strategies, Majetich and co-workers used an A +C→AC→ABC strategy to synthesize natural (±)-1(15),8-dolastadien-2-ol (±)-**23** (also called 14-deoxyisoamijiol).[12] In this synthesis, a functionalized A-ring (cf. **19**) was coupled with a C-ring containing an allylsilane (cf. **20**), followed by the addition of vinyllithium to the C-8 carbonyl group to produce dienone **21**. An intramolecular 1,6-addition of the allylsilane to the dienone **21** produced the dolastane skeleton with the trans relationship of the C-5 and C-12 angular methyl groups (cf. **22**). Nine steps were needed to introduce the C-1,C-15 double bond and the β-oriented C-2 hydroxyl group of **23**.

We have found that intramolecular Friedel–Crafts reactions, or cyclialkylations,[13] of conjugated dienones represent a powerful strategy to assemble various tricyclic frameworks.[14] We speculated that conformational biasing prior to ring formation would also create stereogenic centers (Scheme 2). However, the examination of a Dreiding model of **24** suggests that steric interactions between the C-16 and C-20 methyl groups in conformer **i**, and the steric interactions between the C-16 and C-15 methyl groups in conformer **ii** are comparable. We have observed that when the ortho and para positions are both substituted with identical groups (H, CH_3, or Cl), cyclization occurs at the para position relative to the electron donating substitutent (cf. **ii**). Thus, ring closure via conformer **ii** would produce the central cyclohexane ring and a trans relationship between the C-12 and C-5 angular methyl groups. If so, the functionality present in the A- and C-rings of enone **25** makes it an attractive precursor for the synthesis of several dolastanes. Herein, we report the synthesis of tricyclic enone **25** and its conversion into (±)-14-*epi*-hydroxydolasta-1(15),7,9-triene (**3**) and (±)-7-*epi*-acetoxy-14-*epi*-hydroxydolasta-1(15),8-diene (**4**).

Our study began with the preparation of the A- and C-rings. The A-ring was synthesized from 4-methylpentan-2-one (**26**), using our published procedure (Scheme 3);[12] commercially available 1,3-dimethyl-2-nitrobenzene (**29**) was our starting material for the C-ring synthesis (Scheme 4).

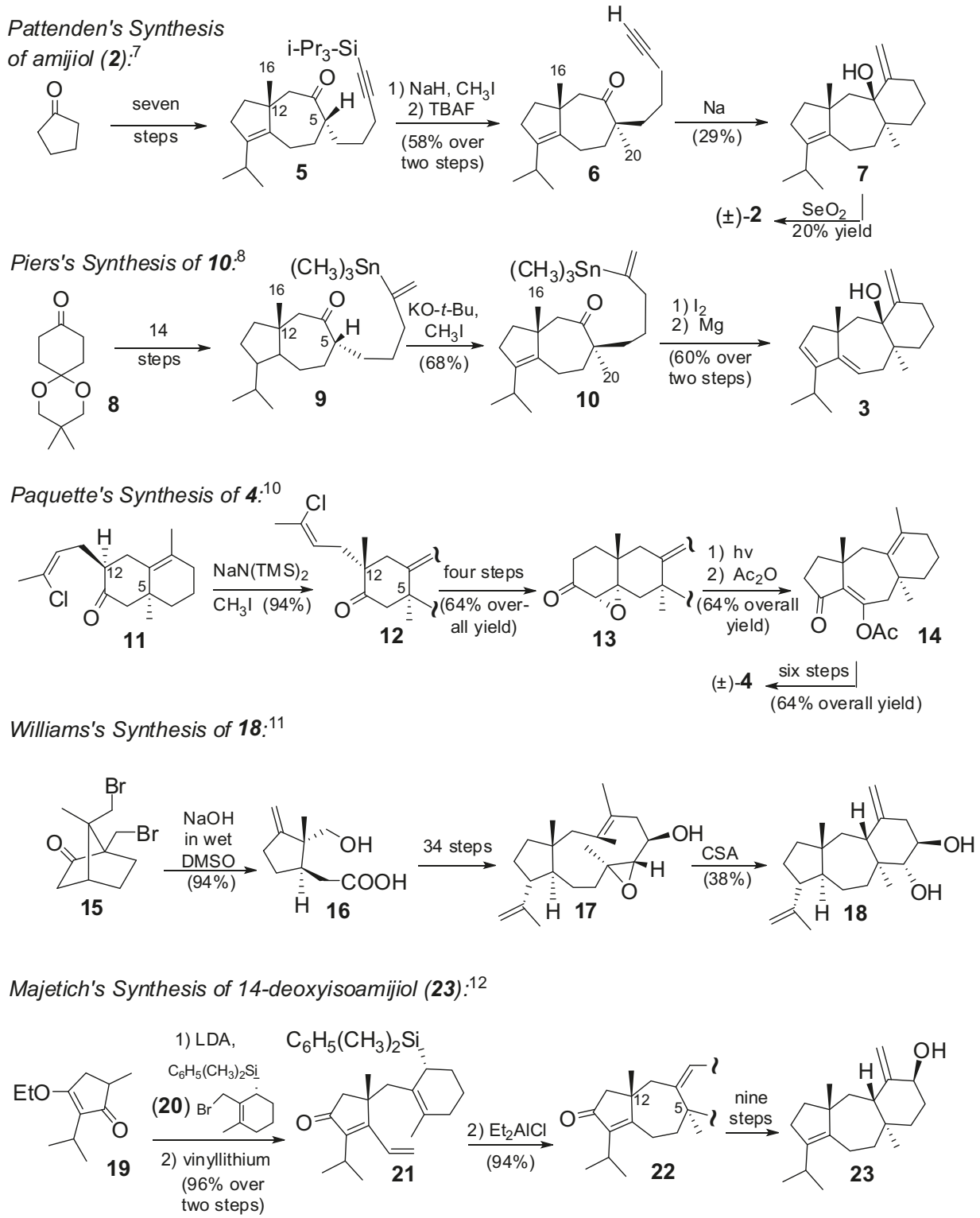
Monobromination of **29** followed by nucleophilic aromatic substitution gave anisole derivative **30** in 83% yield.[15] Zinc metal reduction of the nitro group provided aniline compound **31**.[16] The next step, a Sandmeyer reaction,[17] gave an inseparable mixture of mono- and di-bromination products **32** and **35**, respectively. Fortunately, the reaction of the organolithium reagents derived from **32** and **35** with DMF produced aldehyde **33** and dialdehyde **36**, which were easily separated. Reduction of aldehyde **33** to an alcohol with LAH was followed by the conversion of the benzylic alcohol to the corresponding benzyl bromide **34** by treatment with PBr_3.

With the A- and C-rings in hand, we set out to prepare dienone **24**, the key cyclization precursor. Coupling of **19** with **34** gave adduct **37** in excellent yield (Scheme 5). Addition of vinyllithium to ketone **37**, followed by acidic work-up, gave dienone **24** in high yield. There are two facial-selective products possible from the cyclization of dienone **24** (cf. **25** and **25a**) and two possible regioisomers (cf. **25b** and **25c**). In each case, cyclialkylation would produce a C-ring dienone, since the newly created quaternary carbon center (either at C-5 or at C-1) precludes re-aromatization. In a related cyclialkylation,[18] we found that under Lewis acid catalysis, dienone **38** produces tricycle **39** having an angularly fused quaternary carbon center (Scheme 6). We were pleased to find that treatment of dienone **24** with $TiCl_4$ at –60 °C for 30 min produced only enone **25**, albeit the isolated yield varied between 61% and 75%. An X-ray crystal structure analysis of **25** verified the trans configuration of the two angular methyl groups.

Several of the dolastanes have a β-hydroxyl group at C-2 and a C-1, C-15 exocyclic double bond, or a C-14 β-hydroxyl group, or a hydroxyl group or an acetate at C-4 (Scheme 7). To achieve a synthesis of (±)-7,14-*epi*-1(15),8-dolastadiene-7,14-diol 7-acetate (**4**), we needed to selectively reduce the C-2 and C-10 carbonyl groups and the C-3,C-4 double bond of enone **25**, as well as selectively introduce an acetate at C-7 and an α-oriented hydroxyl group at C-14 (cf. **4**). We were confident that the A-ring enone moiety would permit the introduction of the C-7,C-9 diene (cf. **40**) thereby facilitating a synthesis of **10**.

The C-2 carbonyl group, which is conjugated to two double bonds, has more resonance contributors with a negative charge on oxygen, thereby making it less reactive than the C-10 carbonyl group (Scheme 8). Indeed, treatment of enone

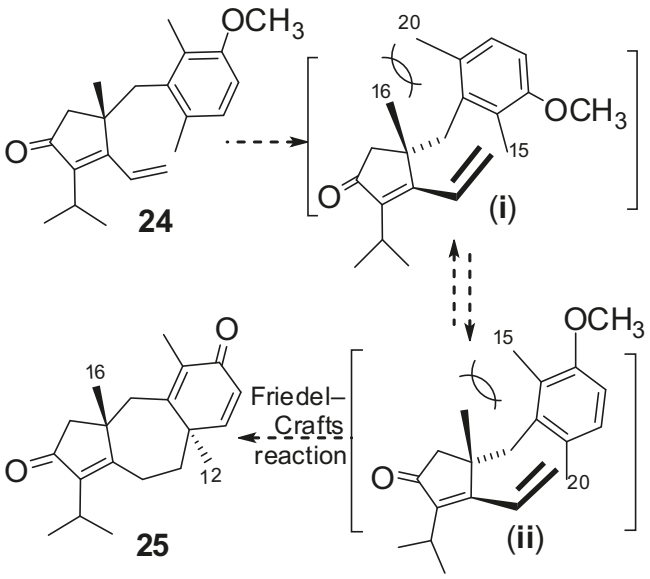
Chart 1.



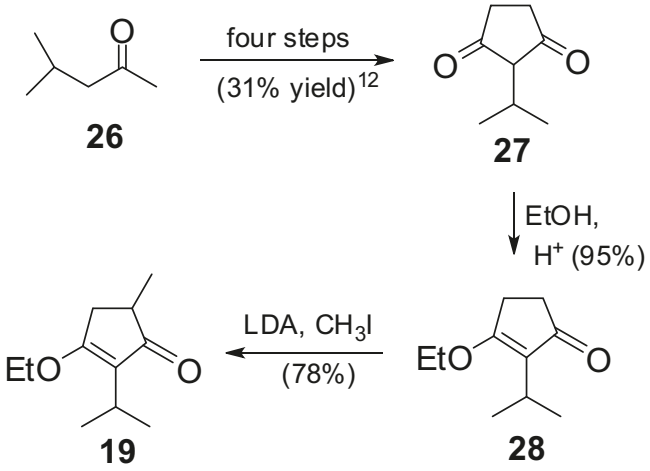
25 with sodium borohydride in the presence of TFA in dichloromethane selectivity reduced the C-10 carbonyl group to a methylene unit.[19] If, however, we first reduced the C-3, C-4 double bond (cf. **42**), the C-2 carbonyl group was found to be more reactive, presumably a result of the steric hindrance by the isopropyl group. Note that under the reaction conditions, enone **43** is rapidly reduced to produce diene **44**.

In their synthesis of **4**, Paquette et al. found that singlet oxygen migrated the C-1,C-14 double bond to the C-1,C-15 position and introduced an α-oriented alcohol at C-14.[10a] Reaction of enone **43** with singlet oxygen, followed by reduction of the intermediate allylic peroxide, introduced an alcohol from the α-face because of the steric effect of the C-16 methyl, which added in Michael fashion to the A-ring enone

Scheme 2.



Scheme 3.

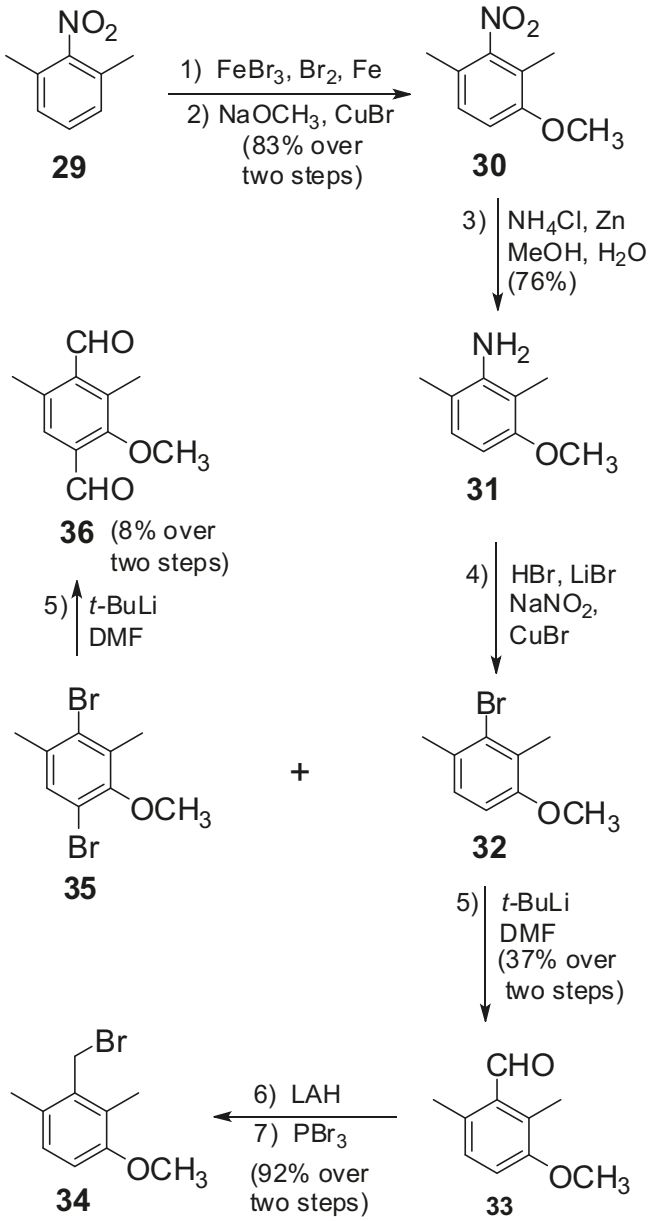


to form tetrahydrofuran **45** in 92% yield. This result indicated that the C-10 carbonyl group had to be removed, or protected, before the C-14 α-hydroxyl group is introduced.

Another way to introduce the C-14 α-allylic alcohol was by opening a C-1,C-14 α-epoxide. However, because of the steric influence of the C-16 methyl group, the epoxidation of **43** gave only epoxide **46** (Scheme 9). The reduction of the C-10 carbonyl group with LAH gave an allylic alcohol, which rapidly dehydrated to form diene **47**. Treatment of **47** with LDA at 50 °C overnight gave alcohol **48** in 93% yield; this compound is epimeric at C-14 to natural dolastane **10**. A traditional way to prepare an epimeric epoxide is to make the bromohydrin from the alkene and then treat it with base. Since the C-16 methyl blocks the β-face of the C-1,C-14 double bond, bromonium ion formation must occur from the α-face so that the addition of water to the bromonium ion generated in situ must add from the β-face to provide the β-epoxide. However, when **43** was treated with NBS in wet acetone, allylic oxidation at C-2 produced dienone **42** in 71% yield.

Scheme 10 presents a formal synthesis of **4** from diene **44**. Longer reaction time in the reduction of enone **42** produced

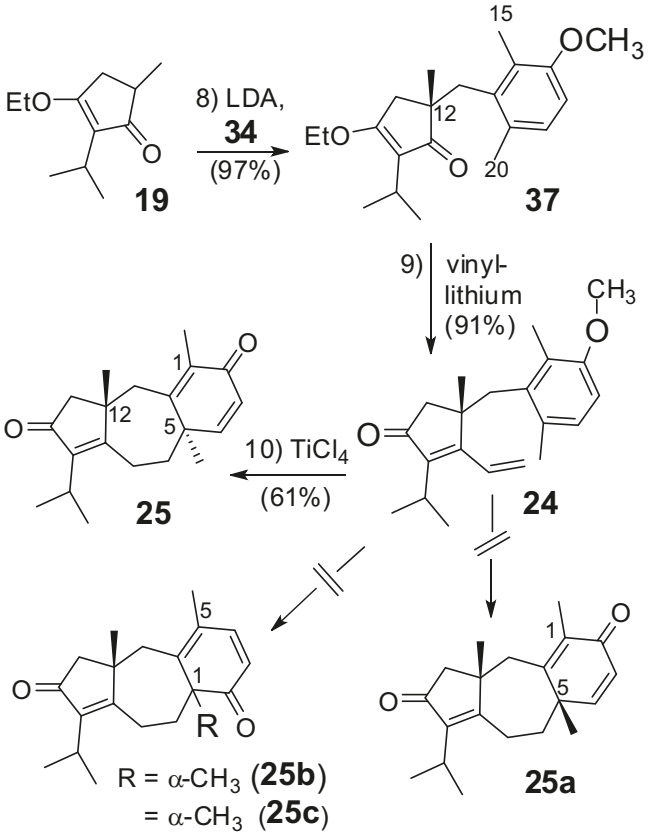
Scheme 4.



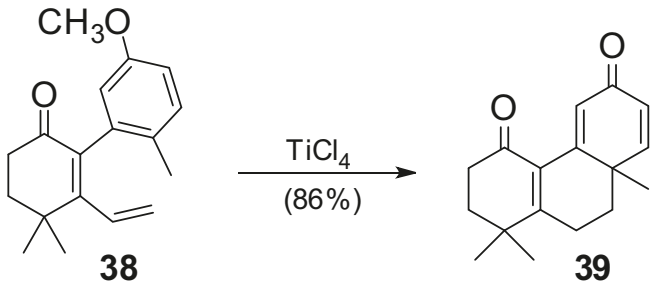
diene **44** in 73% yield. The reaction of diene **44** with selenium dioxide and *t*-butylhydroperoxide produced alcohol **49** in 45% yield and triene **50** in 40% yield; all efforts to prevent the in situ dehydration of **49** failed. Allylic alcohol **49** was oxidized using freshly activated MnO_2 to enone **51**, which Paquette and co-workers converted to **4** using the three transformations shown in 64% overall yield.[10c]

In summary, 1,3-dimethyl-2-nitrobenzene was converted in ten steps into tricyclic dienone **25.** In the key reaction, diene **24** was cyclized to produce the central seven-membered ring and created the required stereochemistry of the C-5 and C-12 quaternary carbon atoms. Changing the oxidation states at C-3, C-4, C-10, C-14, and C-15 required six transformations and produced (±)-14-*epi*-hydroxydolasta-1(15),7,9-triene (**48**), which is epimeric at C-14 to the natural dolastane. Diene **44**, at first an unwanted side product in the reduction of dienone **42**, was optimized and then converted in two steps into enone **51**, an intermediate in Paquette's synthesis of

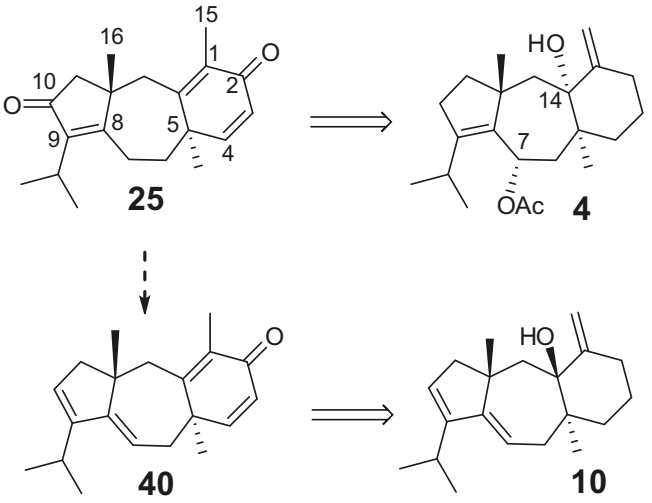
Scheme 5.



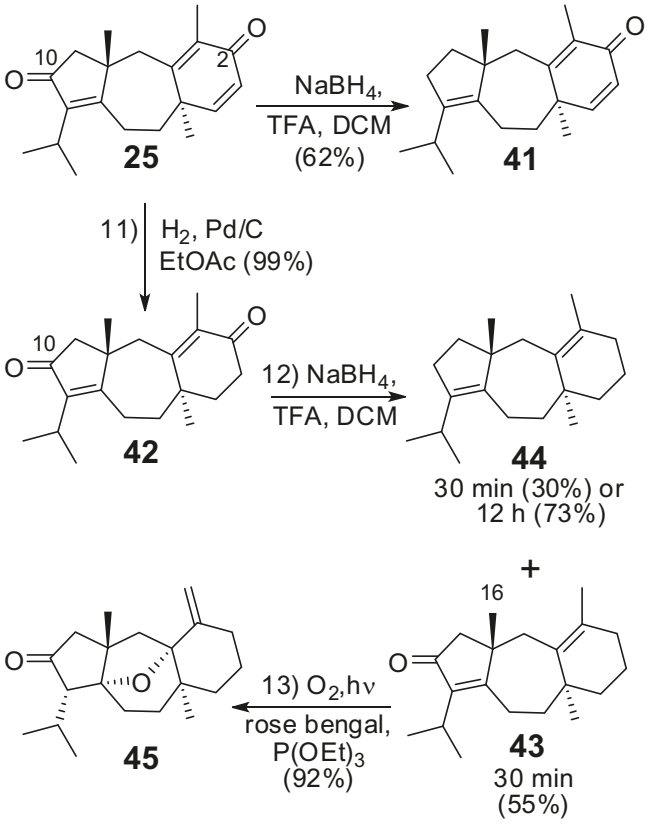
Scheme 6.



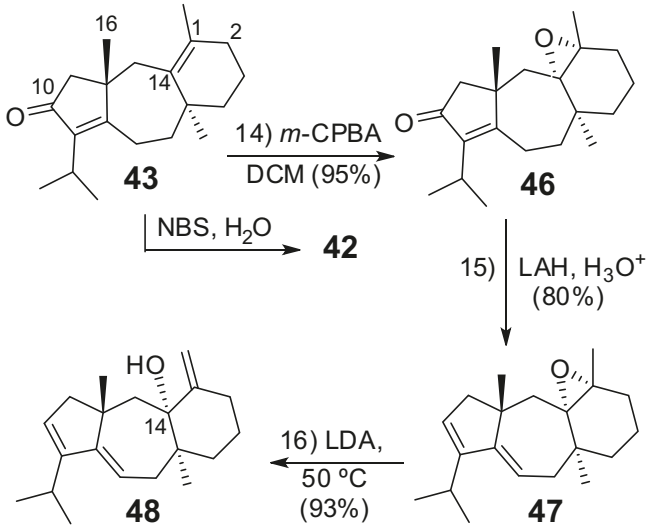
Scheme 7.



Scheme 8.



Scheme 9.



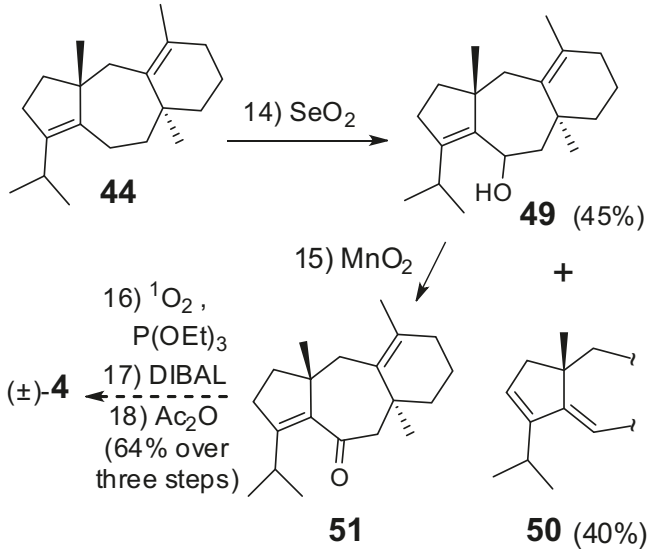
(±)-7-*epi*-acetoxy-14-*epi*-hydroxydolasta-1(15),8-diene (**4**). We are confident that dienone **25,**, or a derivative thereof, will permit the efficient synthesis of the more oxygenated naturally occurring dolastanes.

Experimental section

General procedures

All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all ethereal work-ups consisted of the following procedure. The

Scheme 10.



reaction was quenched at RT (RT) with water. The organic solvent was removed under reduced pressure on a rotary evaporator, and the residue was extracted with diethyl ether twice. The combined organic layer was washed with water, brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 torr (1 torr = 133.322 4 Pa) to constant weight, afforded a crude residue that was purified by flash chromatography using silica gel 60 (230–400 mesh ASTM) eluted with distilled reagent grade petroleum ether and diethyl ether. Melting points were recorded on a Laboratory Devices Mel–Temp 3.0. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVB–400 and DRX–500 MHz spectrometers with ^{13}C operating frequencies of 100 and 125 MHz, respectively. ^{1}H NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. ^{13}C NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 77.23) as an internal reference. The IR spectra were obtained using an Avatar 360FT-IR spectrophotometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbances are reported. High-resolution MS spectra were taken using a LCT Premier mass spectrometer from Waters.

1-Methoxy-2,4-dimethyl-3-nitrobenzene (30)

To a solution of 1,3-dimethyl-2-nitrobenzene (**29**) (50.0 g, 331 mmol) in freshly distilled DCM (150 mL) was added $FeBr_3$ (2.0 g, 6.8 mmol) and Fe (5.0 g, 89 mmol). Molecular bromine (18.6 mL, 361 mmol) was added dropwise, and 100 mL of DCM was added to the mixture. The reaction mixture was refluxed for 8 h. The reaction mixture was cooled to RT, followed by standard ethereal work-up. The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated under vacuum using rotary evaporator to give 74.3 g (98.0%) of the bromide as a crude red oil. IR (film): λ_{max}: 2927, 1517, 1370, 815 cm^{-1}. ^{1}H (400 MHz) δ: 7.55 (d, J = 4.8 Hz, 1H), 7.02 (d, J = 4.8 Hz, 1H), 2.35 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz) δ: 134.0 (d), 129.9 (d), 129.6 (s), 128.7 (s), 123.2 (s), 18.3 (q), 17.3 (q) ppm. HR-MS: $[M]^+_{obs}$ = 228.9738, $[M]^+_{calcd}$ = 228.9738. This crude bromide was used in the next reaction without purification.

A solution of sodium methoxide was prepared by adding small pieces of sodium metal (21.0 g, 0.913 mol) to anhydrous methanol (300 mL). After the complete consumption of the sodium, a solution of the above bromide (70.0 g, 304 mmol) in anhydrous DMF (300 mL) was added, followed by the addition of CuBr (4.0, 28.0 mmol). The reaction mixture was heated at 110 °C for 12 h, then cooled to RT, and water (100 mL) was added dropwise to quench the reaction. Standard ethereal work-up gave 46.8 g (85%) of nitrobenzene **30** as a crude red solid, which was recrystallized (benzene) to give white crystals. Mp 48.7–49.0 °C. IR (film) λ_{max}: 2930, 1524, 1263, 810 cm^{-1}. ^{1}H (400 MHz) δ: 7.06 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H), 2.23 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz) δ: 181.1 (s), 156.4 (s), 128.9 (d), 120.6 (s), 118.7 (s), 111.8 (d), 56.2 (q), 16.7 (q), 10.9 (q) ppm. HR-MS: $[M]^+_{obs}$ = 181.0741, $[M]^+_{calcd}$ = 181.0739.

3-Methoxy-2,6-dimethylaniline (31)

To a solution of anisole **30** (30.0 g, 166 mmol) in MeOH (270 mL) and H_2O (30 mL) was added NH_4Cl (26.0 g, 486 mmol), followed by Zn powder (110 g, 1.68 mol) in small portions. The reaction mixture was stirred at RT for 2 h, followed by standard ethereal work-up, to give 19.0 g (76.0%) of aniline **31** as a crude red oil which was used in the next step without purification. IR (film) λ_{max}: 3393, 2910, 1626, 1496, 1262, 791 cm^{-1}. ^{1}H (400 MHz) δ: 6.89 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 3.80 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz) δ: 156.7 (s), 143.8 (s), 127.6 (d), 115.1 (s), 110.9 (s), 101.0 (d), 55.9 (q), 17.4 (q), 9.4 (q) ppm. HR-MS: $[M]^+_{obs}$ = 152.1074, $[M]^+_{calcd}$ = 152.1075.

2-Bromo-4-methoxy-1,3-dimethylbenzene (32) and 1,4-dibromo-2-methoxy-3,5-dimethylbenzene (35)

A round bottom flask at 0 °C was charged with HBr (4.67 g, 27.7 mmol), THF (60 mL), LiBr (1.14 g, 13.1 mmol), $NaNO_2$ (1.0 g, 14.5 mmol), and CuBr (2.26 g, 15.8 mmol). The ice bath was removed, and aniline **31** (3.0 g, 2.00 mmol) in THF (15 mL) was added dropwise. The reaction mixture was stirred at RT for an additional 1 h, followed by standard ethereal work-up, to give 3.43 g of a black oil which was predominantly bromide **32** along with dibromide **35**, which could not be separated. Albeit a mixture, the following data is for bromide **32**, the major component. ^{1}H (400 MHz) δ: 7.08 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 2.20 (s, 3H), 2.18 (s, 3H).

3-Methoxy-2,6-dimethylbenzaldehyde (33) and 2-methoxy-3,5-dimethylterephthalaldehyde (36)

To a solution of **32** and **35** (34 g) in THF (250 mL) at –78 °C was slowly added *t*-BuLi (180 mL, 306 mmol). This mixture was stirred at –78 °C for 2 h, followed by the addition of DMF (40 mL). The reaction mixture was warmed to RT and stirred overnight. Water (10 mL) was added slowly to quench the reaction, followed by standard ethereal work-up. Column chromatography (elution with pet. ether/EtOAc, 10:1) gave 1.22 g (37% over two steps) of aldehyde **33** (hexane/EtOAc, 4:1, R_f **33** = 0.66) as a

white solid. IR (film) λ_{max}: 2939, 1691, 1262 cm^{-1}. ^{1}H (400 MHz) δ: 10.6 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 2.51 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (125 MHz) δ: 194.5 (d), 156.4 (s), 133.8 (s), 132.1 (s), 129.8 (s), 129.6 (d), 115.0 (d), 56.1 (q), 20.1 (q), 11.5 (q) ppm. HR-MS: $[M]^+_{obs}$ = 164.0840, $[M]^+_{calcd}$ = 164.0837. Further elution gave 0.31 g (8.1% over two steps) of *bis*-aldehyde **36** as a white solid (hexane/EtOAc, 4:1, R_f **36** = 0.45). Mp = 82.0–82.3 °C. IR (film) λ_{max}: 2930, 1691, 1409, 1232 cm^{-1}. ^{1}H (400 MHz) δ: 10.6 (s, 1H), 10.4 (s, 1H), 7.54 (s, 1H), 3.85 (s, 3H), 2.55 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz) δ: 193.7 (d), 190.1 (d), 160.4 (s), 138.8 (s), 136.2 (s), 134.9 (s), 131.4 (s), 128.9 (d), 63.8 (q), 19.9 (q), 11.8 (q) ppm. HR-MS: $[M]^+_{obs}$ = 192.0790, $[M]^+_{calcd}$ = 192.0786.

2-(Bromomethyl)-4-methoxy-1,3-dimethylbenzene (34)

A solution of aldehyde **33** (10.0 g, 61.0 mol) in Et_2O (150 mL) was cooled to 0 °C and LAH (2.55 g, 67.1 mmol) was added portion-wise. The ice bath was removed and the solution was stirred at RT for 1 h. The solution was poured into a 2 L Erlenmeyer flask containing Na_2SO_4 (20 g) and EtOAc (300 mL). Water was added slowly until the heterogeneous mixture turned to white. Standard ethereal work-up, followed by column chromatography (elution with pet ether/EtOAc = 4:1), afforded 9.60 g (95%) (3-methoxy-2,6-dimethylphenyl)methanol as a white solid (hexane/EtOAc, 4:1, R_f alcohol = 0.25). IR (film) λ_{max}: 3396, 2957, 1464, 1258 cm^{-1}. ^{1}H (400 MHz) δ: 7.02 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.75 (s, 2H), 3.82 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (125 MHz) δ: 156.4 (s), 137.8 (s), 129.2 (s), 128.4 (d), 126.4 (s), 110.4 (d), 59.8 (t), 55.9 (q), 19.2 (q), 11.6 (q) ppm. HR-MS: $[M]^+_{obs}$ = 166.0999, $[M]^+_{calcd}$ = 166.0994.

A solution of the above alcohol (5.00 g, 30.1 mmol) in Et_2O (150 mL) was cooled to 0 °C and PBr_3 (3.1 mL, 33.1 mmol) was added dropwise. The resulting solution was removed from the ice bath and stirred at RT for 1 h. The resulting solution was cooled to 0 °C, and brine (30 mL) was added slowly. The aqueous phase was removed and the organic layer was dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure, and column chromatography (elution with pet ether/EtOAc, 15:1) afforded 6.69 g (97%) of bromide **34** as a white solid (hexane/EtOAc, 4:1, R_f **34** = 0.80). Mp = 62.3–62.5 °C. IR (film) λ_{max}: 3000, 2833, 1486, 1261 cm^{-1}. ^{1}H (400 MHz) δ: 7.03 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 4.60 (s, 2H), 3.83 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (125 MHz) δ: 156.4 (s), 135.3 (s), 129.3 (s), 128.4 (d), 126.5 (s), 111.0 (d), 55.9 (q), 29.9 (t), 19.0 (q), 11.4 (q) ppm. HR-MS: $[M+H]^+_{obs}$ = 228.0140, $[M+H]^+_{calcd}$ = 228.0150.

3-Ethoxy-2-isopropyl-5-(3-methoxy-2,6-dimethylbenzyl)-5-methylcyclopent-2-en-1-one (37)

To a solution of diisopropylamine (2.40 mL, 17 mmol) in THF (20 mL) at –78 °C was added *n*-butyllithium (6.30 mL, 16 mmol) over a 5 min period. The resulting mixture was stirred at RT for 10 min then cooled to –78 °C. A solution of enone **19** (2.60 g, 14.3 mmol) and HMPA (2.60 g, 14.3 mmol) in THF (10 mL) was cannulated over a 5 min period. The resulting solution was stirred for 1 h at –78 °C then raised to –63 °C. A solution of bromide **34** (2.94 g, 17.2 mmol) in THF (10 mL) was cannulated into the reaction mixture over a 2 min period, and the resulting mixture was stirred overnight. Standard ethereal work-up, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 4.2 g (97%) of adduct **37** as a light yellow oil (hexane/EtOAc, 4:1, R_f **37** = 0.47). IR (film) λ_{max}: 2981, 1622, 1342, 1253 cm^{-1}. ^{1}H (400 MHz) δ: 6.94 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 3.99 (m, 1H), 3.87 (m, 1H), 3.79 (s, 3H), 3.28 (d, J = 14.8 Hz, 1H), 3.74 (d, J = 14.8 Hz, 1H), 2.71 (septet, J = 7.2 Hz, 1H), 2.38 (d, J = 17.2 Hz, 1H), 2.18 (s, 3H), 2.16 (d, J = 17.2 Hz, 1H), 2.10 (s, 3H), 1.28 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz) δ: 209.3 (s), 181.9 (s), 156.3 (s), 137.9 (s), 129.7 (s), 128.0 (d), 126.4 (s), 122.9 (s), 108.5 (d), 64.9 (t), 55.8 (q), 46.9 (s), 36.8 (t), 36.4 (t), 27.9 (q), 23.0 (d), 21.0 (q), 20.3 (q), 20.3 (q), 15.1 (q), 13.5 (q) ppm. HR-MS: $[M+H]^+_{obs}$ = 331.2266, $[M+H]^+_{calcd}$ = 331.2273.

2-Isopropyl-4-(3-methoxy-2,6-dimethylbenzyl)-4-methyl-3-vinylcyclopent-2-en-1-one (24)

To a solution of vinyl bromide (3.2 mL, 45 mmol) in freshly distilled Et_2O (60 mL) at –78 °C, *t*-butyllithium (54 mL, 1.7 mol/L, 91 mmol) was added over a 15 min period. After stirring 2.5 h at RT, the vinyllithium mixture was cannulated into **37** (2.00 g, 6.1 mmol) in THF (60 mL) solution at –78 °C. The resulting mixture was warmed to RT and stirred for an additional 8 h. Hydrochloric acid (20.0 mL, 1.0 mol/L) was added dropwise at 0 °C, and the resulting mixture was stirred for 30 min. Standard ethereal work-up, followed by column chromatography (elution with pet ether/EtOAc, 8:1), gave 1.76 g (91%) of conjugated dienone **24** as a light yellow oil (hexane/EtOAc, 2:1, R_f **24** = 0.75). IR (film) λ_{max}: 2960, 1693, 1258, 1102 cm^{-1}. ^{1}H (400 MHz) δ: 6.96 (d, J = 8.0 Hz, 1H), 6.90 (dd, $J1$ = 11.2 Hz, $J2$ = 17.6 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.63 (d, J = 17.6 Hz, 1H), 5.47 (d, J = 11.2 Hz, 1H), 3.79 (s, 3H), 3.43 (m, 1H), 3.08 (dd, $J1$ = 6.4 Hz, $J2$ = 14.0 Hz, 1H), 2.93 (septet, J = 7.2 Hz, 1H), 2.57 (dd, $J1$ = 10.0 Hz, $J2$ = 14.0 Hz, 1H), 2.28 (m, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 1.28 (s, 3H), 1.26 (d, J = 6.8 Hz, 1H), 1.22 (d, J = 6.8 Hz, 1H). ^{13}C NMR (125 MHz) δ: 208.3 (s), 166.9 (s), 156.4 (s), 145.0 (s), 138.1 (s), 130.4 (d), 128.4 (s), 128.3 (d), 125.2 (), 121.5 (t), 108.4 (d), 55.5 (q), 41.1 (t), 36.8 (d), 35.8 (t), 20.9 (q), 20.6 (q), 20.5 (q), 15.1 (q), 12.8 (q) ppm.

(3a*S*,8a*R*)-1-Isopropyl-3a,5,8a-trimethyl-3a,4,9,10-tetrahydrobenzo[*f*]azulene-2,6(3*H*,8a*H*)-dione (25)

To a solution of conjugated dienone **24** (200 mg, 0.641 mmol) in fresh distilled DCM (2 mL) at –78 °C was added $TiCl_4$ (10 μL, 0.91 mmol). The resulting mixture was stirred at –78 °C for 1 h, and the temperature was raised to –60 °C, then stirred for an additional 0.5 h. Water (5 mL) was added dropwise to quench the reaction, followed by standard ethereal work-up. Column chromatography (elution with pet ether/EtOAc, 4:1) afforded 115 mg (61%) of tricyclic enone **25** as a white solid (hexane/EtOAc, 2:1, R_f **25** = 0.41). IR (film) λ_{max}: 2963, 1738, 1693, 1658, 1627, 1379 cm^{-1}. ^{1}H (500 MHz) δ: 6.81 (d, J = 9.5 Hz, 1H), 6.31 (d, J = 9.5 Hz, 1H), 3.03 (d, J = 13.5 Hz, 1H),

2.74 (m, 1H), 2.67 (septet, J = 7.0 Hz, 1H), 2.35 (m, 3H), 2.17 (m, 1H), 1.96 (s, 3H), 1.71 (m, 1H), 1.59 (m, 1H), 1.22 (s, 3H), 1.13 (m, 6H), 1.09 (s, 3H). ^{13}C NMR (125 MHz) δ: 207.4 (s), 186.2 (s), 179.3 (s), 158.0 (s), 157.7 (d), 140.9 (s), 136.0 (s), 128.2 (d), 52.0 (t), 45.6 (t), 45.1 (s), 40.0 (t), 38.4 (t), 29.9 (q), 25.7 (q), 24.7 (d), 23.9 (t), 20.8 (q), 20.7 (q), 13.8 (q) ppm. HR-MS: $[M+H]^+_{obs}$ = 299.2010, $[M+H]^+_{calcd}$ = 299.2011.

(3a*R*,8a*R*)-1-Isopropyl-3a,5,8a-trimethyl-2,3,3a,4,9,10-hexahydrobenzo[*f*]azulen-6(8a*H*)-one (41)

To a solution of tricycle **25** (100 mg, 0.336 mmol) in freshly distilled DCM (10 mL) was added 10% TFA in DCM solution (5 mL), followed by $NaBH_4$ (64 mg, 1.7 mmol). The resulting mixture was stirred for 0.5 h. Water (5 mL) was added to quench the reaction, followed by standard ethereal work-up. Column chromatography (elution with pet ether/EtOAc, 10:1) gave 64 mg (67%) of dienone **41** as a light yellow oil (hexane/EtOAc, 4:1, R_f **41** = 0.55). IR (film) λ_{max}: 2963, 1658, 1462, 1151 cm^{-1}. ^{1}H (500 MHz) δ: 6.81 (d, J = 9.5 Hz, 1H), 6.31 (d, J = 9.5 Hz, 1H), 2.67 (septet, J = 7.0 Hz, 1H), 2.15–1.5 (m, 11H), 1.96 (s, 3H), 1.22 (s, 3H), 1.13 (m, 6H), 1.09 (s, 3H). HR-MS: $[M+H]^+_{obs}$ = 285.2222, $[M+H]^+_{calcd}$ = 285.2218.

(3a*R*,8a*R*)-1-Isopropyl-3a,5,8a-trimethyl-2,3,3a,4,8,8a,9,10-octahydrobenzo[*f*]azulen-6(7*H*)-one (42)

To a dry 20-mL round-bottomed flask was added tricycle **25** (100 mg, 0.336 mmol) under nitrogen atmosphere, followed by addition of anhydrous EtOAc (5 mL) and 5% of Pd/C (10 mg, 10% in weight). The nitrogen in the reaction flask was removed by bubbling H_2 into the reaction medium for a 5 min period. A balloon filled with H_2 was connected to the round-bottomed flask and the resulting mixture was stirred under H_2 for 2 h. The H_2 balloon was disconnected and the residue H_2 gas was removed by bubbling N_2 into the reaction mixture, followed by filtration through a short pad of silica gel to remove the catalyst. Standard ethereal work-up, followed by column chromatography (elution with pet ether/EtOAc, 4:1), gave 100 mg (99%) of *bis*-enone **42** as a white solid (hexane/EtOAc, 2:1, R_f **42** = 0.40). Mp = 147.0–147.2 °C. IR (film) λ_{max}: 3376, 2959, 1697, 1460, 1379, 1118 cm^{-1}. ^{1}H (400 MHz) δ: 2.87 (d, J = 13.2 Hz, 1H), 2.52–2.79 (m, 4H), 2.39 (d, J = 18.0 Hz, 1H), 2.30 (d, J = 18.8 Hz, 1H), 2.21 (m, 2H), 2.04 (m, 1H), 1.85 (s, 3H), 1.79 (m, 1H), 1.58 (m, 2H), 1.17 (m, 9H), 1.13 (s, 3H). ^{13}C NMR (100 MHz) δ: 207.3 (s), 198.5 (s), 179.5 (s), 160.6 (s), 140.6 (s), 135.3 (s), 52.0 (t), 44.5 (s), 41.0 (t), 40.1 (t), 34.9 (t), 34.4 (t), 26.6 (q), 25.5 (q), 24.7 (d), 22.5 (t), 20.9 (q), 20.8 (q), 13.7 (q) ppm. HR-MS: $[M+H]^+_{obs}$ = 301.2167, $[M+H]^+_{calcd}$ = 301.2168.

(3a*S*,8a*S*)-1-Isopropyl-3a,5,8a-trimethyl-3a,4,6,7,8,8a,9,10-octahydrobenzo[*f*]azulen-2(3*H*)-one (43) and (3a*R*,8a*S*)-1-isopropyl-3a,5,8a-trimethyl-2,3,3a,4,6,7,8,8a,9,10-decahydrobenzo[*f*]azulene (44)

To a solution of *bis*-enone **42** (153 mg, 0.510 mmol) in fresh distilled DCM (15 mL) was added 10% TFA in DCM solution (10 mL), followed by $NaBH_4$ (97 mg, 2.6 mmol). The resulting mixture was stirred for 0.5 h at RT. Water (5 mL) was added to quench the reaction, followed by standard ethereal work-up. Column chromatography (elution with pet ether/EtOAc, 10:1) gave 44 mg (30%) of diene **44** as a light yellow oil (hexane/EtOAc, 4:1, R_f **44** = 0.90). IR (film) λ_{max}: 2933, 1464, 1372 cm^{-1}. ^{1}H (400 MHz) δ: 1.70–2.35 (m, 17H), 1.67 (s, 3H), 1.13–1.19 (m, 6H), 1.10 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz) δ: 208.6 (s), 182.5 (s), 139.7 (s), 132.9 (s), 131.9 (s), 52.0 (t), 44.9 (s), 41.7 (t), 38.3 (s), 37.9 (t), 37.2 (t), 32.3 (t), 28.4 (q), 25.7 (q), 24.6 (d), 22.9 (t), 21.8 (q), 20.9 (q), 19.3 (t) ppm. HR-MS: $[M]^+_{obs}$ = 286.2295, $[M]^+_{calcd}$ = 286.2297. Further elution gave 76 mg (55%) of enone **43** as a light yellow oil (hexane/EtOAc, 4:1, R_f **43** = 0.55). ^{1}H (400 MHz) δ: 2.58–2.74 (m, 3H), 2.30 (d, J = 18.4 Hz, 1H), 2.20 (d, J = 18.0 Hz, 1H), 2.12 (m, 1H), 1.95 (m, 3H), 1.68–1.84 (m, 3H), 1.67 (s, 3H), 1.25–1.44 (m, 3H), 1.15 (m, 6H), 1.10 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz) δ: 208.6 (s), 182.5 (s), 139.7 (s), 132.9 (s), 131.9 (s), 52.0 (t), 44.9 (s), 41.7 (t), 38.3 (s), 37.9 (t), 37.2 (t), 32.3 (t), 28.4 (q), 25.7 (q), 24.6 (d), 22.9 (t), 21.8 (q), 20.9 (q), 19.3 (t) ppm. HR-MS: $[M+H]^+_{obs}$ = 287.2376, $[M+H]^+_{calcd}$ = 287.2375. Note: Allowing the reduction to proceed overnight (12 h) gave diene **44** in 73% yield.

(1*S*,3a*S*,8a*S*)-1-Isopropyl-3a,8a-dimethyl-5-methylenedecahydro-4a,10a-epoxybenzo[*f*]azulen-2(1H)-one (45)

A solution of **43** (10 mg, 0.034 mmol) and rose bengal (2.0 mg) in 5 mL of a solution of methanol/dichloromethane (1:9) was irradiated at –5 °C with a 500 W tungsten lamp, while oxygen was bubbled through the reaction mixture. After 40 min, the reaction mixture was treated with triethyl phosphite (0.3 mL) at RT for 1 h with vigorous stirring. After concentration, standard ethereal work-up provided a crude residue, which was purified by column chromatography (elution with pet ether: EtOAc, 10:1) and gave 9.9 mg (92%) of furan **45** (hexane: EtOAc, 4:1, R_f **45** = 0.45) as a colorless oil. IR (film) λ_{max}: 2933, 1740, 1075, 895 cm^{-1}. ^{1}H (400 MHz) δ: 4.76 (s, 1H), 4.66 (s, 1H), 2.93 (d, J = 17.6 Hz, 1H), 2.61–2.74 (m, 2H), 2.08–2.41 (m, 6H), 1.72–1.80 (m, 1H), 1.58–1.69 (m, 4H), 1.25–1.40 (m, 2H), 1.20 (m, 6H), 1.12 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz) δ: 217.0 (s), 148.7 (s), 103.1 (t), 90.9 (s), 86.6 (s), 59.2 (d), 54.6 (t), 46.6 (t), 44.9 (q), 36.2 (s), 35.8 (t), 32.8 (t), 31.4 (t), 25.7 (d), 24.4 (t), 21.9 (q), 21.2 (t), 19.9 (q), 18.8 (q), 18.1 (q) ppm. HR-MS: $[M+H]^+_{obs}$ = 303.2316, $[M+H]^+_{calcd}$ = 303.2324.

(1a*R*,4a*S*,9a*S*,10a*S*)-7-Isopropyl-1a,4a,9a-trimethyl-2,3,4,4a,5,6,9a,10-octahydro-1aH-azuleno[5′,6′:1,6]benzo[1,2-*b*]oxiren-8(9*H*)-one (46)

To a solution of diene **43** (35 mg, 0.12 mmol) in freshly distilled DCM (4 mL) under nitrogen atmosphere was added *m*-CPBA (77%, 33 mg, 0.15 mmol, 1.2 equiv.). The resulting mixture was stirred at RT for 1 h. Standard ethereal work-up, followed by column chromatography (elution with pet ether/EtOAc, 5:1), afforded 35.0 mg (95%) of epoxide **46** as a white foam (hexane/EtOAc, 2:1, R_f **46** = 0.49). IR (film) λ_{max}: 3006, 2918, 1717, 1364, 1224 cm^{-1}. ^{1}H (400 MHz) δ: 2.87 (m, 1H), 2.73 (septet, J = 7.2 Hz, 1H), 2.42 (m, 1H), 2.22 (d, J = 8.8 Hz, 2H), 1.90–2.12 (m, 3H), 1.64–1.83 (m, 3H), 1.39–1.52 (m, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.20–

1.25 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H) 0.97 (s, 3H). ^{13}C NMR (100 MHz) δ: 207.3 (s), 179.4 (s), 141.2 (s), 68.6 (s), 65.3 (s), 53.3 (t), 42.8 (s), 42.2 (t), 37.7 (s), 36.8 (t), 36.7 (t), 31.4 (t), 25.9 (q), 24.8 (d), 24.2 t), 23.4 (q), 23.0 (q), 20.4 (q), 20.3 (q), 16.6 (q) ppm. HR-MS: $[M]^+_{obs}$ = 302.2243, $[M]^+_{calcd}$ = 302.2246.

(1a*R*,4a*S*,9a*R*,10a*S*)-7-Isopropyl-1a,4a,9a-trimethyl-2,3,4,4a,5,9,9a,10-octahydro-1a*H*-azuleno[5′,6′:1,6]benzo[1,2-*b*]oxirene (47)

To a solution of enone **46** (60 mg, 0.20 mmol) in freshly distilled Et_2O (10 mL) at 0 °C under nitrogen atmosphere was added LAH (7.6 mg, 0.20 mmol). The resulting reaction mixture was stirred for 1 h at RT. Water (4 mL) was slowly added to quench the reaction, followed by standard ethereal work-up. Concentration of the filtered organic phase afforded yellow oil. Silica gel was added to the bottle, and the resulting mixture was allowed to sit on the bench overnight. Column chromatography (elution with pet ether/EtOAc, 15:1) afforded 45.5 mg (80%) of diene **47** (hexane/EtOAc, 8:1, R_f **47** = 0.50) as a colorless oil. IR (film) λ_{max}: 3247, 2952, 1660, 1359, 1010 cm^{-1}. ^{1}H (500 MHz) δ: 5.60 (s, 1H), 5.45 (m, 1H), 2.90 (d, *J* = 15.0 Hz, 1H), 2.41 (m, 1H), 2.14–2.33 (m, 3H), 1.70–1.98 (m, 4H), 0.80–1.62 (m, 4H), 1.39 (s, 3H), 1.18 (s, 3H), 1.07–1.13 (m, 6H), 1.03 (s, 3H). ^{13}C NMR 154.5 (s), 149.5 (s), 125.6 (d), 113.6 (d), 70.4 (s), 65.8 (s), 49.6 (t), 43.5 (s), 39.2 (t), 37.9 (s), 37.2 (t), 34.8 (t), 30.1 (t), 25.7 (d), 24.0 (q), 23.7 (q), 23.3 (q), 22.3 (q), 22.3 (q), 16.7 (t) ppm. HR-MS: $[M]^+_{obs}$ = 286.2297, $[M]^+_{calcd}$ = 286.2297.

(3a*R*,4a*R*,8a*S*)-1-Isopropyl-3a,8a-dimethyl-5-methylene-3,3a,4,4a,5,6,7,8,8a,9-decahydrobenzo[*f*]azulen-4a-ol (48)

To a solution of diisopropylamine (0.70 mL, 5.0 mmol) in freshly distilled Et_2O (10 mL) at 0 °C was added *n*-butyllithium (2 mL, 5 mmol). The resulting mixture was stirred at RT for 10 min. Epoxide **47** (8.0 mg, 0.028 mmol) was transferred into a sealed tube, and 2 mL of the above LDA solution was added. The reaction vessel was closed, and it was heated to 50 °C and kept at this temperature for 36 h. Water (2 mL) was added to quench the reaction followed by standard ethereal work-up. Column chromatography (elution with pet ether/EtOAc, 15:1) afforded 7.4 mg (93%) of allylic alcohol **48** (hexane/EtOAc, 8:1, R_f **48** = 0.81) as a colorless oil. IR (film) λ_{max}: 3556, 2923, 1466, 1115 cm^{-1}. ^{1}H (500 MHz) δ: 5.74 (t, *J* = 7.0 Hz, 1H), 5.70 (s, 1H), 5.02 (s, 1H), 4.69 (s, 1H), 3.01 (s, 1H), 2.61 (d, *J* = 17.0 Hz, 1H), 2.44 (septet, *J* = 7.0 Hz, 1H), 2.36 (m, 2H), 2.27 (m, 1H), 2.12 (dd, *J*1 = 3.0 Hz, *J*2 = 16.5 Hz, 1H), 2.03 (dt, *J*1 = 12.5 Hz, *J*2 = 5 Hz, 1H), 1.83 (m, 2H), 1.40–1.62 (m, 3H), 1.44 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.11 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 3H). ^{13}C NMR (125 MHz) δ: 157.5 (s), 153.6 (s), 148.6 (s), 128.3 (d), 125.8 (d), 107.1 (t), 79.2 (s), 50.5 (t), 45.4 (t), 44.4 (s), 41.7 (t), 39.0 (t), 34.7 (t), 30.6 (q), 28.4 (q), 25.9 (d), 23.6 (t), 79.2 (s), 50.5 (t), 45.4 (t), 44.4 (s), 41.7 (t), 39.0 (t), 34.7 (t), 30.6 (q), 28.4 (q), 25.9 (d), 23.6 (t), 22.2 (q), 21.7 (q), 21.3 (q) ppm. HR-MS: $[M]^+_{obs}$ = 286.2300, $[M]^+_{calcd}$ = 286.2297.

(3a*S*,8a*R*)-1-Isopropyl-3a,5,8a-trimethyl-3a,4,8,8a,9,10-hexahydrobenzo[*f*]azulene-2,6(3*H*,7*H*)-dione (42) from enone (43)

To a solution of enone **43** (10 mg, 0.035 mmol) in acetone (2 mL) and H_2O (1 mL) was added *N*-bromosuccinimide (8.1 mg, 0.046 mmol, 1.3 equiv.) in one portion. The resulting mixture was stirred at RT for 5 min and was quenched with water (2 mL). Acetone was removed under vacuum using a rotary evaporator, followed by standard ethereal work-up. Column chromatographic purification (elution with pet ether/EtOAc, 4:1) gave 7.4 mg (71%) of *bis*-enone **42** (hexane/EtOAc, 2:1, R_f **42** = 0.40) as a white solid, which was identical to that previously characterized (i.e., the reduction of **25** to give **42**).

(3a*R*,8a*S*,10*S*)-1-Isopropyl-3a,5,8a-trimethyl-2,3,3a,4,6,7,8,8a,9,10-decahydrobenzo[*f*]azulen-10-ol (49)

To a solution of SeO_2 (9.1 mg, 0.089 mmol) in freshly distilled DCM (0.50 mL) was added *t*-BuOOH (37 μL, 0.36 mmol). The resulting mixture was stirred for 25 min at RT. Diene **44** (48 mg, 0.18 mmol) in DCM (0.50 mL) was added dropwise. The resulting mixture was stirred at RT for 8 h, followed by standard ethereal work-up. Column chromatography (elution with pet ether/EtOAc, 10:1) afforded 19 mg (40%) of triene **50** as a light yellow oil (hexane/EtOAc, 4:1, R_f **50** = 0.95). Further elution gave 23 mg (45%) of allylic alcohol **49** as a light yellow oil (hexane/EtOAc, 4:1, R_f **49** = 0.39).

(3a*R*,8a*S*)-1-Isopropyl-3a,5,8a-trimethyl-2,3,3a,4,7,8,8a,9-octahydrobenzo[*f*]azulen-10(6*H*)-one (51)

To a solution of allylic alcohol **49** (5.2 mg, 0.018 mmol) in CCl_4 (0.5 mL) was added MnO_2 (16 mg, 0.18 mmol). The resulting mixture was heated at 60 °C for 6 h. Standard ethereal work-up, followed by column chromatography (elution with pet ether/EtOAc, 12:1), gave 3.4 mg (65%) of enone **51** as a light yellow oil (hexane/EtOAc, 4:1, R_f **51** = 0.75). ^{1}H (400 MHz) δ: 3.34 (heptet, *J* = 7.2 Hz, 1H), 2.85 (d, *J* = 14.8 Hz, 1H), 2.57 (d, *J* = 14.0 Hz, 1H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.22 (d, *J* = 14.8 Hz, 1H), 2.16 (d, *J* = 14.0 Hz, 1H), 2.01 (bs, 2H), 1.67 (s, 3H), 1.46–1.75 (m, 6H), 1.08 (s, 3H), 0.98–1.04 (m, 9H). ^{13}C NMR (125 MHz) δ: 202.7, 161.7, 142.9, 133.7, 129.0, 58.0, 48.7, 42.0, 40.8, 39.6, 36.1, 33.4, 29.1, 27.9, 25.6, 23.0, 20.9, 20.7, 20.7, 19.1 ppm.

Supplementary data

Supplementary data for this article are available on the journal Web site (www.nrcresearchpress.com/doi/suppl/10.1139/v11-116). The X-ray data for key intermediate **25**, CCDC 835868, has also been deposited with the Cambridge Crystallographic Data Centre. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1Ez, UK; fax +44 1223 336033; or e-mail deposit@ccdc.cam.ac.uk).

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