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Asymmetric total synthesis of humulane sesquiterpenoids alashanoids B, C, E, and F and 2,9-humuladien-6-ol-8-one†

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Naturally occurring sesquiterpenes having humulane frameworks are structurally intriguing and possess significant biological profiles. Asymmetric synthesis of the alashanoids B, C, E, and F and 2,9-humuladien-6-ol-8-one is achieved for the first time through a linear synthetic strategy. Intramolecular late-stage Nozaki–Hiyama–Kishi (NHK) coupling is employed to access the eleven-membered macrocyclic core present in the target molecules. The NHK precursors are accessed using the Evans and non-Evans *syn* and *anti*-aldol reaction as a key transformation. X-ray and ECD analysis reconfirmed the synthesized compounds' structures and chirotopical properties.

Introduction

Syringa pinnatifolia, belonging to the Oleaceae family, is a deciduous shrub of height 8 to 12 feet and has an elegant bushy habit and is mainly found in western China. The extract from this plant's peeled roots, stems, and twigs have been used for a long time as a traditional folk medicine for the treatment of cardiovascular diseases and for pain management. The stems of this plant contain zerumbone, a humulane type sesquiterpenoid exhibiting a cardio protective effect against acute myocardial ischemia (AMI) in rats.[1,2] Recently, a few structurally new sesquiterpenoids were isolated from the stem of *Syringa pinnatifolia*; among them are alashanoids A–G (**1**, **2**, **4**–**7** and **8a**) and 2,9-humuladien-6-ol-8-one (**3**), which are unique and have been isolated from the first time from this species.[3] Alashanoid A (**1**) has a rare 2,2,5,9-tetramethylbicyclo [6.3.0]-undecane skeleton and both the enantiomers have been isolated from the same plant. Alashanoids B–G (**2**, **4**–**7** and **8a**) and 2,9-humuladien-6-ol-8-one (**3**) have a humulane-type framework in their structure (Fig. 1). Zerumbone (**8b**) is another known humulane-type sesquiterpenoid which contains a di-enone functionality and is known for its cardioprotective effect, as shown in earlier studies.[1,2] The structures of all the isolated natural products have been established through extensive NMR analysis and X-ray crystallographic analysis. Their absolute stereo-configuration was also assigned through theoretical and experimental ECD data analysis. Few of these compounds exhibit a wide range of bioactivities, including protective effects against hypoxia injury to H9c2 cells and the ability to inhibit NO production in LPS-induced RAW264.7 macrophage cells; hence such compounds might be of tremendous significance for clinical use in traditional medicines used to treat coronary diseases.

In the literature, it was reported that alashanoid A (**1**), 2,9-humuladien-6-ol-8-one (**3**), and alashanoids C–F (**4**–**7**) were obtained as a scalemic (racemic) mixture, but separation through chiral phase HPLC was performed and after CD measurement, the absolute configuration was assigned to the individual enantiomers (Fig. 1). Alashanoid B (**2**) and alashanoid G (**8a**) were obtained as enantiopure compounds from the stem of *Syringa pinnatifolia*, and their absolute configuration was assigned through theoretically calculated and experimentally measured ECD spectra. Recently, a comprehensive review of the synthesis of humulanolides (sesquiterpene lactones) has been reported.[4] Synthetic studies towards naturally occurring humulanes, shown in Fig. 1, are not available in print yet.

Results and discussion

In this article, we report the first asymmetric total synthesis of (+)-alashanoid B, (−)-2,9-humuladien-6-ol-8-one, (−)-alashanoid C and (+)-alashanoids E and F and also establish their absolute configuration *via* comparison with those of reported natural products. Close structural visualization revealed that compounds **2**, **3a**, **4b**, **6a**, and **7a** all contain eleven-membered humulane ring systems with two stereocenters and enone systems; in addition, they also contain two all-carbon-quatern-

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† Electronic supplementary information (ESI) available: Experimental procedures for all the synthesized compounds, spectral data (^{1}H, ^{13}C, and 2D NMR), ECD curve, and X-ray crystallographic data. CCDC 2301568 and 2305842. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ob00393d

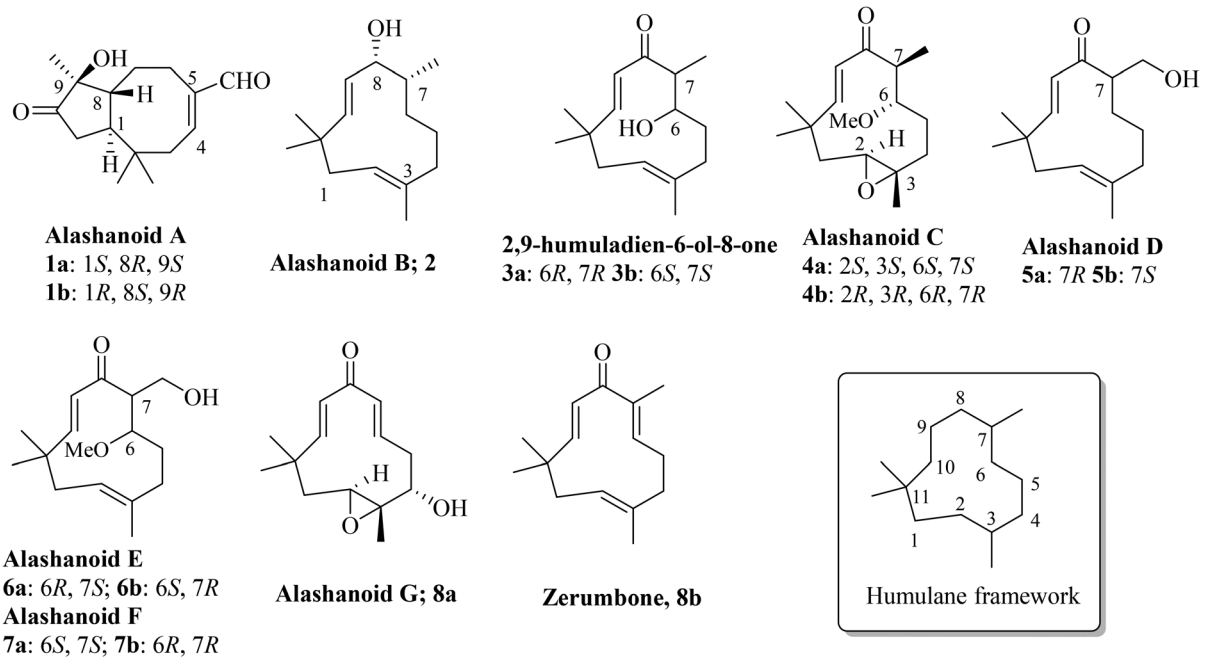
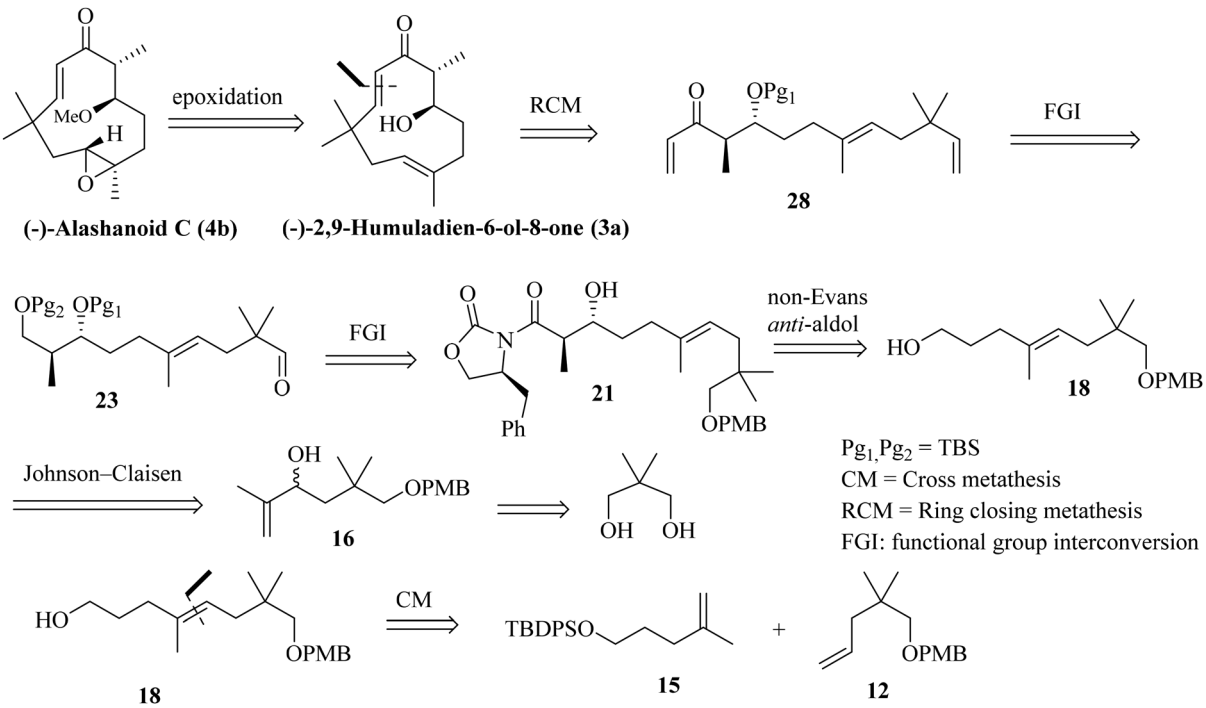


Fig. 1 Naturally occurring humulane-type sesquiterpenoids alashanoids and 2,9-humuladien-6-ol-8-one.

ary centers (C_{11} bearing the *gem*-dimethyl group and C_3 with the *E*-olefinic geometry is stereogenic). (−)-Alashanoid C (**4b**) contains an oxirane ring at the C_2–C_3 carbon, and the C_6 carbon contains a methoxy (–OMe) substitution. (−)-2,9-Humuladien-6-ol-8-one can be regarded as a precursor for (−)-alashanoid C. The retrosynthetic disconnection for alashanoid C and (−)-2,9-humuladien-6-ol-8-one is shown in Scheme 1. A late-stage RCM reaction[5] is proposed to access **3a**, and the subsequent regioselective epoxidation should furnish **4b**. The RCM precursor can be conveniently prepared through an Evans auxiliary mediated *anti*-selective aldol reaction (non-Evans *anti*) through an open TS (transition state) model.[6] The



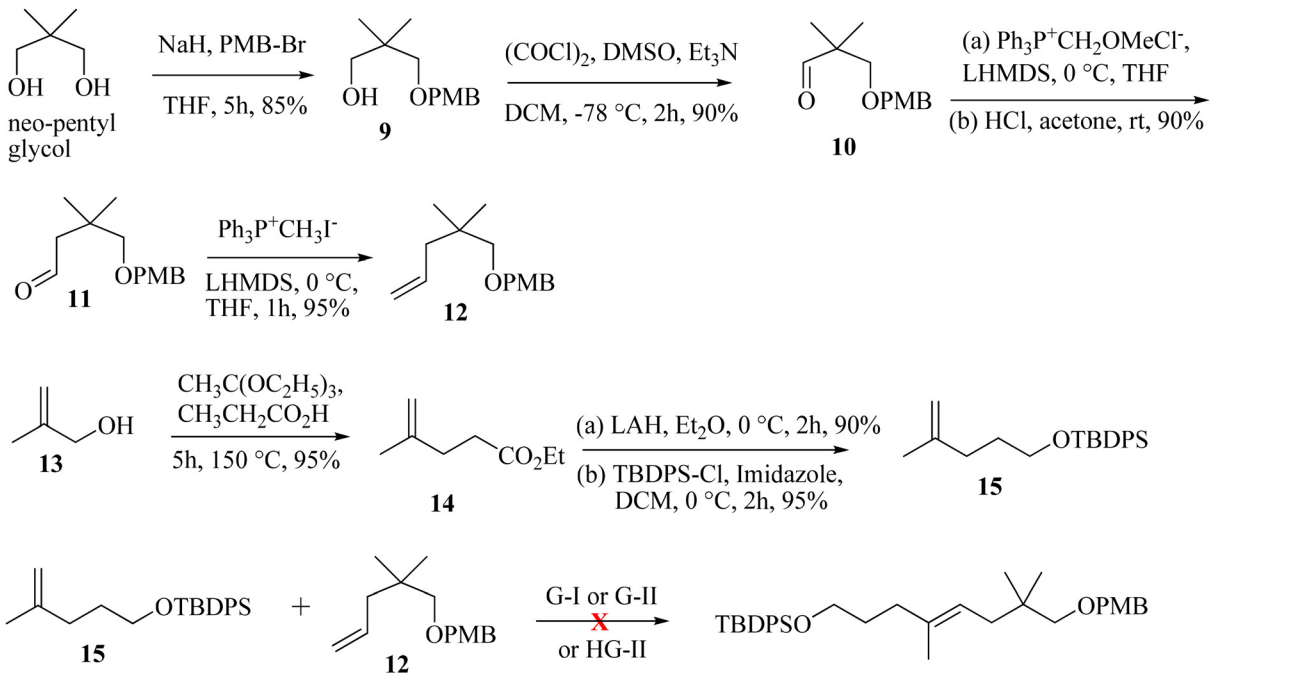
Scheme 1 Retrosynthetic disconnection for (−)-alashanoid C and (−)-2,9-humuladien-6-ol-8-one.

aldol precursor could be accessed through the Johnson–Claisen rearrangement of allylic alcohol,[7] which could easily be accessed using neo-pentyl glycol as a starting precursor. A cross-metathesis (CM) reaction[8] is also envisioned to access the aldol precursor, as shown in Scheme 1.

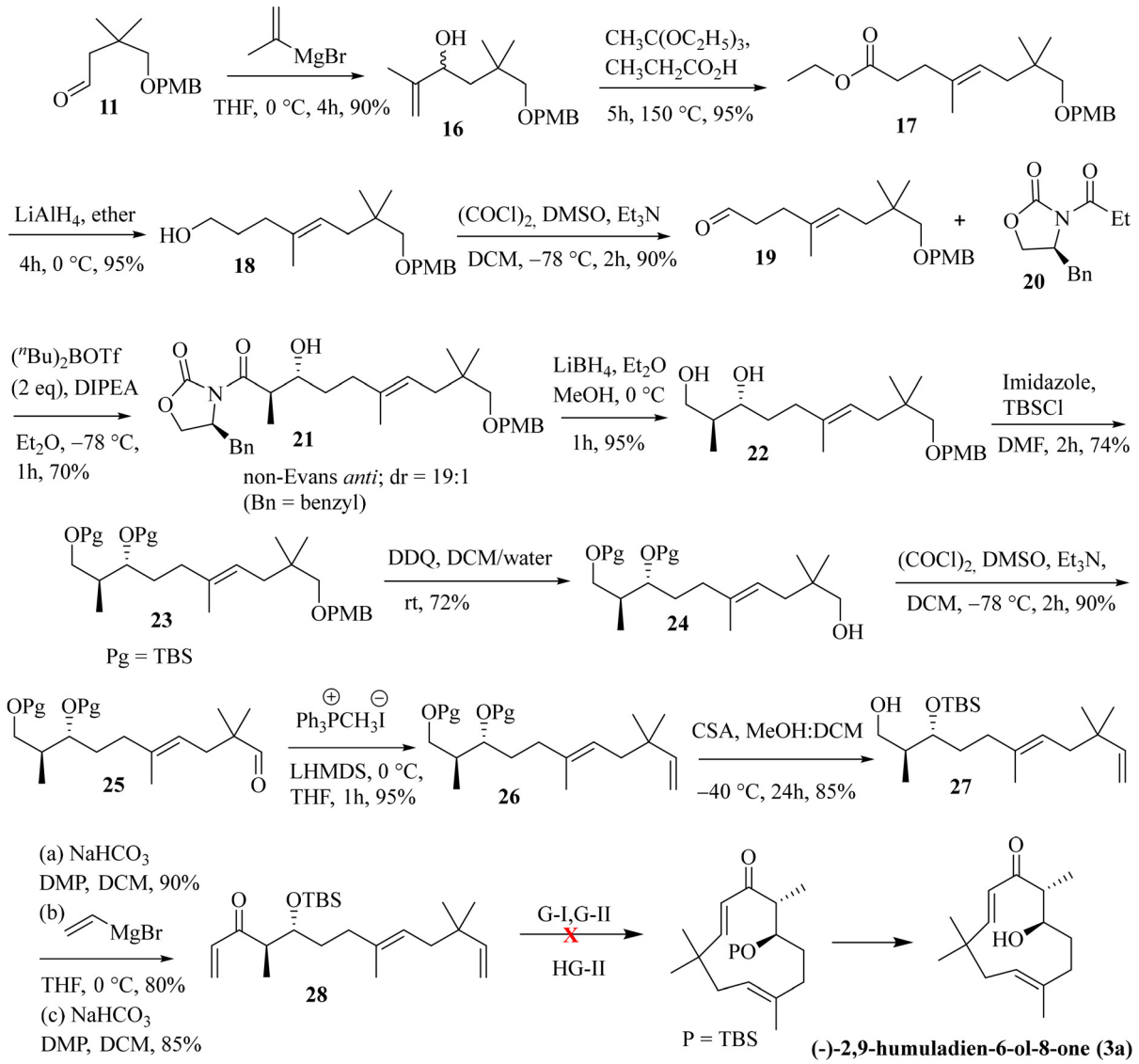
Synthesis of (−)-alashanoid C and (−)-2,9-humuladien-6-ol-8-one

The synthesis is initiated from the known aldehyde **10** prepared from neo-pentylglycol.[9] Aldehyde **10** on homologation through the Wittig protocol[10] and the subsequent hydrolysis of the enol-ether furnished aldehyde **11** in 90% yield. The Wittig olefination of **11** provided olefin **12** in 95% yield. The other CM partner was synthesized from 2-methylprop-2-en-1-ol (**13**), which undergoes the Johnson–Claisen rearrangement and furnishes the γ,δ-unsaturated ester **14**; subsequent reduction with $LiAlH_4$ and treatment with TBDPS-Cl afforded compound **15** (81% yield in three steps). The proposed CM reaction was next attempted with the G-I or G-II or HG-II catalyst (5 mol%);[8] unfortunately the CM product was not observed as anticipated. Unwanted self-dimerization occurred, and the desired CM product was not obtained (Scheme 2).

Next, we have explored the feasibility of preparing a suitably substituted γ,δ-unsaturated ester that will lead us to the aldol precursor (Scheme 1). Aldehyde **11** was reacted with freshly prepared Grignard reagent generated from 2-bromoprop-1-ene to furnish the allylic alcohol **16** in 90% yield. The Johnson–Claisen rearrangement of **16** afforded the desired γ,δ-unsaturated ester **17** in 95% yield, and the subsequent reduction[11] with $LiAlH_4$ then furnished alcohol **18** (95% yield). Oxidation of alcohol **18** under the Swern conditions then produced aldehyde **19** in 90% yield. The asymmetric aldol reaction of Evans oxazolidinone **20** with aldehyde **19** then afforded the *anti*-aldol product (non-Evans *anti*) **21** in 70% yield with excellent diastereoselectivity and enantioselectivity.[12] The excellent stereoselectivity can be explained through the Heathcock open-chain transition state (*via* non-chelated acyclic stereocontrol) model.[12a] Reductive removal of the auxiliary with $LiBH_4$ furnished the corresponding diol **22** (95% yield). Both the hydroxy groups were then protected as –TBS ether to provide compound **23** in a quantitative yield (98%). The –PMB ether group in **23** was oxidatively removed by DDQ treatment to furnish alcohol **24** in 72% yield. The Swern oxidation of **24** afforded aldehyde **25** in 90% yield. The Wittig olefination of aldehyde **25** gave olefin **26**, as shown in Scheme 3. Chemoselective deprotection of the primary TBS-ether group[13] was next achieved by treating **26** with CSA/MeOH at −40 °C for 24 h to afford compound **27** in 85% yield. Functional group manipulation with **27** then afforded the enone compound **28** (a three-step protocol involving DMP oxidation, vinyl Grignard addition, and further DMP oxidation; 60% yield in three steps), which served as the RCM precursor. The RCM reaction, mainly with the G-II and HG-II catalysts, was next attempted with compound **28**. But to our disappointment, the desired ring closed product remained elusive (Scheme 3). We reasoned that the RCM precursor **28** bearing a terminal olefinic unsaturated group with two adjacent *gem*-dimethyl groups is creating enough steric crowding to inhibit the initial complexation with the Ru-based alkylidene catalyst. Such instances depicting the unsuccessful RCM reaction with the sterically crowded olefin and Ru-based metathesis catalysis have been reported.[8e]



Scheme 2 Unsuccessful CM approach towards the advanced intermediate for (–)-2,9-humuladien-6-ol-8-one.

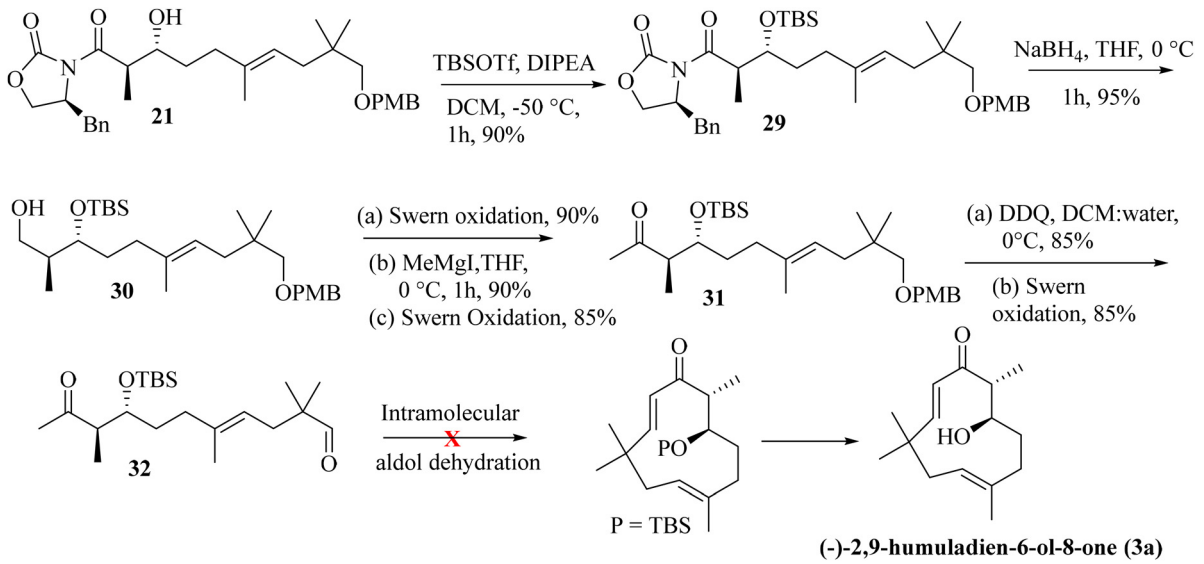


Scheme 3 Attempted RCM reaction for accessing the humulane core in the target molecule.

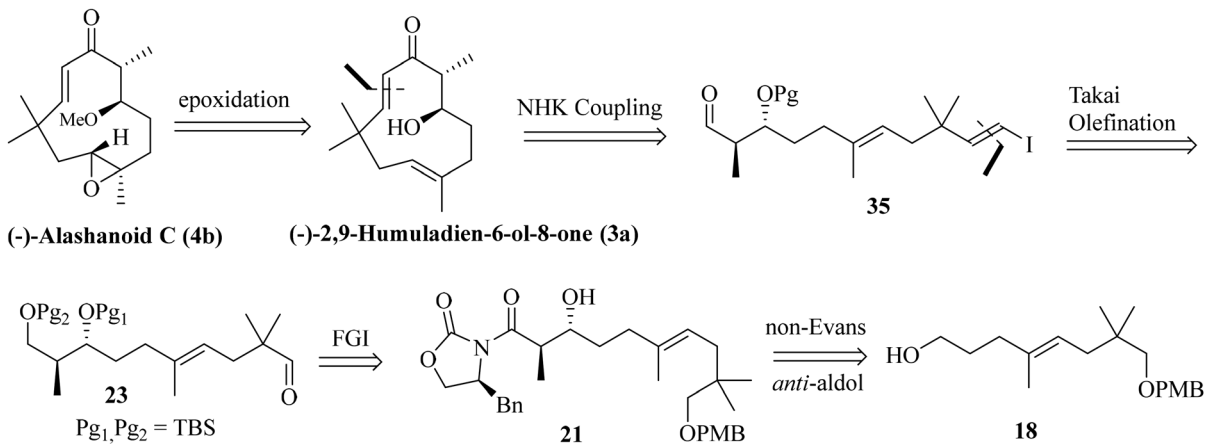
As the attempted RCM reaction was unsuccessful, we envisioned that an intramolecular aldol reaction[14] might be suitable for achieving *E*-olefinic unsaturation (C_9–C_{10}) in the target structure. The aldol product **21** was protected as its TBS-ether by treatment with TBS-OTf and DIPEA at −50 °C (at a higher temperature, the protection becomes futile, and subsequent epimerization was observed at the α-carbon attached to the Evans-auxiliary) to furnish compound **29** in 90% yield. Removal of the Evans-auxiliary with $NaBH_4$ reduction[15] then produced alcohol **30** in 95% yield. Functional group manipulation (the Swern oxidation, MeMgI addition, and the Swern oxidation) led to the keto-methyl compound **31** in 70% yield (in three steps). Removal of the PMB group with DDQ and oxidation of the resulting alcohol under the Swern conditions then furnished the intramolecular aldol precursor **32**. We attempted the intramolecular aldol dehydration under numerous base-mediated conditions, but it was unsuccessful as in most cases, intermolecular condensation seems to be the main product (Scheme 4).

As both the RCM and intramolecular aldol routes did not help us our pursuit of the humulane core of the target natural products, we decided to explore the feasibility of an intramolecular NHK coupling with a suitably substituted *E*-vinylic iodide-aldehyde.[16] A revised retrosynthetic disconnection is depicted in Scheme 5. As shown earlier, the required stereocenters were constructed through the non-Evans *anti*-aldol pathway (Scheme 5).

Previously synthesized aldehyde **25** was reacted with $CrCl_2$/CHI_3 under Takai olefination conditions[17] to access the *E*-vinylic iodide **33** in a good yield and with excellent diastereoselectivity. Chemoselective deprotection of the primary TBS-ether group was next achieved by treating **33** with CSA/MeOH at −40 °C for 24 h to afford compound **34** in 85% yield. Oxidation of the primary hydroxy group in **34** was next



Scheme 4 Attempted intramolecular aldol reaction for accessing the humulane core in the target molecule.

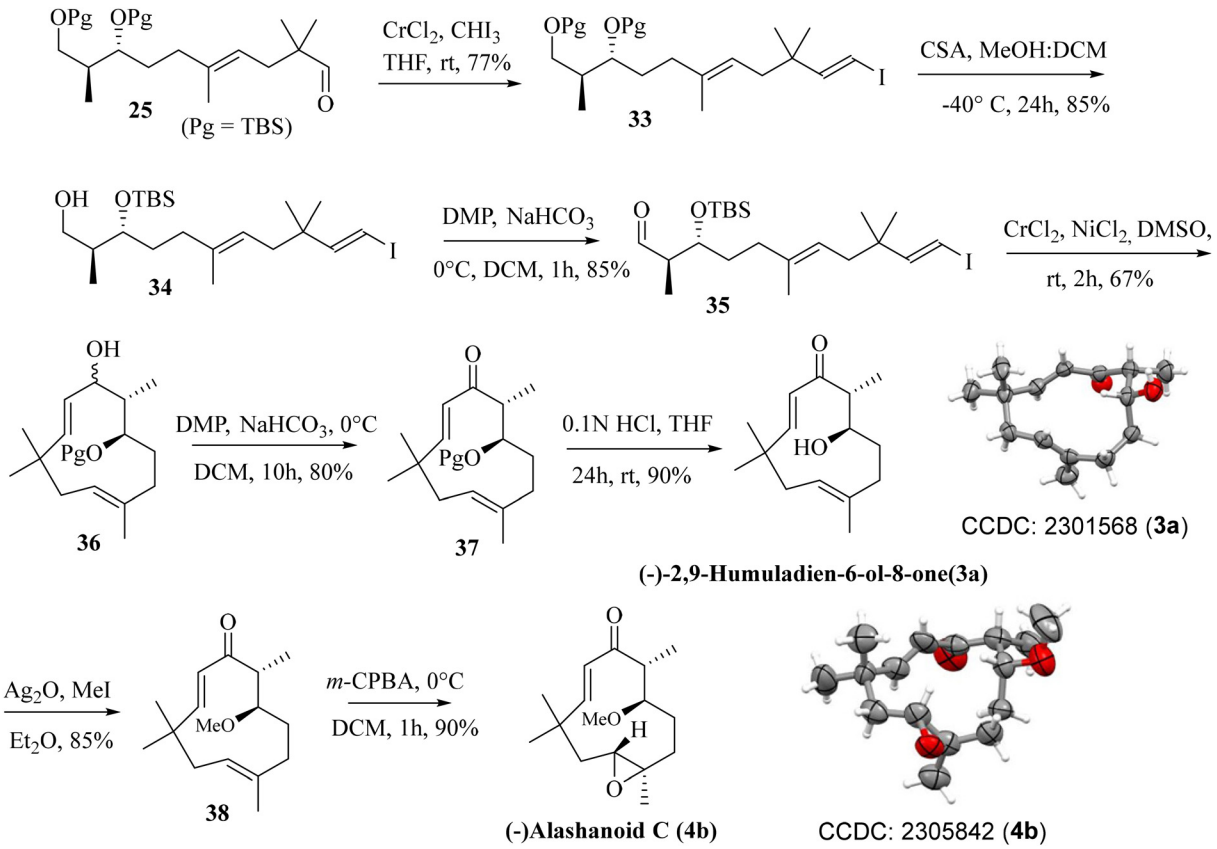


Scheme 5 A revised retrosynthetic route towards the humulane core through intramolecular NHK coupling.

achieved by treatment with DMP[18] to afford the desired aldehyde **35** in 85% yield. The crucial intramolecular NHK coupling worked smoothly, and the ring-closed alcohol **36** (humulane framework) was obtained in a pleasing 67% yield. Subsequent oxidation of **36** under DMP conditions then afforded ketone **37** in 80% yield. Finally, removal of the –TBS group from **37** with 0.1 N HCl furnished (−)-2,9-humuladien-6-ol-8-one (yield 90%, overall yield 4.3% from neo-pentyl glycol in 18 steps). The secondary hydroxy group in **3a** reacted with Ag_2O and MeI[19] to furnish the corresponding methoxy derivative of compound **3a**. Chemoselective epoxidation of **32** with *m*CPBA[20] then furnished (−)-alashanoid C (**4b**) (overall yield 3.3% from neo-pentyl glycol in 20 steps; Scheme 6). The spectroscopic (^{1}H, ^{13}C, 2D-NMR) and optical rotation values of the synthesized sample match well with those of the isolated natural product (see the ESI† for detailed information). The ECD spectra of the synthesized (−)-2,9-humuladien-6-ol-8-one (**3a**) and (−)-alashanoid C (**4b**) match perfectly with those of natural samples, as reported.[3] The experimental ECD curve of **4b** exhibited a positive Cotton effect (CE) at 235 nm and a negative CE at 308 nm, which match well with the reported ECD spectrum for the natural product. Hence, the absolute configuration of both the synthesized natural products has been reconfirmed as (6*R*,7*R*) for **3a** and (2*R*,3*R*,6*R*,7*R*) for **4b**. Single crystal X-ray analysis for **3a** and **4b** also revealed the structural integrity of both the natural products, as shown in Scheme 6.

Total synthesis of alashanoids E and F

Next, we have focused on the total synthesis of alashanoids E and F. As the late-stage intramolecular NHK coupling reaction successfully constructed the humulane framework, we also intended to explore the same strategy here. Hence, the known aldehyde **19**, when subjected to an asymmetric aldol reaction



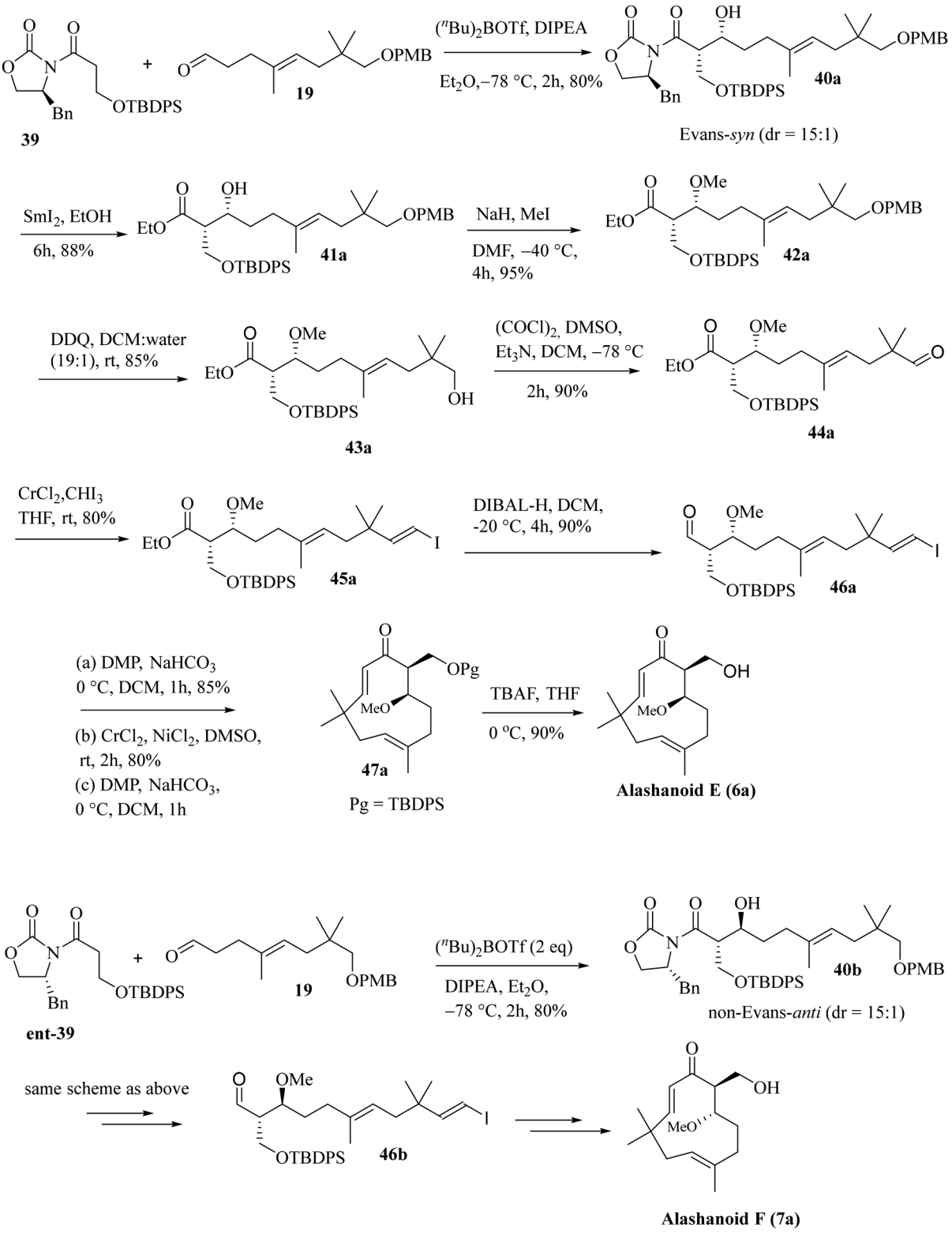
Scheme 6 Completion of the total synthesis of (–)-2,9-humuladien-6-ol-8-one and (–)-alashanoid C.

with auxiliary **39** (see the ESI† for its synthesis), afforded the Evans-*syn*-aldol[21] product **40a** in a reasonable yield (80%) with excellent diastereoselectivity (15 : 1). The oxazolidinone auxiliary was removed on treatment with SmI_2 and EtOH[22] and under hydrolytic conditions afforded compound **41a** in 88% yield. Treatment of compound **41a** with excess NaH/MeI installed the –OMe group present at the C_6 of alashanoids E and F to furnish **42a** in 95% yield. Oxidative removal of the –PMB group with DDQ in a DCM buffer solution afforded alcohol **43a** in 85% yield, which on Swern oxidation produced the corresponding aldehyde **44a** in 90% yield. Stereoselective Takai olefination of aldehyde **44a** with $CrCl_2/CHI_3$ delivered the corresponding *E*-vinylic iodide **45a** in 80% yield. Reduction of the ester functionality with DIBAL-H furnished the corresponding alcohol **46a** in 90% yield. The alcohol on oxidation under DMP conditions yielded the corresponding aldehyde. The intramolecular NHK coupling with $CrCl_2/NiCl_2$ (similar conditions as depicted earlier) of the resulting aldehyde afforded the ring closed product (humulane scaffold) as a diastereomeric mixture. Oxidation under DMP conditions furnished the corresponding ketone **47a** in 80% yield. Deslilylation[23] of **47a** with TBAF, AcOH in THF at 0 °C afforded the desired target product alashanoid E (**6a**) (90% yield; overall yield 7% from neo-pentyl glycol in 18 steps; Scheme 7).

The synthesis of another naturally occurring compound, alashanoid F (**7a**) (structurally similar to alasahnoid E, only differing in the absolute configuration at C_6 and C_7), was initiated with Evans auxiliary *ent*-**35**. Asymmetric aldol reaction through a non-Evans-*anti* selective TS model[6] furnished the aldol adduct **40b** in good yield (70%) and diastereoselectivity (19 : 1). The rest of the synthesis of alashanoid F is precisely similar to that of alashanoid E (Scheme 7). The spectroscopic (^1H, ^{13}C, and 2D-NMR) and optical rotation values of the synthesized sample match well with those of the isolated natural product (see the ESI† for detailed information). As reported, the recorded ECD spectra of the synthesized (+)-alashanoids E and F match perfectly with those of the natural samples.[3,27] Hence, the absolute configuration of the synthesized (+)-alashanoid E has been reconfirmed as 6*R*,7*S* and that of (+)-alashanoid F as 6*S*,7*S*, as reported for the natural samples. HPLC chromatogram also unambiguously proves that both the synthesized compounds are enantiopure (see the ESI† for HPLC traces).

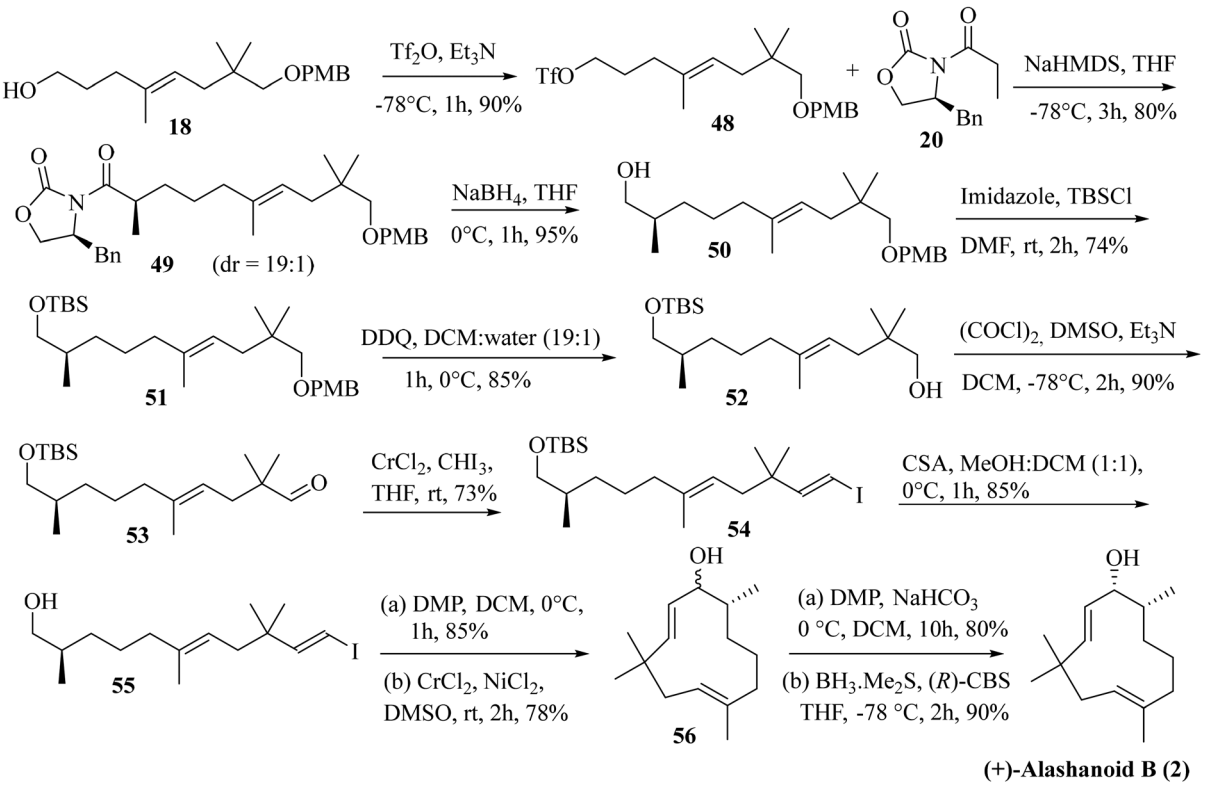
Total synthesis of (+)-alashanoid B

Next, we focused our attention on the enantioselective total synthesis of another structurally related humulane sesquiterpenoid alashanoid B. Close structural analysis revealed that alashanoid B has structural similarity with (–)-2,9-humuladien-6-ol-8-one (the difference being the presence of the –OH functionality at C_8 and the absence of the –OMe group at C_6). We have started our synthetic venture from the previously syn-



Scheme 7 Total synthesis of alashanoids E and F.

thesized alcohol **18.** The hydroxy group in compound **18** was converted to its triflate by treatment with Tf_2O and Et_3N. Asymmetric alkylation by employing an Evans oxazolidinone-based auxiliary (**20**) was next attempted with NHMDS as a base.[24] The alkylated product **49** was obtained with good yield (80%) and excellent diastereoselectivity. Reductive elimination of the chiral auxiliary with $NaBH_4$ then furnished alcohol **50** in 95% yield. Protection of the hydroxy group in **50** as its –TBS



Scheme 8 Total synthesis of (+)-alashanoid B.

ether provided compound **51** in 74% yield. Removal of the –PMB group in **51** was next achieved by treatment with DDQ to afford alcohol **52** in 85% yield. The Swern oxidation of **52** afforded aldehyde **53**, which was immediately subjected to Takai olefination to furnish the vinylic iodide **54** in 73% yield (exclusively *E* isomer was obtained). Removal of the –TBS group in **54** was achieved by treatment with CSA to furnish compound **55** in 85% yield. Oxidation of **55** with DMP followed by intramolecular NHK coupling of the resulting aldehyde proceeded smoothly as anticipated and yielded compound **56** in 66% yield (in two steps; dr is not determined). Oxidation of **56** under DMP conditions produced the cyclic ketone with the required humulane framework present in the target alashanoid B. Stereoselective reduction of the carbonyl group with (*R*)-CBS[25] furnished (+)-alashanoid B (**2**) as a single diastereomer (95% yield; 6.4% overall yield from neo-pentyl glycol in 18 steps, Scheme 8). The spectroscopic (^{1}H, ^{13}C, and 2D-NMR) and optical rotation values of the synthesized sample match well with the isolated natural product (see the ESI† for detailed information). The absolute configuration of the C_8 stereocenter in alashanoid B was further confirmed through the Mosher ester analysis[26] (see the ESI† for details). The recorded ECD spectrum of the synthesized (+)-alashanoid B cannot be compared with those of natural samples as it was not reported in the literature.[3,27] The optical rotation value confirms the absolute configuration of the synthesized alashanoid B as 7*R*,8*R*, the same as those reported for the natural samples.

Conclusion

In conclusion, we have completed the first asymmetric synthesis of a few naturally occurring humulane-type sesquiterpenoids, alashanoids B, C, E, and F, and (−)-2,9-humuladien-6-ol-8-one through a late-stage intramolecular NHK coupling as a key reaction from simple building blocks. The non-Evans-*anti* aldol reaction was successfully explored to construct the required stereocenter present in (−)-2,9-humuladien-6-ol-8-one and then a stereoselective epoxidation completes the total synthesis of alashanoid C. A divergent and flexible asymmetric aldol reaction was adopted by employing an Evans oxazolidinone-based auxiliary through two independent pathways to access alashanoids E (Evans-*syn*) and F (non-Evans-*anti*). For alashanoid B, Evans oxazolidinone-based asymmetric enolate alkylation was used to construct the C_7 stereocenter, and finally, stereoselective reduction through the CBS protocol installed the desired C_8 stereocenter present in the target natural product. Further studies towards the total synthesis of the remaining humulane-based sesquiterpenoids in the series (Fig. 1) are underway in our laboratory.

Experimental section

Detailed experimental procedures and characterization data for all the synthesized compounds are provided in the ESI.†

The characterization data of the final compounds are given in the following sections.

(−)-2,9-Humuladien-6-ol-8-one (3a)

$[\alpha]_D^{25}$ = −97.8 (*c* = 0.1, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.15 (d, *J* = 16.0 Hz, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 5.08 (dd, *J* = 11.0, 3.5 Hz, 1H), 4.22 (m, 1H), 2.90 (m, 1H), 2.21 (t, *J* = 12.0 Hz, 1H), 2.07 (dd, *J* = 12.5, 3.5 Hz, 1H), 1.95 (t, *J* = 12.0 Hz, 1H), 1.86 (dd, *J* = 13.0, 3.5 Hz, 1H), 1.37 (s, 3H), 1.30 (m, 1H), 1.16 (s, 3H), 1.11 (m, 1H), 1.12 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** {^{1}H} (125 MHz, $CDCl_3$) δ 201.0 (C═O), 152.0 (C-10), 137.8 (C-3), 128.1 (C-9), 122.2 (C-2), 73.0 (C-6), 54.3 (C-7), 41.3 (C-1), 40.0 (C-11), 37.7 (C-4), 30.7 (C-5), 28.9 (C-15), 23.0 (C-14), 16.4 (C-12), 6.1 (C-13). **IR**: 3480, 2965, 2936, 2872, 2856, 1669, 1619, 1453, 1387, 1302, 1083, 1049, 1007, 999, 988 cm^{-1}.

HRMS (ESI) *m*/*z*: for $C_{15}H_{25}O_2$ $[M + H]^+$, calculated: 237.1855; found: 237.1853.

(−)-Alashanoid C (4b)

$[\alpha]_D^{25}$ = −140.2 (*c* = 0.1, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.29 (s, 2H), 3.59 (dd, *J* = 8.5, 3.5 Hz, 1H), 3.38 (s, 3H), 3.10 (m, 1H), 2.71 (d, *J* = 11.0 Hz, 1H), 2.14 (dd, *J* = 14.0, 8.5 Hz, 1H), 1.92 (d, *J* = 14.0 Hz, 1H), 1.46 (m, 1H), 1.38 (dd, *J* = 14.0, 11.5 Hz, 1H), 1.28 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.06 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.96 (overlap, 1H). **^{13}C NMR** {^{1}H} (125 MHz, $CDCl_3$) δ 202.3 (C═O), 150.8 (C-10), 128.0 (C-9), 83.6 (C-6), 61.9 (C-3), 60.8 (C-2), 57.2 (C-16), 48.2 (C-7), 40.5 (C-1), 37.4 (C-4), 36.4 (C-11), 29.7 (C-15), 25.8 (C-5), 23.5 (C-14), 16.8 (C-12), 6.0 (C-13). **IR**: 2963, 2940, 2878, 1693, 1631, 1455, 1388, 1372, 1303, 1269, 1232, 1094, 1060, 1037, 1024, 1001, 983, 967, 913, 894, 677 cm^{-1}. **HRMS (ESI) *m*/*z***: for $C_{16}H_{27}O_3$ $[M + H]^+$, calculated: 267.1960; found: 267.1962.

(+)-Alashanoid E (6a)

$[\alpha]_D^{25}$ = +19.0 (*c* = 0.1, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.23 (d, *J* = 16.0 Hz, 1H), 6.05 (d, *J* = 16.0 Hz, 1H), 5.08 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.98 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.77 (dd, *J* = 13.5, 4.5 Hz, 1H), 3.72 (dd, *J* = 5.5, 4.0 Hz, 1H), 3.45 (s, 3H), 3.26 (m, 1H), 2.22 (t, *J* = 14.0 Hz, 1H), 2.12 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.86 (overlap, 2H), 1.48 (m, 1H), 1.37 (s, 3H), 1.21 (overlap, 1H), 1.18 (s, 3H), 1.14 (s, 3H). **^{13}C NMR** {^{1}H} (125 MHz, $CDCl_3$) δ 201.0 (C═O), 152.9 (C-), 138.1 (C-3), 127.8 (C-9), 122.2 (C-2), 82.3 (C-6), 58.1 (C-13), 57.6 (C-7), 56.6 (C-16), 41.3 (C-1), 40.3 (C-11), 39.0 (C-4), 29.0 (C-15), 23.1 (C-14), 16.4 (C-12). **IR**: 3464, 2955, 2929, 2855, 1690, 1658, 1625, 1456, 1386, 1367, 1303, 1215, 1105, 1081, 1033, 1000 cm^{-1}. **HRMS (ESI) *m*/*z***: for $C_{16}H_{27}O_3$ $[M + H]^+$, calculated: 267.1960; found: 267.1961.

(+)-Alashanoid F (7a)

$[\alpha]_D^{25}$ = +18.4 (*c* = 0.1, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.25 (d, *J* = 16.5 Hz, 1H), 5.92 (d, *J* = 16.5 Hz, 1H), 5.17 (dd, *J* = 11.5, 4.5 Hz, 1H), 4.02 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.88 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.54 (m, 1H), 3.30 (s, 3H), 2.82 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.33–2.21 (overlap, 2H), 2.00 (m, 1H), 1.92 (dd, *J* = 13.5, 4.5 Hz, 1H), 1.75–1.72 (m, 2H), 1.56 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H). **^{13}C NMR** {^{1}H} (125 MHz, $CDCl_3$) δ 203.2 (C═O), 155.5 (C-10), 137.0 (C-3), 126.3 (C-9), 123.7 (C-2), 82.4 (C-6), 60.8 (C-7), 60.4 (C-13), 57.5 (C-16), 41.6 (C-1), 39.8 (C-4), 39.2 (C-11), 32.5 (C-5), 28.9 (C-15), 23.8 (C-14), 16.5 (C-12). **IR**: 3437, 2957, 2932, 2872, 2855, 1686, 1621, 1461, 1386, 1366, 1216, 1175, 1105, 1083, 1059, 1001, 754 cm^{-1}. **HRMS (ESI) *m*/*z***: for $C_{16}H_{27}O_3$ $[M + H]^+$, calculated: 267.1960; found: 267.1964.

(+)-Alashanoid B (2)

$[\alpha]_D^{25}$ = +51.3 (*c* = 0.1, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.17 (d, *J* = 16.5 Hz, 1H), 5.05 (dd, *J* = 8.5, 7.0 Hz, 1H), 4.13 (d, *J* = 5.0 Hz, 1H), 2.10 (m, 1H), 1.99 (dd, *J* = 12.5, 10.5 Hz, 1H), 1.86 (dd, *J* = 3.0, 12.0 Hz, 1H), 1.81 (overlap, 1H), 1.62 (m, 1H), 1.50 (s, 3H), 1.42 (m, 1H), 1.24, 1.20 (overlap, 2H), 1.10 (s, 3H), 1.08 (s, 3H), 1.04 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** {^{1}H} (125 MHz, $CDCl_3$) δ 137.4 (C-10), 134.3 (C-3), 131.3 (C-9), 124.9 (C-2), 76.6 (C-8), 42.4 (C-7), 40.9 (C-4), 40.7 (C-1), 37.6 (C-11), 29.1 (C-15), 26.5 (C-6), 25.1 (C-14), 23.7 (C-5), 17.7 (C-13), 16.2 (C-12). **IR**: 3422, 2929, 2858, 1687, 1516, 1451, 1385, 1364, 1270, 1254, 1215, 1180, 1165, 1103, 1079, 1058, 997, 971, 751, 719, 697, 668 cm^{-1}.

Author contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript. SN designed the project. RB did all the experimental work reported in this manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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27 The ECD spectrum of the (*R*)-MTPA ester of (+)-alashanoid B was recorded and it showed a positive Cotton effect, confirming its enantiopurity. HPLC analysis also confirms the enantiopurity (see the ESI†).