Total synthesis of avenaol

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Avenaol, isolated from the allelopathic plant black oat, was the first C₂₀ germination stimulant related to strigolactones. Structurally, it consisted of a bicyclo[4.1.0]heptanone skeleton containing a cyclopropane ring bearing three main chains projecting in the same direction (i.e. all-cis-substituted cyclopropane). Herein, we report the total synthesis of avenaol using a robust strategy involving the formation of an all-cis-substituted cyclopropane via an alkylidenecyclopropane. The key factors in the success of this total synthesis include the Rh-catalysed intramolecular cyclopropanation of an allene, an Ir-catalysed stereoselective double-bond isomerisation, and the differentiation of two hydroxymethyl groups via the regioselective formation and oxidation of a tetrahydropyran based on the reactivity of a cyclopropyl group. This strategy effectively avoids the undesired ring opening of the cyclopropane ring and the formation of a caged structure. Furthermore, this study confirms the proposed structure of avenaol, including its unique all-cis-substituted cyclopropane moiety.
Natural products containing complex three-dimensional structures represent challenging synthetic targets, and compounds of this type have consequently received considerable interest from research groups all over the world. Notably, cage-shaped natural products have been reported to show several interesting biological activities, and numerous polycyclic terpenes and alkaloids targets of this type have inspired synthetic chemists to develop innovative new strategies to access these compounds. Non-cage-shaped natural products that are capable of being converted to cage-shaped materials also exhibit interesting range of biological activities, as exemplified by avenaol, shagene A, erythrolide A and arisanlactone (Fig. 1a). These compounds are characterised by their bicyclo[4.1.0]heptane (avenaol, shagene A), bicyclo[3.1.0]hexane (erythrolide A), and bicyclo[6.1.0]nonane (arisanlactone C) skeletons, all of which contain a cyclopropane ring bearing three main chains projecting in the same direction (i.e. an all-cis-substituted cyclopropane). Although the synthesis of these natural products is considered to be as challenging as the synthesis of their cage-shaped counterparts, there have been very few reports to date pertaining to the synthesis of all-cis-substituted cyclopropanes. In fact, there have been no reports to date concerning the total synthesis of non-cage-shaped natural products containing an all-cis-substituted cyclopropane. Furthermore, it is envisaged that these syntheses would lead to the identification of several stereochemically interesting structures. With this in mind, we became interested in investigating the synthesis of natural products containing an all-cis-substituted cyclopropane.

Avenaol (1), which was first isolated from the allelopathic plant black oat (Avena strigosa Schreb.) by Yoneyama and co-workers in 2014, was the first reported natural C<sub>20</sub> germination stimulant structurally related to strigolactones (SLs). Extensive NMR and high-resolution mass spectrometry analyses indicated that the structure of 1 consisted of a bicyclo[4.1.0]heptanone skeleton, a C ring lactone, four contiguous stereoengines and an all-cis-substituted cyclopropane. Although the all-cis-substituted cyclopropane ring in 1 might readily cyclise to form a caged structure via the formation of a C–C bond between the A and C rings, the analytic data for this compound were consistent with a non-cage structure (Fig. 1b). Given that the structure of avenaol differs from those of typical SLs such as strigol and orobanchol, it was designated as a novel class of SL. Avenaol shows potent germination-stimulating activity for Phelipanche ramosa seeds, but much lower activities for Striga hermonthica and Orobanche minor. Although the biosynthetic pathways and target protein of a few typical SLs have recently been reported, the biological properties of compound 1 have been poorly explored. Further study is therefore required to understand the relationship between the properties of avenaol and those of a few typical SLs. Although a variety of different strategies have been reported for the synthesis of typical SLs, there have been no reports to date for the synthesis of avenaol.

Herein, we report the total synthesis of avenaol based on a strategy for the construction of all-cis-substituted cyclopropanes using alkylidenecyclopropane as a key intermediate. The core structure is constructed through the Rh-catalysed intramolecular cyclopropanation of an allene, and an Ir-catalysed stereoselective double-bond isomerisation. This strategy effectively avoids the undesired ring opening of the cyclopropane ring and the formation of a caged structure. Furthermore, this study confirms the proposed structure of avenaol, including its unique all-cis-substituted cyclopropane moiety.
Results

Retrosynthetic analysis. The main challenges associated with the synthesis of avenaol include the construction of a bicyclo[4.1.0]heptanone skeleton containing an all-cis-substituted cyclopropane, controlling the stereochemistry at the C8 position of the C ring, and the introduction of a C3 hydroxyl group on the A ring. The construction of bicyclo[4.1.0]heptanone skeletons has mainly been investigated in the context of constructing caged structures. For non-caged structure, the direct synthesis of these systems has been limited to the 1,4-addition of a suitable anion of a trans-chloroallylphosphonamide or Ir-catalysed or Rh-catalysed cis-selective cyclopropanation reactions. However, preliminary work in our own group has shown that these methods are unsuitable for the synthesis of avenaol.

Fig. 2 Retrosynthesis of avenaol (1). Our strategy is characterised by the use of an alkylidenecyclopropane intermediate 5, providing a robust route to the required all-cis-substituted cyclopropane, while avoiding the undesired ring opening of the cyclopropane ring and the formation of a caged structure. The numbering of the carbon atoms is consistent with that used for avenaol.
reaction\textsuperscript{32–34}, further highlighting the difficulties of this approach. On the basis of these issues, we envisioned that the use of alkylidenecyclopropane\textsuperscript{35} as an appropriate intermediate would avoid an unwanted ring-opening reaction and the formation of a caged structure. We also envisioned that avenaol could be obtained from 2 by the dihydroxylation of its convex face and the introduction of the D ring (Fig. 2). The C ring lactone could be constructed by the diastereoselective transformation of the diol based on the reactivity of the cyclopropyl group in 3, which could be obtained by introduction of a hydroxymethyl group to the all–cis-substituted cyclopropane 4. Compound 4 could be synthesised by the intramolecular cyclopropanation of allene 6, which could be readily prepared from aldehyde 7, followed by double-bond isomerisation of alkylidenecyclopropane 5. The intramolecular cyclopropanation of an allene to form a six-membered carbocycle has not been reported, indicating that development work would be required to allow for the construction of the bicyclo[4.1.0]heptanone core.

**Construction of an all–cis-substituted cyclopropane.** Our synthesis began with the preparation of the cyclisation precursor 6 (Fig. 3). The treatment of known aldehyde 7\textsuperscript{36} with 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran and BnMe\textsubscript{3}NOH\textsuperscript{37}, followed by methylation and acidic treatment gave 8. The subsequent hydroalumination of 8, followed by the treatment of the resulting intermediate with iodine gave 9\textsuperscript{38}, which was converted to carboxylic acid 10\textsubscript{a} via sequential protection as a trisopropylsilyl (TIPS) ether, hydroboration and oxidation by 9-azanoradamantane N-oxyl (nor-AZADO)\textsuperscript{39}. The cyclisation precursor α-diazo-β-ketonitrile 6\textsubscript{a} was synthesised by sequential β-ketonitrile formation and diazo transfer reactions\textsuperscript{40}. A similar sequence was used to prepare the benzyl-protected methyl diazoketone 6\textsubscript{b}. The α-diazo-β-ketoester 6\textsubscript{c} and ketonitrile 6\textsubscript{d} were also synthesised via 10\textsubscript{b} (Supplementary Fig. 2).

We subsequently investigated the formation of the alkylidenecyclopropane intermediates via the intramolecular cyclopropagation of allenes 6\textsubscript{a–d} using a Rh or Cu catalyst\textsuperscript{11}. We initially investigated the cyclisation of methyl diazoketone 6\textsubscript{b} with Rh\textsubscript{2}(OAc)\textsubscript{4}, but this reaction failed to afford the desired cyclised product (Table 1, entry 1). Substrates bearing a β-ketoester or ketonitrile instead of a methyl group were also evaluated in an attempt to stabilise the metal carbene. The reaction of 6\textsubscript{c} with Rh\textsubscript{2}(OAc)\textsubscript{4} or Cu(CH\textsubscript{3}CN)\textsubscript{2}PF\textsubscript{6} did not give the desired product (Table 1, entries 2 and 3). In sharp contrast, the cyclisation reactions of the α-diazo-β-ketonitriles 6\textsubscript{a} and 6\textsubscript{d} with Rh\textsubscript{2}(OAc)\textsubscript{4} proceeded smoothly to give the alkylidenecyclopropanes 11\textsubscript{a} and 11\textsubscript{d}, respectively, in excellent yields, most likely because of the more electrophilic nature of the metal carbene (Table 1, entries 4 and 5)\textsuperscript{42}. It is noteworthy that this reaction only afforded the E isomer, because the metal carbene only approached from the less hindered face of the allene. For further transformation toward the all–cis-substituted cyclopropane, we used compound 11\textsubscript{a} because of the ease with which this compound could undergo protecting group manipulation.

Next, we focused on the construction of the all–cis-substituted cyclopropane structure from alkylidenecyclopropane 11\textsubscript{a}. We initially investigated the hydrogenation of the alkylidenecyclopropanes (Supplementary Fig. 3). For example, compound 12, which was prepared by reduction of 11\textsubscript{a}, followed by the PMB protection of the resulting alcohol, was hydrogenated over a Pd on carbon catalyst using H\textsubscript{2} gas. Surprisingly, this reaction gave the undesired trans isomer as the major product, most likely because of the steric effect of the nitrile group. We subsequently investigated the transition-metal-catalysed isomerisation of the double bond in this system using a directing group to reverse this selectivity. To determine the best position for the directing groups, we prepared alcohol 13, silyl ether 14 and allyl alcohol 5 by the stepwise reduction of the nitrile group (Fig. 3). Despite our initial concerns regarding the ring-opening of the cyclopropane system during these transformations, the cyclopropane ring remained intact because it was stabilised as an alkylidenecyclopropane. Compound 12 was initially treated with Crabtree’s catalyst\textsuperscript{43}, which was preactivated with H\textsubscript{2}, but failed to afford the all–cis-substituted cyclopropane (Table 2, entry 1). Use of a substrate having nitrile and hydroxyl groups resulted in no reaction, and recovery of the starting material (Supplementary Fig. 4). These results indicated that the nitrile group deactivated the Ir catalyst rather than acting as a directing group. In contrast, the reaction of 13 bearing a hydroxymethyl group under these conditions, allowed for the successful isomerisation of the olefin under H\textsubscript{2} to give the silyl enol ether 15\textsubscript{a} in 92% yield with excellent stereoselectivity (Table 2, entry 2). The success of this

### Table 1 Formation of alkylidenecyclopropane by allene cyclopropanation

| Entry | Substrate | R<sub>1</sub> | R<sub>2</sub> | Catalyst | Yield<sup>a</sup> |
|-------|-----------|-------------|-------------|-----------|-----------------|
| 1     | 6b        | Me          | Bn          | Rh<sub>2</sub>(OAc)<sub>4</sub> | 0%<sup>b</sup> |
| 2     | 6c        | CO<sub>2</sub>Et | Bn          | Rh<sub>2</sub>(OAc)<sub>4</sub> | 0%<sup>c</sup> |
| 3     | 6c        | CO<sub>2</sub>Et | Bn          | Cu(CH<sub>3</sub>CN)<sub>2</sub>PF<sub>6</sub> | 0%<sup>d</sup> |
| 4     | 6d        | CN          | Bn          | Rh<sub>2</sub>(OAc)<sub>4</sub> | 85% |
| 5     | 6a        | CN          | TIPS        | Rh<sub>2</sub>(OAc)<sub>4</sub> | 84% |

<sup>a</sup>Isolated yield.

<sup>b</sup>Carboxylic acid 10<sub>b</sub> was obtained in 26% yield.

<sup>c</sup>Carboxylic acid 10<sub>b</sub> was obtained in 35% yield.

<sup>d</sup>The reaction gave a complex mixture.
reaction indicated that the Ir catalyst approached from one face after its coordination to the alcohol (i.e. X, Fig. 4a), resulting in the exclusive formation of the all-cis isomer. However, the hydroxymethyl group on 15a could not be converted to a methyl group without opening the cyclopropane ring. Notably, the treatment of silyl ether 14 with Crabtree’s catalyst resulted in very little reaction, because of the lack of a directing group of the substrate and relatively low reactivity of the catalyst (Table 2, entry 3). The reactivity improved when we used Pfaltz’s modified Ir catalyst bearing a non-coordinating counter anion (i.e. BArF)

Table 2 Formation of all-cis-substituted cyclopropane

| Entry | Substrate | R¹ | R² | X | Yield (all-cis:trans)ᵃᵇ |
|-------|-----------|----|----|---|------------------------|
| 1     | 12        | CN | TIPS | PF₆ | No reaction |
| 2     | 13        | CH₂OH | TIPS | PF₆ | 15a: 92% (all-cis only) |
| 3     | 14        | Me | TIPS | PF₆ | 15b: 6% (2.3:1)ᶜ |
| 4     | 14        | Me | TIPS | BArF | 15b: 17% (trans only) |
| 5     | 5         | Me | H   | PF₆ | 16a: 75% (trans only) |
| 6     | 5         | Me | H   | BArF | 16b: 5% (2.7:1) |

BaRₓ (3,5-bisCF₃C₆H₃)₄B⁻, cod, cyclooctadiene, pyr, pyridine, Cy, cyclohexyl
Isolated yield
The ratio was estimated using ¹H NMR spectroscopy
Starting material 14 was recovered (64%)
formation of reaction intermediate Z1 over Z2, which would suffer considerable steric hindrance (Fig. 4c). The diastereomeric ratio improved considerably when we used Pfaltz’s modified Ir catalyst to promote the coordination of the substrate to the catalyst, affording an all-cis-trans ratio of 10:1 (Table 2, entry 6). Most notably, the selectivity of this step was found to be highly reproducible, allowing us to generate gram-scale quantities of the all-cis-substituted cyclopropane 4 for further transformations.

**Total synthesis of avenaol.** Having established a successful route to the all-cis-substituted cyclopropane, we turned our attention to the formation of the C ring. Aldehyde 4 was converted to diol 3 by the introduction of an exo methylene at the α position of the aldehyde, followed by a hydroboration (Fig. 5). We subsequently screened a wide range of conditions to allow for the differentiation of the hydroxymethyl group. Surprisingly, the diastereoselective DDQ-mediated intramolecular cyclisation of 3 to give acetal 17 resulted in the formation of the caged compound 18 in ~30% yield as a single isomer (Supplementary Table 1, entry 1). We envisaged that the selective transformation of 18 to 22 via an oxidative ring cleavage reaction would allow for the two hydroxymethyl groups to be differentiated. Thus, we switched our focus to the unexpected formation of the tetrahydropyran ring. The treatment of this system with Cu(OTf)2 was found to be ineffective, whilst Zn(OTf)2 and Sc(OTf)3 gave the cyclised products 18 and 19 (Supplementary Table 1, entries 2–4). These results indicated that acidic conditions would be important, and that this transformation would proceed via the secondary cation intermediate A. With this in mind, we investigated the addition of BF3·OEt2 and p-toluenesulfonic acid (pTsOH) (Supplementary Table 1, entries 6 and 7). The results revealed that pTsOH gave a best yield, although a large portion of the other hydroxy group also reacted with a by-product derived from PMB group to give mixture of 18 and 19. The addition of thiophenol (PhSH) was effective for trapping this by-product, allowing for the diastereoselective formation of the desired product 18 as a single product. Interestingly, the ring-opening product was not observed under these conditions, most likely because of the stability of the bisected cyclopropylcarbinyl cation intermediate A, where the π-orbitals of the cation would interact with the sp2-like orbitals of the cyclopropane ring.

The C–H oxidation of the tetrahydropyran ring in 18 was investigated for the construction of compound 22. The alcohol moiety in compound 18 was initially protected by a benzoyl group. The addition of a stoichiometric charge of CrO3 or a combination of RuCl3 and NaIO4 resulted in the oxidation of the ring to give the undesired lactone 23 and carboxylic acid 24, respectively (Table 3, entries 1 and 2). We also conducted the C–H oxidation according to the procedure reported by White’s group using (25S,2′S-(-)-[N,N′-bis(2-pyridylmethyl)]-2,2′-bipyridylidinebis(acetonitrile)iridium(II)) hexafluoroantimonate ((S,S)-Fe(pdp))50, which gave the desired alcohol 22 in 65% yield via 21. It is noteworthy, however, that this reaction required a stoichiometric amount of an iron reagent (Table 3, entry 3). In an attempt to improve the yield, we investigated the use of dimethyldioxirane (DMDO) and methyltrifluromethyldioxirane (TFDO)51. The use of an excess of DMDO resulted in a slow reaction (i.e. starting
Table 3 C–H oxidation of tetrahydrofuran 20

| Entry | Conditions | Yield of 22a |
|-------|------------|-------------|
| 1     | CrO3, AcOH, rt | 0% (23: 35%) |
| 2     | RuCl3, NaIO4, CCl4, MeCN-pH7 buffer, rt | 0% (23: 7%, 24: 33%) |
| 3     | (S,S)-Fe(dpdp), ACOH, acq, H2O2, rt | 65% |
| 4     | DMDO, CH2Cl2, rt | 22% (30% brsm) |
| 5     | TFDO, CH3Cl, 0 °C | 24% (23: 36%) |
| 6     | TFDO, CH2Cl2, −78 °C | 96% |

DMDO, dimethylidioxirane, pdp, N,N′-bis(2-pyridylmethyl)-2,2′-bipyridilime, TFDO, methyl trifluoromethylidioxirane

*Isolated yield

Discussion

In summary, we have achieved the total synthesis of avenaol. The key feature of this synthesis is the use of an alkylidene cyclopropane, which allowed for the robust formation of an all-cis-substituted structure via a stereoselective double-bond isomerisation and avoided the cleavage of the cyclopropane ring and the formation of a caged structure. The regioselective formation and C–H oxidation of a tetrahydrofuran ring were also important steps in this synthesis. The interesting structural features of avenaol, including its all-cis-substituted cyclopropane were confirmed to be correct as a consequence of our total synthesis. This established route has provided synthetic samples for further biological evaluation and is also suitable for the synthesis of a range of analogues. Furthermore, this strategy will provide a platform for the synthesis of other natural products containing this structure. The extension of this strategy to structurally related natural products, as well as structure–activity relationship studies of avenaol, are currently underway.

Methods

General. All non-aqueous reactions were run in dried glassware under a positive pressure of argon atmosphere. Reactions were monitored by thin-layer chromatography using Silica gel 60 plates (Merck, Darmstadt, Germany). Silica gel column chromatography was performed using Chromatorex BW-300 (Fujio silysia, Aichi, Japan) and Kanto silica gel 60 (particle size 63–210 μm, Kanto, Tokyo, Japan). Proton nuclear magnetic resonance (1H NMR) spectra were taken with a JNM-AL 400 (JEOL) at 400 MHz or a JNM-ECA 500 (JEOL, Tokyo, Japan) at 500 MHz. Chemical shifts were measured relative to the residual solvent peak in CDCl3 (δ 7.16) or MeSi (δ 0.00) in CDCl3. Multiplicity was indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (13C NMR) spectra were recorded on a JNM-AL 400 at 100 MHz or a JNM-ECA 500 at 125 MHz. Chemical shifts were measured relative to CDCl3 (δ 77.0) or CD3OH (δ 49.0). Infrared spectra were collected on a FTIR-4100 Fourier-transform infrared spectrometer (JASCO, Tokyo, Japan) as ATR (attenuated total reflectance). Low and high-resolution mass spectra were recorded on a LCMS-IT-TOF (Shimadzu, Kyoto, Japan) for ESI-MS and JMS-700 mass spectrometer (JEOL) for FAB-MS.

Experimental data. For the experimental procedures and spectroscopic and physical data of the compounds and the crystallographic data of C2′-epi avenaol, see Supplementary Methods. For NMR spectra of synthetic intermediates, see Supplementary Figs. 5–35. For the comparisons of 1H and 13C NMR spectra of the natural and synthetic avenaol, see Supplementary Figs. 36 and 37.

Data availability. The X-ray crystallographic coordinates for the structure of C2′-epi avenaol have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number 1544731. These data can be obtained for a fee from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Other data are available from the authors upon reasonable request.
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Competing interests: The authors declare no competing financial interests.

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