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First Enantioselective Synthesis of Marine Diterpene Ambliol-A

Stefano Serra*[a] and Veronica Lissoni[b]

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The first enantioselective synthesis of furanditerpene ambliol-A, which is a major metabolite of marine sponge *Dysidea amblia*, has been accomplished by starting from racemic α-ionone. The key steps of the synthesis include lipase-mediated resolution of 4-hydroxy-γ-ionone, its stereoselective transformation into *trans*-α-epoxy-dihydroionone, C_2 homologation to *trans*-α-epoxy-monocyclofarnesyl acetate and Li_2CuCl_4-catalysed sp^3–sp^3 cross-coupling reaction of the latter ester with (furan-3-ylmethyl)magnesium chloride. This work confirms the chemical structure previously assigned to ambliol-A and proves that the natural levorotatory isomer does not possess (1*S*,2*S*) absolute configuration, as previously indicated, but is the opposite enantiomer, (1*R*,2*R*)-2-[(*E*)-6-(furan-3-yl)-3-methylhex-3-enyl]-1,3,3-trimethylcyclohexanol.

Introduction

Diterpene Ambliol-A (**1**) is a major metabolite of marine sponge *Dysidea amblia* and occurs alongside structurally related metabolite dehydroambliol-A (**2**; Figure 1). These furanditerpenes were isolated for the first time by Faulkner et al.[1] who determined their chemical structures on the basis of both spectroscopic data and chemical degradation experiments.

More specifically, both the hydroxy group and the side chain of ambliol-A proved to be equatorial with respect to the cyclohexane ring. Ozonolysis of **1** provided enol ether **3**, which was identical to the known synthetic material obtained through cyclization reaction of geranylacetone.

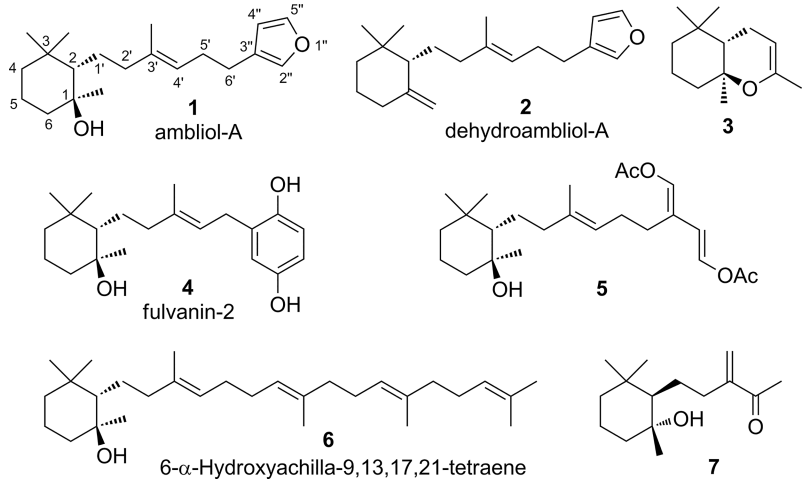

Figure 1. The chemical structures previously assigned to natural ambliol-A (**1**) and dehydroambliol-A (**2**). Enol ether **3** obtained by ozonolysis of ambliol-A. Other natural compounds (**4**–**7**) that feature a substituted hydroxy-monocyclofarnesane moiety with the hydroxy group and side chain in relative *trans* configuration.

[a] C.N.R., Istituto di Chimica del Riconoscimento Molecolare, Via Mancinelli 7, 20131 Milano, Italy
E-mail: stefano.serra@cnr.it
stefano.serra@polimi.it
http://www.icrm.cnr.it/serra.htm
[b] Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano,
Via L. Mangiagalli 25, 20133 Milano, Italy

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The absolute configuration was depicted as (1*S*,2*S*), although there was no evidence to indicate which one of the two enantiomers was the natural one. The latter study did not clearly state how the assignment was done, which left some ambiguity on this point. Afterwards, ambliol-A was also isolated from the sponge *Oceanapia bartschi*[2] and a number of natural products of terpenic origin that featured

a substituted hydroxy-monocyclofarnesane moiety and possessed relative *trans* configuration, as described above, were also identified. These compounds were isolated from sources very different from each other. For example fulvanin-2 (**4**),[3] enol-acetate **5**,[4] triterpene 6-α-hydroxy-achilla-9,13,17,21-tetraene (**6**)[5] and sesquiterpene **7**[6] were isolated from sponge, seaweed, fern, and plant, respectively, and the absolute configuration was assigned unambiguously only for compounds **6** and **7**.

All the aforementioned natural products are difficult to access through chemical synthesis. More specifically, the introduction of the hydroxy functional group with the required *trans* stereochemistry is especially demanding. As a consequence, the attribution of the stereochemical structure of some of them is still unconfirmed, because their total synthesis has not been accomplished yet. In this context, we recently described the synthesis of (*S*)-dehydroambliol-A,[7a] which showed an optical rotation sign opposite to that recorded for natural **2**. Because the latter metabolite is most likely derived from ambliol-A through elimination of water, this study suggests that both natural **1** and **2** could have been assigned the wrong absolute configuration.

By taking advantage of our previously acquired expertise in the enantioselective synthesis of monocyclofarnesyl derivatives,[7] we investigated a new stereoselective synthesis of ambliol-A. Herein we describe the results of this study, which assign unambiguously the (1*R*,2*R*)-configuration of natural **1** as well as outline a new synthetic approach to natural compounds of similar structure.

Results and Discussion

According to a retrosynthetic analysis (Figure 2), we planned to synthesize ambliol-A from enantioenriched *trans*-epoxy-α-dihydroionone **11** by exploiting three different stereoselective transformations. The tertiary carbinol is obtained through regioselective reduction of epoxide **8**, the C_{20} framework of which is prepared by means of a copper-catalyzed cross-coupling reaction between C_{15} acetate **9** and C_5 Grignard reagent **10**. The trisubstituted double bond of **9** is stereoselectively created through Horner–Wadsworth–Emmons reaction of triethylphosphonoacetate with ketone **11**. The latter compound requires a particular enantioselective synthesis, which was also studied.

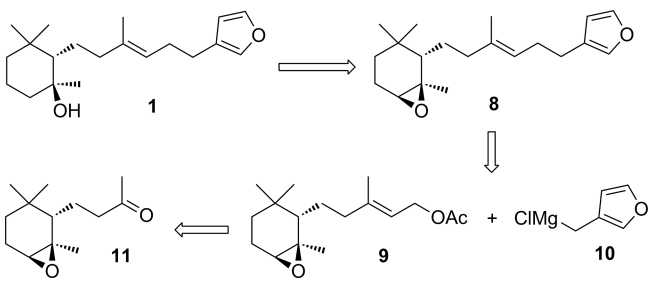
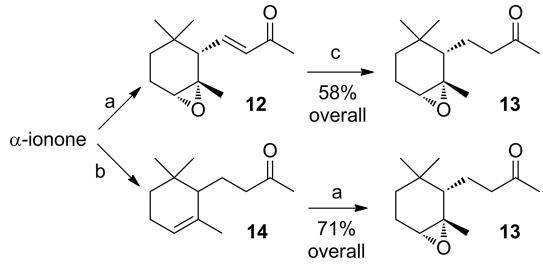


Figure 2. Retrosynthetic analysis of ambliol-A.

It is worth noting that only two syntheses of racemic ambliol-A have been reported so far.[8] The most recent research[8b] described the preparation of racemic **1** by using *trans*-epoxy-α-dihydroionone as a key intermediate, which was in turn obtained by epoxidation with *m*-chloroperoxybenzoic acid (*m*CPBA) of α-dihydroionone. These results seem to be in disagreement with the general behavior of α-ionone and α-damascone isomers, which react with peracids to give *cis*-epoxy derivatives.[9]

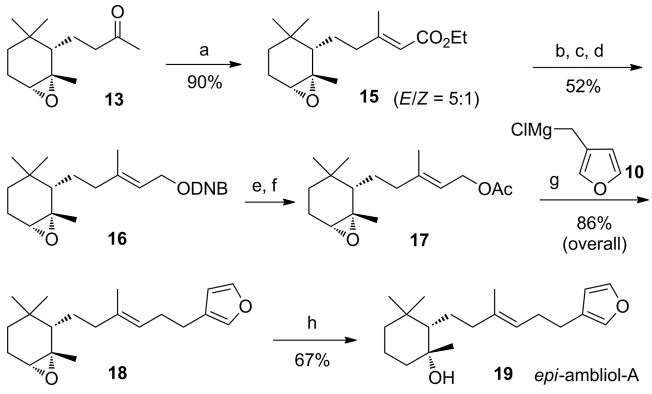
This stereochemical outcome has been unambiguously demonstrated only for the epoxidation of α-ionone.[9b] In principle, *m*CPBA epoxidation could proceed with opposite stereoselectivity when α-dihydroionone is used as the substrate. To verify the stereochemical trend of this reaction and to exclude the fact that ambliol-A could possess a *cis*-relationship between the hydroxy group and the side chain, we decided to prepare this isomeric form of ambliol by starting from *cis*-epoxy-α-dihydroionone. Accordingly, we began with the experiments described in Scheme 1.



Scheme 1. The stereochemical outcome of the epoxidation reaction between α-ionone and α-dihydroionone with *m*CPBA. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, 0 °C; (b) H_2, atmospheric pressure, Raney Ni, THF/MeOH; (c) H_2, atm. pressure, Pd $BaCO_3$, EtOH.

Epoxidation reaction of racemic α-ionone with *m*CPBA gave diastereoselectively *cis*-epoxy-ionone **12**, which was hydrogenated with Pd/$BaCO_3$ as catalyst to afford *cis*-epoxy-α-dihydroionone **13**. The NMR spectroscopic data of the latter compound were identical in all respects to those recorded for the epoxide obtained from α-dihydroionone (**14**) by reaction with *m*CPBA. These results demonstrated that the previous synthesis of ambliol-A afforded the epimer of racemic **1** instead of **1**, which raises new doubts about the attribution of the relative configuration of the natural product. Therefore, to analyze the experimental data of these isomers, we decided to synthesize *epi*-ambliol-A from *cis*-epoxy-α-dihydroionone (**13**; Scheme 2).

By following the previously described retrosynthetic analysis, racemic **13** was treated with an excess of triethylphosphonoacetate sodium salt in tetrahydrofuran (THF) solution. Obtained ester **15** consisted of a 5:1 mixture of *E*/*Z* isomers, which were not separated and were reduced with diisobutylaluminium hydride (DIBAH) to give the corresponding allylic alcohols. The latter mixture was treated with 3,5-dinitrobenzoyl chloride and pyridine and the resulting esters were recrystallized twice from hexane. The collected crystals were isomerically pure ester **16**, which possessed both the required *cis*-epoxide and the *E* double bond configuration.



Scheme 2. The synthesis of *epi*-ambliol-A. Reagents and conditions: (a) $(EtO)_2POCH_2CO_2Et$, NaH, THF; (b) DIBAH, THF, –40 °C; (c) 3,5-dinitrobenzoyl chloride, Py, DMAP cat.; (d) crystallization from hexane; (e) NaOH, MeOH, room temperature; (f) Ac_2O, Py; (g) Li_2CuCl_4 cat., THF, **10** (1.5 equiv.), –20 °C to 0 °C; (h) $LiAlH_4$, THF, reflux.

The hydrolysis of the latter ester afforded the corresponding alcohol, which was acetylated by using acetic anhydride and pyridine. According to our previous studies,[7a] Li_2CuCl_4 catalyzed the coupling of monocyclofarnesyl derivative **17** with Grignard reagent **10** with very high chemoselectivity. Actually, the addition of **10** to a cooled THF solution of acetate **17** that contained Li_2CuCl_4 (0.05 equiv.) smoothly afforded S_N2 derived product **18** without any detectable amount of the corresponding S_N2' adduct, double bond isomerized derivatives or epoxide-opened side products. Lastly, reduction of epoxide **18** with $LiAlH_4$ in THF at reflux temperatures afforded diastereoisomerically pure *epi*-ambliol-A **19**.

The NMR spectroscopic data of this synthetic material was analyzed with that reported for natural ambliol-A.[1] Although the ^1H NMR spectra of the two compounds are very similar, the ^{13}C NMR spectra show significant differences in the signals of some specific carbons. More specifically, the chemical shifts of the carbons in position 1, 2, and 5, as well as that of one of the methyl groups, clearly allow us to distinguish natural ambliol-A from its synthetic epimer (Table 1). As a consequence, we can conclude that the hydroxy group and the side chain of ambliol-A has *trans* relationship, as correctly indicated by Faulkner et al.[1] Therefore, the product obtained by Ray et al.[8b] was *epi*-ambliol-A, which could not be differentiated from its epimer by means of ^1H NMR spectroscopic analysis alone.

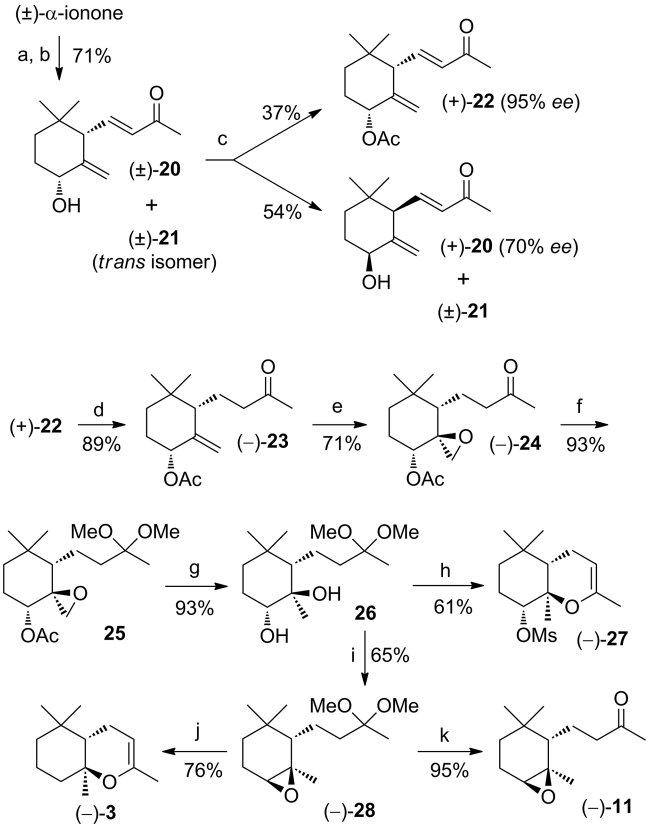
Because our approach to *epi*-ambliol-A was effective and reliable, we decided to study a stereoselective preparation of enantioenriched *trans*-epoxy-α-dihydroionone to be used as a chiral building block for the synthesis of ambliol-A. To this end, we planned to transform racemic α-ionone into racemic 4-hydroxy-γ-ionone (**20**; Scheme 3) through a two-step process of epoxidation of the ionone followed by base-mediated rearrangement of the obtained epoxy-ionone.[10] Racemic alcohol **20** can be resolved by means of lipase-mediated acetylation reaction. The exocyclic double bond

Table 1. The ^{13}C NMR spectroscopic data of natural ambliol-A, *epi*-ambliol-A, and synthetic ambliol-A.

Position[a]	Natural ambliol-A[a] δ_C (C_6D_6)[b]	Synthetic *epi*-ambliol-A δ_C (C_6D_6)[b]	Synthetic ambliol-A δ_C (C_6D_6)[b]
1	73.7	72.5	73.6
2	56.7	54.1	56.8
3	35.6	35.0	35.6
4, 6, 2′	43.9, 43.2, 41.8	44.0, 42.4, 41.7	44.0, 43.2, 41.9
5	20.8	18.8	20.9
1′, 5′, 6′	28.8, 25.3, 25.3	28.9, 25.4, 25.2	28.9, 25.4, 25.3
Me(1), Me(3)	33.0, 23.5, 21.6	32.3, 31.1, 21.8	33.0, 23.6, 21.6
3′	137.0	136.7	137.1
Me(3′)	16.2	16.3	16.2
4′	124.1	124.0	124.2
2′′, 5′′	139.2, 142.8	139.2, 142.9	139.2, 142.8
3′′	125.2	125.2	125.2
4′′	111.3	111.3	111.3

[a] Data reported in ref.[1]. [b] 100 MHz, room temperature.

of the obtained enantioenriched derivatives can be epoxidized diastereoselectively to give, after a number of functional-group transformations, *trans*-epoxide **11**.



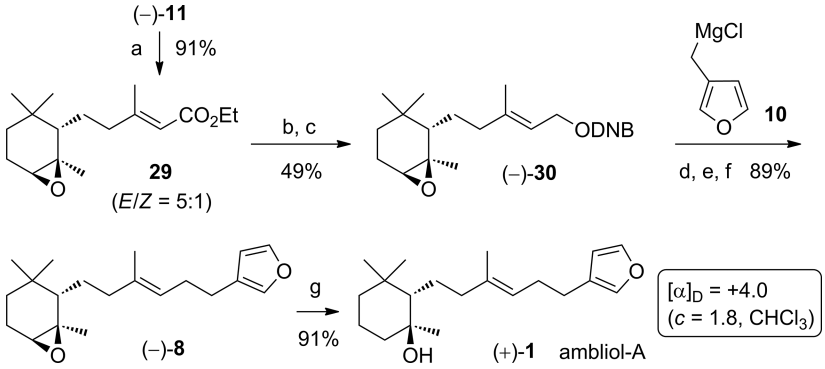
Scheme 3. Stereoselective synthesis of *trans*-epoxy-α-dihydroionone. Reagents and conditions: (a) $H_2O_2{\cdot}NH_2CONH_2$, $(CF_3CO)_2O$, CH_3CN/CH_2Cl_2, K_2CO_3, –78 °C then –50 °C; (b) LDA, THF, –78 °C then reflux; (c) lipase PS, *t*BuOMe, vinyl acetate; (d) H_2, atm. pressure, Raney Ni, THF/MeOH; (e) *m*CPBA, CH_2Cl_2, room temperature; (f) $(MeO)_3CH$, PPTS, MeOH; (g) $LiAlH_4$, Et_2O, reflux; (h) MsCl, Py, DBU, room temperature; (i) LDA (1 equiv.), THF, 0 °C then MsCl 30 min.; LDA (1 equiv.) then room temperature; (j) $LiEt_3BH$, THF, room temperature then diluted HCl aq.; (k) THF/H_2O, catalytic pyridinium *p*-toluenesulfonate.

Because we intended to have access to both enantiomeric forms of this compound, we improved the stereoselective synthesis of racemic **20**. We have previously demonstrated[10] that lipase PS catalyzes the acetylation reaction of (4*R*,6*S*)-4-hydroxy-γ-ionone with very high enantioselectivity and complete diastereoselectivity to lead to enantiopure (+)-**22** and enantioenriched alcohol (+)-**20** contaminated with racemic *trans*-4-hydroxy-γ-ionone (**21**). The latter compound derives from *trans*-epoxy-ionone, the formation of which is a result of incomplete diastereoselectivity of the epoxidation reaction step with *m*CPBA. By taking inspiration from Fehr's work,[9e] which indicated trifluoroperacetic acid as a more diastereoselective reagent for this kind of transformation, we selected the combined use of hydrogen peroxide–urea adduct with trifluoroacetic anhydride[11] as the most convenient and safe procedure to generate this unstable peracid on a preparative scale. The reaction of the latter reagent with α-ionone at low temperature (–78 °C) gave the corresponding epoxy derivative with expected high diastereoselectivity (94% of *cis* isomer). The following treatment with more than two equivalents of lithium diisopropylamide (LDA) afforded racemic compound **20**, which was then resolved by means of lipase PS-mediated acetylation. Because (4*R*,6*S*)-4-acetoxy-γ-ionone [(+)-**22**] possesses the same absolute configuration as natural ambliol-A, we used this compound as the starting material for our planned synthesis.

Accordingly, the conjugated double-bond of compound (+)-**22** was regioselectively hydrogenated by using Raney Ni as catalyst.[12] Resulting ketone (–)-**23** was treated with *m*CPBA to afford spiro-epoxide (–)-**24** as the major product. We can explain the latter stereochemical outcome by assuming that the peracid attaches preferentially the less hindered face of the exocyclic double bond. It is worth noting that similar stereoselectivity has been described for *m*CPBA epoxidation of structurally related *cis*-4-hydroxy-γ-ionone.[13] Finally, we were able to confirm *a posteriori* the stereochemistry of compound **24**, by means of its transformation into *trans*-epoxy-dihydroionone [(–)-**11**], the quaternary stereocenter of which was created through the above described epoxidation reaction and establishes a *trans* relationship between the epoxide functional group and the side chain moiety.

Because the quaternary carbinol on the cyclohexanic ring reacts quickly with the ketone on the side chain to give the corresponding dihydropyranyl derivative,[14] we decided to protect the latter functional group before reduction of the spiro-epoxide. Hence, compound (–)-**24** in methanol was treated with trimethyl orthoformate in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate. Resulting dimethylketal **25** was reduced with $LiAlH_4$ to perform simultaneously the acetate functional group removal and the regioselective epoxide reduction. Unfortunately, obtained diol **26** turned out to be very unstable in acidic environments. Therefore, after work-up under basic conditions, it was used directly in the preparation of epoxide (–)-**28**. To this end, we checked the intramolecular ring closure of vicinal diol **26**. The secondary hydroxy group was activated by means of its transformation into a mesylate group and then treated with base to promote the nucleophilic displacement of the mesyl group. A first experiment based on treatment of **26** with an excess of pyridine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), and mesyl chloride gave disappointing results and led to the exclusive formation of enol ether (–)-**27**. However, stepwise treatment of **26** with an equimolar amount of LDA and one equivalent of mesyl chloride followed by addition of a further equivalent of LDA afforded epoxide (–)-**28** in satisfactory yield. The acid-catalyzed hydrolysis of the latter compound gave desired *trans*-epoxy-α-dihydroionone [(–)-**11**], the spectroscopic data of which confirmed the diastereoisomeric relationship between **11** and **13** and thus the *trans* configuration of **11**. In addition, the regioselective reduction of epoxide (–)-**11** with $LiEt_3BH$ followed by acid work-up smoothly afforded bicyclic enol ether (–)-**3**, which turned out to be spectroscopically identical to the enol ether obtained by ozonolysis of natural ambliol-A.[1]

Encouraged by the latter results, we employed epoxide (–)-**11** as a chiral building block for the synthesis of ambliol-A by following the same experimental approach developed for the preparation of epimer **19** (Scheme 4). Accordingly, epoxide (–)-**11** was treated with an excess of triethyl-



Scheme 4. Stereoselective synthesis of (1*S*,2*S*)-ambliol-A. Reagents and conditions: (a) $(EtO)_2POCH_2CO_2Et$, NaH, THF; (b) DIBAH, THF, –40 °C; (c) 3,5-dinitrobenzoyl chloride, Py, DMAP cat.; (d) NaOH, MeOH, room temperature; (e) Ac_2O, Py; (f) Li_2CuCl_4 cat., THF, **10** 1.5 equiv., –20 °C to 0 °C; (g) $LiEt_3BH$, THF, 0 °C then room temperature.

phosphonoacetate sodium salt in THF solution. Obtained ester **29** (5:1 mixture of *E*/*Z* isomers) was reduced with DIBAH to the corresponding allylic alcohols. The latter mixture was treated with 3,5-dinitrobenzoyl chloride and pyridine but the resulting ester mixture proved to be oil, which hampered the isolation of pure *E* isomer by fractional crystallization.

Luckily, we were able to increase the purity of the *E* isomer through chromatographic purification of the ester mixture. A sample of compound (–)-**30**, with a 92:8 *E*/*Z* ratio, was hydrolyzed to give the corresponding alcohol, which was acetylated with acetic anhydride and pyridine. The Li_2CuCl_4 catalyzed coupling of the latter acetate with Grignard reagent **10** smoothly afforded S_N2 deriving product (–)-**8**. Lastly, reduction of the epoxide functional group with $LiAlH_4$ in THF at reflux temperatures did not work as effectively as reported for the *cis*-isomer. Therefore we switched to the use of the more nucleophilic $LiEt_3BH$, which smoothly reduced (–)-**8** to afford ambliol-A (+)-**1** in very good yields.

The obtained synthetic ambliol-A showed spectroscopic data in perfect agreement with those reported for the natural diterpene (Table 1) with exception of the optical rotation sign. We recorded a value of + 4.0 (c 1.8, $CHCl_3$), whereas Faulkner et al. recorded a value of –3.9 (c 2.5 $CHCl_3$). Overall, these data demonstrate unambiguously that natural ambliol-A is the (1*R*,2*R*)-2-[(*E*)-6-(furan-3-yl)-3-methylhex-3-enyl]-1,3,3-trimethylcyclohexanol, confirm the chemical structure previously assigned, and corrects its absolute configuration.

Conclusions

We report here the first enantioselective synthesis of (+)-ambliol-A **1** as well as the diastereoselective synthesis of non-natural epimer **19**. This work confirms the chemical structure assigned to natural (–)-ambliol-A and proves that the diterpene isolated from the marine sponge *Dysidea amblia* is not the (1*S*,2*S*) isomer, as previously indicated, but its enantiomer, (1*R*,2*R*)-2-[(*E*)-6-(furan-3-yl)-3-methylhex-3-enyl]-1,3,3-trimethylcyclohexanol. Because our synthetic approach is based on the use of (4*R*,6*S*)-4-acetoxy-γ-ionone as a chiral building block and both enantiomeric forms of the latter compound can be prepared by lipase-mediated resolution of the corresponding racemic material, formal synthesis of (–)-ambliol-A is also accomplished. Lastly, it is worth noting that this synthetic approach opens the way to the preparation of other natural terpenoids that feature a substituted hydroxy-monocyclofarnesane moiety with the quaternary hydroxy group and the side chain in a relative *trans* configuration.

Experimental Section

General Experimental: All moisture-sensitive reactions were carried out under an atmosphere of nitrogen. All reagents were of commercial quality with the exception of (furan-3-ylmethyl)magnesium chloride (**10**), which was prepared immediately before the use as described previously.[7a] Lipase PS from *Pseudomonas cepacia* (Amano Pharmaceuticals Co., Japan) 30 units/mg was employed in this work. TLC was performed with Merck silica gel 60 F_{254} plates. Column chromatography was performed with silica gel. GC–MS analyses were measured on a HP-6890 gas chromatograph equipped with a 5973 mass detector with a HP-5MS column (30 m × 0.25 mm, 0.25 μm film thickness; Hewlett–Packard) and the following temperature program: 60° (1 min)–6°/min–150° (1 min)–12°/min–280° (5 min); carrier gas, He; constant flow 1 mL/min; split ratio, 1:30; t_R given in min: t_R(**3**) 15.07, t_R(**11**) 19.04, t_R(**13**) 18.48, t_R(**21**, corresponding acetate) 20.50, t_R(**22**) 20.80, t_R(**23**) 21.31, t_R(**24**) 22.82 and t_R(**27**) 24.40. Chiral GC analyses were measured with a DANI-HT-86.10 gas chromatograph and enantiomer excesses determined with a Chirasil-DEX-CB column with the following temperature program; 60° (3 min) – 3°/min – 180° (5 min), carrier gas, He; constant flow 1 mL/min; t_R(+)-**22**: 32.51, t_R(–)-**22**: 32.65. Mass spectra of compounds **1**, **8**, **15**, **16**, **18**, **19**, **25**, **28**, **29**, and **30** were recorded with a Bruker ESQUIRE 3000 PLUS spectrometer (ESI detector). Optical rotations were recorded with a Jasco-DIP-181 digital polarimeter. ^1H and ^{13}C NMR Spectra and DEPT experiments were recorded at room temperature with a Bruker AC-400 spectrometer at 400, 100, and 100 MHz, respectively. Chemical shifts are reported relative to $SiMe_4$. Melting points were measured with a Reichert apparatus equipped with a Reichert microscope.

4-[(1*SR*,2*SR*,6*RS*)-1,3,3-Trimethyl-7-oxabicyclo[4.1.0]heptan-2-yl]-butan-2-one (13)

(a) By Epoxidation of α-Dihydroionone: A solution of racemic α-ionone (10 g, 52 mmol) in THF/methanol (5:1, 80 mL) was hydrogenated at room temperature and atmospheric pressure by using activated Raney nickel as catalyst. After 1.04 mol-equiv. of hydrogen were absorbed the catalyst was filtered and the organic phase was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (80 mL) and *m*CPBA (12.7 g, 77% w/w, 56.7 mmol) was added portionwise at 0 °C whilst stirring. As soon as starting ketone **14** could no longer detected by TLC analysis (6 h), the precipitated *m*-chlorobenzoic acid was filtered off and the organic phase was diluted with CH_2Cl_2 (100 mL) and was washed in turn with aqueous solution of $Na_2S_2O_5$ (5%, 80 mL), saturated aqueous $NaHCO_3$ (150 mL), and brine. The obtained organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/ethyl acetate (9:1–8:2) as eluent to afford pure **13** (7.75 g, 71% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.93 (s, 1 H), 2.74 (ddd, *J* = 16.6, 9.9, 5.4 Hz, 1 H), 2.51 (ddd, *J* = 16.6, 9.9, 5.9 Hz, 1 H), 2.16 (s, 3 H), 1.92 (dd, *J* = 15.6, 6.2 Hz, 1 H), 1.88–1.77 (m, 1 H), 1.76–1.66 (m, 1 H), 1.63–1.51 (m, 1 H), 1.39 (ddd, *J* = 10.3, 4.6, 1.2 Hz, 1 H), 1.36–1.25 (m, 1 H), 1.32 (s, 3 H), 0.89 (s, 3 H), 0.87–0.79 (m, 1 H), 0.84 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.9 (C), 59.9 (CH), 59.0 (C), 46.1 (CH), 43.0 (CH_2), 31.4 (C), 29.8 (Me), 27.6 (Me), 27.2 (Me), 26.9 (Me), 26.6 (CH_2) 22.0 (CH_2), 21.4 (CH_2) ppm. GC–MS (EI): *m*/*z* (%) = 210 $[M]^+$ (7), 195 (100), 177 (16), 167 (21), 153 (68), 137 (49), 125 (39), 111 (66), 95 (62), 81 (35), 69 (40), 55 (53).

(b) By Epoxidation of α-Ionone: A sample of α-ionone (10 g, 52 mmol) in CH_2Cl_2 (80 mL) was transformed into epoxy-α-ionone (8.1 g, 38.9 mmol) by using *m*CPBA, as described previously.[9f] The purified epoxide in EtOH (80 mL) was hydrogenated at room temperature and atmospheric pressure with 10% w/w $Pd/BaCO_3$ as catalyst. After 1.05 mol-equiv. of hydrogen was absorbed the catalyst was filtered and the organic phase was concentrated under re-

duced pressure. The residue was purified by chromatography by eluting with hexane/ethyl acetate (9:1–8:2) as eluent to afford pure **13** (6.3 g, 58% overall yield) as a colorless oil. ^{1}H NMR and ^{13}C NMR spectra were identical to those recorded for **13** obtained through epoxidation of α-dihydroionone.

(*E*)-Ethyl 3-Methyl-5-[(1*SR*,2*SR*,6*RS*)-1,3,3-trimethyl-7-oxabicyclo[4.1.0]heptan-2-yl]pent-2-enoate (15): Triethyl phosphonoacetate (14 g, 62.4 mmol) was added dropwise under nitrogen over a period of 1 h to a stirred suspension of NaH (60% in mineral oil; 2.5 g, 62.4 mmol) in dry THF (40 mL) at 0 °C. To the resulting mixture was slowly added a solution of epoxide **13** (6 g, 28.5 mmol) in dry THF (10 mL). When the addition was complete, the reaction was slowly heated at 50 °C and stirring was continued until the starting ketone was no longer detectable by TLC analysis (3 h). After cooling, the reaction was poured onto a mixture of crushed ice and saturated aqueous NH_4Cl (100 mL). The mixture was extracted with diethyl ether (2 × 150 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography with *n*-hexane/diethyl ether (95:5–9:1) as eluent to afford pure **15** (7.2 g, 90% yield) as a colorless oil consisting of an *E*/*Z* mixture of isomers (*E*/*Z* ratio, 5:1, by NMR analysis). ***E* Isomer:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (m, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 2.94 (br. s, 1 H), 2.44 (dddd, *J* = 13.6, 11.2, 5.4, 0.8 Hz, 1 H), 2.22–2.11 (m, 1 H), 2.19 (d, *J* = 1.2 Hz, 3 H), 1.92 (ddt, *J* = 15.5, 6.2, 1.6 Hz, 1 H), 1.88–1.77 (m, 1 H), 1.65–1.22 (m, 4 H), 1.33 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 0.90 (s, 3 H), 0.89–0.78 (m, 1 H), 0.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 160.4, 115.5, 60.0, 59.3, 59.2, 47.0, 40.6, 31.5, 29.6, 27.7, 27.3, 26.9, 25.6, 22.0, 18.9, 14.3 ppm. MS (ESI): *m*/*z* = 303.5 [M + Na]$^+$.

(*E*)-3-Methyl-5-[(1*SR*,2*SR*,6*RS*)-1,3,3-trimethyl-7-oxabicyclo[4.1.0]heptan-2-yl]pent-2-enyl 3,5-Dinitrobenzoate (16): DIBAH (37.9 mL of a 1.7 M solution in toluene, 64.4 mmol) was added dropwise to a stirred solution of ester **15** (9 g, 32.1 mmol) in dry THF (80 mL) at –40 °C. The reaction was then quenched by addition of a saturated aqueous solution of NH_4Cl (80 mL), followed by acidification with diluted aqueous HCl. The mixture was extracted with diethyl ether (3 × 100 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and was treated with pyridine (10 mL) with 4-dimethylaminopyridine (DMAP; 0.1 g, 0.8 mmol) and with a solution of 3,5-dinitrobenzoyl chloride (9 g, 39 mmol) in CH_2Cl_2 (20 mL). As soon as the starting alcohol was no longer detectable by TLC analysis, the reaction was diluted with CH_2Cl_2 and water. The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ then brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/diethyl ether (95:5–8:2) to afford an *E*/*Z* mixture of the ester **16**. The latter oil was dissolved in hexane and stored overnight at –20 °C. The obtained solid material was recrystallized twice from hexane to afford isomerically pure ester **16** (*E* > 98% by NMR spectroscopic analysis, 7.2 g, 52% yield) as colorless crystals, m.p. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (t, *J* = 2.1 Hz, 1 H), 9.16 (d, *J* = 2.1 Hz, 2 H), 5.54 (t, *J* = 7.2 Hz, 1 H), 4.98 (d, *J* = 7.2 Hz, 2 H), 2.95 (s, 1 H), 2.44–2.35 (m, 1 H), 2.18–2.08 (m, 1 H), 1.93 (dd, *J* = 15.5, 6.2 Hz, 1 H), 1.88–1.77 (m, 1 H), 1.84 (s, 3 H), 1.62–1.45 (m, 2 H), 1.41–1.20 (m, 2 H), 1.34 (s, 3 H), 0.90 (s, 3 H), 0.90–0.79 (m, 1 H), 0.84 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 148.7, 145.2, 134.3, 129.4, 122.2, 116.8, 63.7, 60.1, 59.5, 47.0, 39.4, 31.5, 27.8, 27.3, 26.9, 26.9, 25.7, 22.0, 16.8 ppm. MS (ESI): *m*/*z* = 455.4 [M + Na]$^+$.

(1*SR*,2*SR*,6*RS*)-2-[(*E*)-6-(Furan-3-yl)-3-methylhex-3-enyl]-1,3,3-trimethyl-7-oxabicyclo[4.1.0]heptane (18): A solution of ester **16** (2 g, 4.63 mmol) in methanol (20 mL) was treated with a solution of NaOH (2 g, 50 mmol) in methanol (20 mL) at room temperature. After hydrolysis was complete (1 h), the reaction was diluted with water and extracted twice with ether. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in pyridine (10 mL) and acetic anhydride (10 mL) and was set aside until the acetylation reaction was complete (1 h). The solvents were removed under reduced pressure to leave almost pure acetate **17**. Grignard reagent **10** (13 mL of a 0.57 M solution in THF) was added dropwise under an atmosphere of nitrogen to a stirred and cooled (–20 °C) solution of ester **17** in dry THF (10 mL) to which $Li_2Cu_2Cl_4$ (0.7 mL of a 0.5 M solution in THF) had been previously added.

After stirring for 1 h, the reaction was slowly allowed to warm to 0 °C, stirred at this temperature for a further 2 h and then poured into a ice-cooled mixture of diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography with *n*-hexane/diethyl ether (99:1–95:5) as eluent to afford pure epoxide **18** (1.21 g, 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 1.5 Hz, 1 H), 7.21 (br. s, 1 H), 6.27 (s, 1 H), 5.21 (t, *J* = 7.0 Hz, 1 H), 2.93 (s, 1 H), 2.49–2.42 (m, 2 H), 2.31–2.20 (m, 3 H), 2.06–1.96 (m, 1 H), 1.92 (dd, *J* = 15.5, 6.0 Hz, 1 H), 1.87–1.76 (m, 1 H), 1.62 (s, 3 H), 1.57–1.38 (m, 2 H), 1.36–1.24 (m, 2 H), 1.32 (s, 3 H), 0.88 (s, 3 H), 0.84–0.76 (m, 1 H), 0.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 138.8, 136.5, 125.0, 123.6, 111.1, 60.1, 59.7, 46.9, 39.5, 31.5, 28.5, 27.7, 27.4, 27.1, 26.8, 26.0, 25.0, 22.1, 16.1 ppm. MS (ESI): *m*/*z* = 303.5 [M + H$^+$], 325.5 [M + Na]$^+$.

(1*RS*,2*SR*)-2-[(*E*)-6-(Furan-3-yl)-3-methylhex-3-enyl]-1,3,3-trimethylcyclohexanol (19): A solution of epoxide **18** (0.32 g, 1.06 mmol) in dry THF (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.15 g, 3.95 mmol) in THF (10 mL) at reflux temperatures. As soon as the starting epoxide was no longer detectable by TLC analysis (3 h), the reaction was cooled (0 °C), diluted with diethyl ether (50 mL), and quenched by dropwise addition of aqueous NaOH (40%, 5 mL). The resulting heterogeneous mixture was filtered through a Celite pad and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/diethyl ether (95:5–9:1) to afford pure **19** (215 mg, 67% yield) as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6): δ = 7.13 (t, *J* = 1.5 Hz, 1 H), 7.08 (s, 1 H), 6.11 (s, 1 H), 5.26 (t, *J* = 7.0 Hz, 1 H), 2.39–2.31 (m, 2 H), 2.20 (q, *J* = 7.3 Hz, 2 H), 2.11–1.95 (m, 2 H), 1.83 (qt, *J* = 13.7, 3.3 Hz, 1 H), 1.67–1.56 (m, 1 H), 1.58 (s, 3 H), 1.50–0.95 (m, 6 H), 1.09 (s, 3 H), 1.00 (s, 3 H), 0.88 (s, 3 H), 0.70 (dd, *J* = 4.9, 2.7 Hz, 1 H), 0.50 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 142.9 (CH), 139.2 (CH), 136.7 (C), 125.2 (C), 124.0 (CH), 111.3 (CH), 72.5 (C), 54.1 (CH), 44.0 (CH_2), 42.4 (CH_2), 41.7 (CH_2), 35.0 (C), 32.3 (Me), 31.1 (Me), 28.9 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 21.8 (Me), 18.8 (CH_2), 16.3 (Me) ppm. MS (ESI): *m*/*z* = 327.6 [M + Na]$^+$.

(4*R*,6*S*)-4-Acetoxy-γ-ionone (22), (4*S*,6*R*)-4-Hydroxy-γ-ionone (20), and (4*R*,6*S*)-4-Acetoxy-γ-dihydroionone (23): Trifluoroacetic anhydride (54 g, 257 mmol) was added dropwise at 0 °C to a stirred suspension of hydrogen peroxide-urea adduct (25 g, 266 mmol) in CH_3CN (70 mL). As soon as the solid dissolved, the resulting solution (the temperature of which was kept constant at 0 °C) was added over 10 min, to a cooled (–78 °C) and mechanically stirred mixture of K_2CO_3 (100 g, 724 mmol), α-ionone (38 g, 198 mmol),

and CH_2Cl_2 (300 mL). The reaction was allowed to warm to –50 °C and was stirred at this temperature for a further hour. The reaction was then added to a stirred solution of $Na_2S_2O_5$ (30 g, 158 mmol) in iced water (400 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/ethyl acetate (9:1–7:3) as eluent to afford pure epoxy-α-ionone **12** (37.2 g, 90% yield) as a colorless oil; *cis*/*trans* ratio, 94:6 by ^{1}H NMR spectroscopic analysis.

According to the procedure described in ref.[10] a sample of *cis*-epoxy-α-ionone **12** (35 g, 168 mmol) obtained as above was transformed into *cis*-4-hydroxy-γ-ionone (**20**; 27.7 g, 133 mmol, 79% yield, 96% chemical purity by GC, *cis*/*trans* ratio, 93:7 by NMR spectroscopic analysis). The following lipase PS-mediated acetylation reaction afforded (4*R*,6*S*)-4-acetoxy-γ-ionone [(+)-**22**; 12.4 g, 49.6 mmol, 37% yield, 98% chemical purity and more than 98% *de* by GC analysis, *ee* 95% by chiral GC analysis] with a $[\alpha]_D^{20}$ = +21.5 (*c* = 1.9, $CHCl_3$), and (4*S*,6*R*)-4-hydroxy-γ-ionone [(+)-**20**; 14.9 g, 71.6 mmol, 54% yield, 70% *ee*, *cis*/*trans* ratio, 88:12 by NMR analysis] with a $[\alpha]_D^{20}$ = +5.2 (*c* = 1.9, $CHCl_3$).

According to the procedure described in ref.[12] the hydrogenation of (4*R*,6*S*)-4-acetoxy-γ-ionone [(+)-**22**; 12 g, 48 mmol] in THF/methanol (5:1, 120 mL) with activated Raney nickel as catalyst gave (4*R*,6*S*)-4-acetoxy-γ-dihydroionone [(–)-**23**; 10.8 g, 89% yield, 96% chemical purity by GC] with a $[\alpha]_D^{20}$ = –22.8 (*c* = 1.8, $CHCl_3$).

(3*S*,4*R*,8*S*)-7,7-Dimethyl-8-(3-oxobutyl)-1-oxaspiro[2.5]octan-4-yl Acetate (24): *m*CPBA (5.8 g, 77% w/w, 25.9 mmol) was added portionwise to a cooled (0 °C) and stirred solution of ketone (–)-**23** (5.5 g, 21.8 mmol) in CH_2Cl_2 (40 mL). After the addition was complete, the reaction was left to warm to room temperature and stirring was continued for 12 h. The precipitated *m*-chlorobenzoic acid was filtered off and the organic phase was diluted with CH_2Cl_2 (80 mL) and was washed in turn with aqueous $Na_2S_2O_5$ (5%, 50 mL), saturated aqueous $NaHCO_3$ (100 mL), and with brine. The obtained organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/ethyl acetate (9:1–7:3) as eluent to afford pure (–)-**24** (4.15 g, 71% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.89 (dd, *J* = 10.6, 4.8 Hz, 1 H), 2.84 (d, *J* = 4.6 Hz, 1 H), 2.67 (d, *J* = 4.6 Hz, 1 H), 2.65 (ddd, *J* = 17.8, 9.5, 5.3 Hz, 1 H), 2.41 (ddd, *J* = 17.8, 9.5, 6.1, Hz, 1 H), 2.09 (s, 3 H), 2.01 (s, 3 H), 1.96 (dq, *J* = 12.9, 4.4 Hz, 1 H), 1.72–1.51 (m, 3 H), 1.50–1.39 (m, 2 H), 1.31–1.18 (m, 1 H), 1.03 (s, 3 H), 0.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.6, 169.9, 71.5, 59.6, 48.1, 45.7, 44.4, 37.7, 36.2, 29.9, 29.8, 27.3, 21.3, 20.9, 17.9 ppm. GC–MS (EI): *m*/*z* (%) = 268 $[M]^+$ (<1), 250 (1), 226 (2), 208 (29), 190 (26), 175 (26), 165 (100), 151 (71), 138 (79), 123 (60), 109 (81), 95 (64), 81 (58), 67 (35), 55 (40). $[\alpha]_D^{20}$ = –9.8 (*c* = 2.2, $CHCl_3$).

(3*S*,4*R*,8*S*)-8-(3,3-Dimethoxybutyl)-7,7-dimethyl-1-oxaspiro[2.5]-octan-4-yl Acetate (25): A solution of (–)-**24** (2.4 g, 8.94 mmol) in methanol (20 mL) and trimethyl orthoformate (10 mL) was treated with pyridinium *p*-toluenesulfonate (0.2 g, 0.8 mmol) and stirred at room temperature for 6 h. The reaction was then quenched by addition of Et_3N (2 mL), diluted with ethyl acetate (100 mL), and washed with saturated aqueous $NaHCO_3$ and with brine. The obtained organic solution was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by filtration through a short silica gel column by eluting with hexane/ethyl acetate (7:3) as eluent to afford pure **25** (2.62 g, 93% yield) as a colorless oil. The latter compound is very unstable in acid environments, so TLC analysis and optical rotation measurements in chloroform gave unreliable results. Therefore, a small amount (about 0.1% w/w) of Cy_2NMe was added to compound **25** to ensure chemical stability and to perform NMR spectroscopic analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (dd, *J* = 9.8, 4.6 Hz, 1 H), 3.14 (s, 6 H), 2.85 (d, *J* = 4.7 Hz, 1 H), 2.63 (d, *J* = 4.7 Hz, 1 H), 2.03–1.93 (m, 1 H), 2.01 (s, 3 H), 1.80–1.70 (m, 1 H), 1.70–1.62 (m, 1 H), 1.62–0.98 (m, 6 H), 1.23 (s, 3 H), 1.03 (s, 3 H), 0.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 101.5, 71.7, 58.9, 49.1, 47.9, 47.9, 46.0, 37.7, 36.8, 36.0, 29.6, 27.1, 22.0, 20.9, 20.7, 18.5 ppm. MS (ESI): *m*/*z* (%) = 337.1 $[M + Na]^+$.

(1*R*,2*R*,6*S*)-6-(3,3-Dimethoxybutyl)-1,5,5-trimethylcyclohexane-1,2-diol (26): Epoxide **25** (7.3 g, 23.2 mmol) in dry diethyl ether (30 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.3 g, 34.2 mmol) in diethyl ether (50 mL) at reflux temperatures. As soon as the starting epoxide was transformed into diol **26** (TLC analysis, 1 h), the reaction was cooled (0 °C), diluted with ether (100 mL), and quenched by dropwise addition of aqueous NaOH (40%, 30 mL), before being stirred vigorously for 1 h. The resulting heterogeneous mixture was filtered through a Celite pad and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue of almost pure diol **26** (5.95 g, 93% yield), which was very unstable in acid environments, could not be purified by chromatography. Therefore compound **26** was immediately used without further purification in the next step.

(4a*S*,8*R*,8a*R*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromen-8-yl Methanesulfonate (27): A solution of crude diol **26** (0.14 g, 0.51 mmol) in pyridine (5 mL) was treated with mesyl chloride (0.2 mL, 2.58 mmol) and DBU (0.4 mL, 2.68 mmol), and stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/ethyl acetate (9:1–8:2) to afford pure (–)-**27** (90 mg, 61% yield) as colorless crystals, m.p. 65–67 °C. $[\alpha]_D^{20}$ = –1.4 (*c* = 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51–4.47 (m, 1 H), 4.51 (dd, *J* = 12.2, 4.9 Hz, 1 H), 3.11 (s, 3 H), 2.05–1.76 (m, 4 H), 1.66 (br. s, 3 H), 1.57–1.39 (m, 3 H), 1.22 (s, 3 H), 0.92 (s, 3 H), 0.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 95.1, 88.5, 77.8, 47.6, 39.2, 38.1, 32.8, 31.4, 27.1, 20.5, 19.9, 18.9, 13.7 ppm. GC–MS (EI): *m*/*z* (%) = 288 $[M]^+$ (45), 192 (44), 177 (75), 159 (21), 149 (88), 136 (96), 121 (79), 107 (100), 93 (95), 79 (52), 69 (29), 55 (30).

(1*R*,2*S*,6*S*)-2-(3,3-Dimethoxybutyl)-1,3,3-trimethyl-7-oxabicyclo-[4.1.0]heptane (28): A solution of diol **26** (4.2 g, 15.3 mmol) in dry THF (25 mL) at 0 °C under nitrogen was treated with LDA (14.9 mL of a 1.05 M solution in THF) followed by dropwise addition of mesyl chloride (1.9 g, 16.6 mmol, in 4 mL of dry THF). The mixture was stirred for half an hour at 0 °C, then LDA (14.9 mL of a 1.05 M solution in THF) was added dropwise, the reaction was left to warm to room temperature. The reaction mixture was stirred for a further 12 h, before being quenched by dilution with diethyl ether (250 mL) and water (100 mL). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/diethyl ether (95:5–9:1) to afford pure (–)-**28** (2.55 g, 65% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (s, 3 H), 3.17 (s, 3 H), 2.89 (br. s, 1 H), 2.01–1.78 (m, 3 H), 1.72–1.59 (m, 1 H), 1.56–1.43 (m, 1 H), 1.42–1.21 (m, 3 H), 1.35 (s, 3 H), 1.29 (s, 3 H), 1.11–1.00 (m, 1 H), 0.90 (s, 3 H), 0.75 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.7, 61.0,

58.8, 50.4, 48.0, 48.0, 38.9, 33.9, 32.0, 29.5, 22.6, 22.1, 21.7, 20.9, 19.9 ppm. MS (ESI): m/z = 279.4 $[M + Na]^+$. $[\alpha]_D^{20}$ = –26.5 (c = 2, $CHCl_3$).

(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromene (3): $LiEt_3BH$ (2 mL of a 1 M solution in THF) was added dropwise under nitrogen to a stirred solution of epoxide (–)-**28** (0.2 g, 0.78 mmol) in dry THF (3 mL) at 0 °C. After the addition was complete, the reaction was left to warm to room temperature and was stirred until the starting epoxide was not longer detectable by TLC analysis (6 h). The mixture was then diluted with diethyl ether, quenched with HCl (3% aq.), and stirred for 15 min. The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/diethyl ether (95:5–8:2) followed by bulb-to-bulb distillation to afford pure (–)-**3** (0.115 g, 76% yield) as a colorless oil. ^1H NMR (400 MHz, C_6D_6): δ = 4.45 (br. d, J = 5.3 Hz, 1 H), 1.89–1.79 (m, 2 H), 1.74 (m, 3 H), 1.74–1.66 (m, 1 H), 1.60–1.43 (m, 2 H), 1.42–1.26 (m, 2 H), 1.23 (dm, J = 13.2 Hz, 1 H), 1.17 (s, 3 H), 1.14–1.02 (m, 1 H), 0.78 (s, 3 H), 0.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 148.6, 94.7, 76.3, 48.7, 42.0, 40.5, 33.3, 32.4, 20.9, 20.6, 20.1, 19.6, 19.4 ppm. GC–MS (EI): m/z (%) = 194 $[M]^+$ (30), 179 (11), 161 (19), 151 (7), 136 (13), 123 (27), 109 (100), 95 (22), 81 (24), 71 (21), 55 (16). $[\alpha]_D^{20}$ = –20.8 (c = 1.5, $CHCl_3$).

4-[(1*R*,2*S*,6*S*)-1,3,3-Trimethyl-7-oxabicyclo[4.1.0]heptan-2-yl]butan-2-one (11): A solution of ketal (–)-**28** (2.1 g, 8.2 mmol) in THF/H_2O (7:3, 20 mL) was treated with pyridinium *p*-toluenesulfonate (60 mg, 0.24 mmol) and stirred at room temperature until the starting ketal was not longer detectable by TLC analysis (4 h). The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL) and the resulting mixture was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/ethyl acetate (9:1–7:3) to afford pure (–)-**11** (1.64 g, 95% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.88 (s, 1 H), 2.70 (ddd, J = 17.7, 9.9, 4.9 Hz, 1 H), 2.53 (ddd, J = 17.7, 9.3, 6.6 Hz, 1 H), 2.15 (s, 3 H), 1.95 (dd, J = 15.4, 6.0 Hz, 1 H), 1.90–1.75 (m, 2 H), 1.60–1.46 (m, 1 H), 1.37–1.22 (m, 2 H), 1.31 (s, 3 H), 1.10–1.02 (m, 1 H), 0.90 (s, 3 H), 0.76 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9 (C), 61.0 (CH), 58.5 (C), 49.6 (CH), 45.6 (CH_2), 33.9 (CH_2), 31.9 (C), 30.0 (Me), 29.4 (Me), 22.5 (Me), 21.5 (CH_2), 21.1 (CH_2), 19.7 (Me) ppm. GC–MS (EI): m/z (%) = 210 $[M]^+$ (4), 195 (93), 177 (16), 167 (60), 152 (77), 137 (57), 121 (50), 109 (100), 95 (78), 81 (49), 69 (58), 55 (61). $[\alpha]_D^{20}$ = –34.8 (c = 1.7, $CHCl_3$).

Ethyl (*E*)-3-Methyl-5-[(1*R*,2*S*,6*S*)-1,3,3-trimethyl-7-oxabicyclo-[4.1.0]heptan-2-yl]pent-2-enoate (29): According to the procedure outlined for the synthesis of compound **15**, ketone (–)-**11** (1.79 g, 8.51 mmol) gave ester **29** (2.18 g, 91% yield) as a colorless oil as a *E*/*Z* mixture of isomers (*E*/*Z* ratio, 5:1, by NMR spectroscopic analysis). ***E* Isomer:** ^1H NMR (400 MHz, $CDCl_3$): δ = 5.70 (m, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 2.89 (br. s, 1 H), 2.42 (ddd, J = 14.2, 11.2, 4.3 Hz, 1 H), 2.21–2.10 (m, 1 H), 2.19 (d, J = 1.2 Hz, 3 H), 1.96 (ddt, J = 15.4, 5.9, 1.7 Hz, 1 H), 1.90–1.80 (m, 1 H), 1.65–1.56 (m, 1 H), 1.53–1.24 (m, 3 H), 1.35 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.07 (ddd, J = 13.4, 5.9, 1.7 Hz, 1 H), 0.88 (s, 3 H), 0.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 159.3, 115.8, 60.9, 59.5, 58.6, 49.6, 43.1, 33.9, 31.9, 29.4, 25.7, 22.6, 21.6, 19.8, 18.9, 14.3 ppm. MS (ESI): m/z = 303.5 $[M + Na]^+$.

(*E*)-3-Methyl-5-[(1*R*,2*S*,6*S*)-1,3,3-trimethyl-7-oxabicyclo[4.1.0]-heptan-2-yl]pent-2-enyl 3,5-Dinitrobenzoate (30): According to the procedure outlined for the synthesis of compound **16**, ester **29** (2.75 g, 9.82 mmol) was transformed into ester **30** as a 5:1 mixture of *E*/*Z* isomers. The latter material remained an oil even at low temperature (–20 °C) and by using either hexane or methanol as solvents. Through chromatographic separation by using *n*-hexane/diethyl ether (99:1–95:5) as eluent a sample of (–)-**30** was obtained as a colorless oil as a 92:8 *E*/*Z* mixture (2.1 g, 49% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.20 (t, J = 2.1 Hz, 1 H), 9.16 (d, J = 2.1 Hz, 2 H), 5.54 (t, J = 7.3 Hz, 1 H), 4.98 (d, J = 7.3 Hz, 2 H), 2.89 (s, 1 H), 2.42–2.29 (m, 1 H), 2.18–2.07 (m, 1 H), 1.95 (dd, J = 15.3, 5.8 Hz, 1 H), 1.91–1.78 (m, 1 H), 1.84 (s, 3 H), 1.65–1.20 (m, 4 H), 1.36 (s, 3 H), 1.07 (ddd, J = 13.5, 6.0, 1.8 Hz, 1 H), 0.88 (s, 3 H), 0.75 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 148.7, 144.2, 134.3, 129.4, 122.2, 117.6, 63.6, 60.9, 58.7, 49.4, 41.6, 34.0, 31.9, 29.5, 25.6, 22.7, 21.6, 19.9, 16.8 ppm. MS (ESI): m/z = 455.4 $[M + Na]^+$. $[\alpha]_D^{20}$ = –9.9 (c = 1.9, $CHCl_3$).

(1*R*,2*S*,6*S*)-2-[(*E*)-6-(Furan-3-yl)-3-methylhex-3-enyl]-1,3,3-trimethyl-7-oxabicyclo[4.1.0]heptane (8): According to the procedure outlined for the synthesis of compound **18**, ester (–)-**30** (0.29 g, 0.67 mmol) gave epoxide (–)-**8** (0.18 g, 89% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, J = 1.5 Hz, 1 H), 7.21 (m, 1 H), 6.27 (s, 1 H), 5.21 (t, J = 7.0 Hz, 1 H), 2.88 (s, 1 H), 2.49–2.43 (m, 2 H), 2.31–2.18 (m, 3 H), 2.12–1.90 (m, 2 H), 1.89–1.78 (m, 1 H), 1.61 (s, 3 H), 1.55–1.25 (m, 4 H), 1.35 (s, 3 H), 1.05 (ddd, J = 13.4, 6.0, 1.8 Hz, 1 H), 0.85 (s, 3 H), 0.73 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 138.8, 135.7, 124.9, 124.3, 111.1, 60.9, 58.9, 49.3, 41.9, 34.0, 31.8, 29.5, 28.5, 26.1, 25.0, 22.7, 21.7, 19.9, 16.1 ppm. MS (ESI): m/z = 303.5 $[M + H]^+$, 325.5 $[M + Na]^+$. $[\alpha]_D^{20}$ = –19.9 (c = 1.8, $CHCl_3$).

(1*S*,2*S*)-2-[(*E*)-6-(Furan-3-yl)-3-methylhex-3-enyl]-1,3,3-trimethylcyclohexanol (1): $LiEt_3BH$ (2 mL of a 1 M solution in THF) was added dropwise under nitrogen to a stirred solution of epoxide (–)-**8** (0.18 g, 0.60 mmol) in dry THF (3 mL) at 0 °C. After the addition was complete, the reaction was left to warm to room temperature and the reaction mixture was stirred until the starting epoxide was not longer detectable by TLC analysis (6 h). The reaction was then quenched with aqueous NaOH (5%, 20 mL) and extracted with diethyl ether (2 × 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography by eluting with hexane/diethyl ether (95:5–9:1) to afford pure (+)-**1** (165 mg, 91% yield) as a colorless oil. ^1H NMR (400 MHz, C_6D_6): δ = 7.13 (t, J = 1.5 Hz, 1 H), 7.09 (s, 1 H), 6.11 (s, 1 H), 5.29 (t, J = 7.0 Hz, 1 H), 2.45–2.09 (m, 6 H), 1.73–1.52 (m, 2 H), 1.62 (s, 3 H), 1.45–1.03 (m, 7 H), 1.07 (s, 3 H), 0.91 (s, 3 H), 0.74 (s, 3 H), 0.66 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 142.8 (CH), 139.2 (CH), 137.1 (C), 125.2 (C), 124.2 (CH), 111.3 (CH), 73.6 (C), 56.8 (CH), 44.0 (CH_2), 43.2 (CH_2), 41.9 (CH_2), 35.6 (C), 33.0 (Me), 28.9 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 23.6 (Me), 21.6 (Me), 20.9 (CH_2), 16.2 (Me) ppm. MS (ESI): m/z = 327.6 $[M + Na]^+$. $[\alpha]_D^{20}$ = +4.0 (c = 1.8, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR spectra of the key intermediates and final products.

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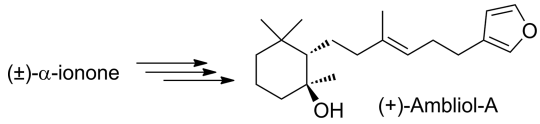
Natural Products



The enantioselective synthesis of diterpene (+)-ambliol-A and diastereoselective synthesis of its non-natural epimer are accomplished from racemic α-ionone. The key steps are diastereoselective epoxidation, lipase-mediated resolution, and copper-catalyzed cross coupling. The chemical structure of natural ambliol-A is confirmed and its absolute configuration corrected and now assigned as (1*R*,2*R*).

Keywords: Natural products / Total synthesis / Biocatalysis / Terpenoids / Cross-coupling

