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Construction of a Diverse Set of Terpenoid Decalin Subunits from a Common Enantiomerically Pure Scaffold Obtained by a Biomimetic Cationic Cyclization

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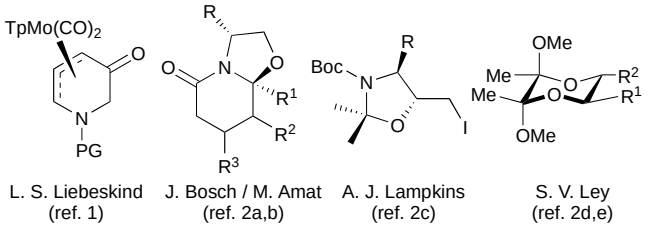
An unprecedented biomimetic cationic cyclization reaction of an alkyne-containing geraniol-derived epoxide is used for the stereoselective synthesis of a novel enantiomerically pure scaffold that is easily transformed into a set of structurally diverse decalin derivatives with potential application in the synthesis of targeted natural products and/or natural-product-inspired new molecules.

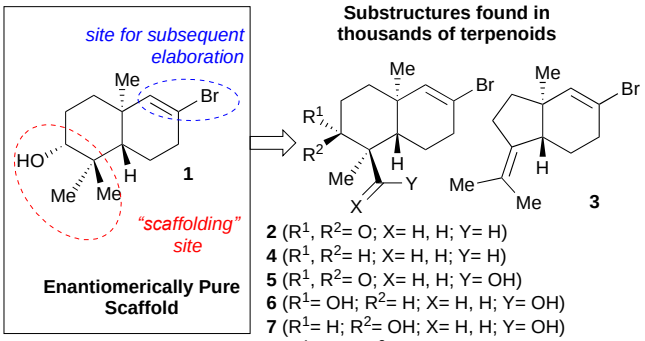
Enantiomeric scaffolding is a concept introduced by L. S. Liebeskind to describe an alternative strategic and structured approach to the enantiocontrolled construction of different complex molecules from a simple precursor.[1] Thus, an *enantiomeric scaffold* could be defined as a conceptually simple core molecule of high enantiopurity that bears some tactically versatile functionalities that enable its elaboration in ways that allow access to diverse families of important molecules. To find application as a platform for complex molecule construction, a scaffold molecule should comprise some key features. First, it should contain a chiral structure overlapping many common motifs in target molecules. Second, it should be easily available in a scalable way in a minimum number of synthetic steps. And finally, it should contain some additional functionality that permits subsequent elaborations. Different scaffolding approaches have been developed in recent years by several research groups and some typical examples are shown in Figure 1a.[1,2] Although these platforms have been used for the construction of different natural products (and natural-product-like molecules), the enantiomeric scaffolding concept has not been fully developed in the context of terpene synthesis.[3] Under these circumstances, we identify the decalin derivative **1** as a broadly-applicable template for the synthesis of diverse terpenes and derivatives (Figure 1b). More precisely, we thought that the left-hand ring of this enantiomerically pure scaffold could be easily transformed into a variety of different skeletons **2**-**10**. It should be noted that thousands of terpenoid natural products contain in their structure some of the structural motifs of the left-hand ring of products **2**-**10**. In the other hand, the alkenyl bromide moiety of the right-hand ring of **1** seemed a perfect functionality for further elaboration and construction of target molecules.[4]

a) Some examples of enantiomerically pure scaffolds



L. S. Liebeskind (ref. 1) | J. Bosch / M. Amat (ref. 2a,b) | A. J. Lampkins (ref. 2c) | S. V. Ley (ref. 2d,e)

b) Our proposed enantiomerically pure scaffold for terpenoid synthesis



2 (R^1, R^2= O; X= H, H; Y= H)
4 (R^1, R^2= H; X= H, H; Y= H)
5 (R^1, R^2= O; X= H, H; Y= OH)
6 (R^1= OH; R^2= H; X= H, H; Y= OH)
7 (R^1= H; R^2= OH; X= H, H; Y= OH)
8 (R^1= OH; R^2= H; X= O; Y= OH)
9 (R^1, R^2= H; X= H, H; Y= OH)
10 (R^1, R^2= H; X= O; Y= OH)

Figure 1 Some examples of enantiomerically pure scaffolds and our proposal.

In addition, we thought that both enantiomers of scaffold **1** could be easily available at large scale. All these features make decalin **1** an ideal enantiomerically pure platform for the synthesis of a great variety of terpenes and related molecules. The synthesis of this enantiomerically pure scaffold along with initial studies on its transformation into key structural motifs as a demonstration of its synthetic utility are herein presented.

Our investigation began with the design of an efficient synthetic sequence that allow the preparation of decalin **1** in an enantioselective way. As shown in Scheme 1, this compound could be easily prepared from commercially available geranyl acetate (**11**).[5] Selective asymmetric dihydroxylation of the gem-

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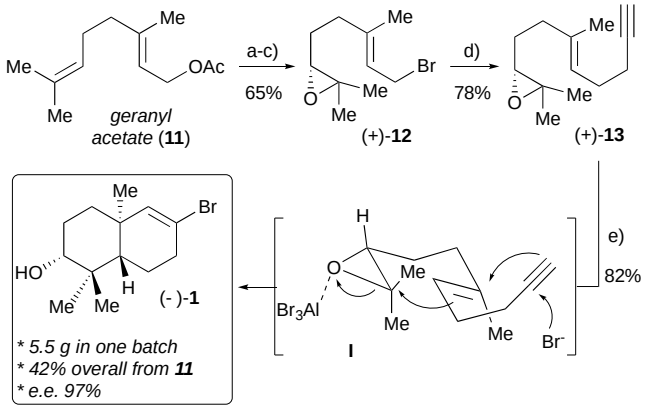
† Electronic Supplementary Information (ESI) available.

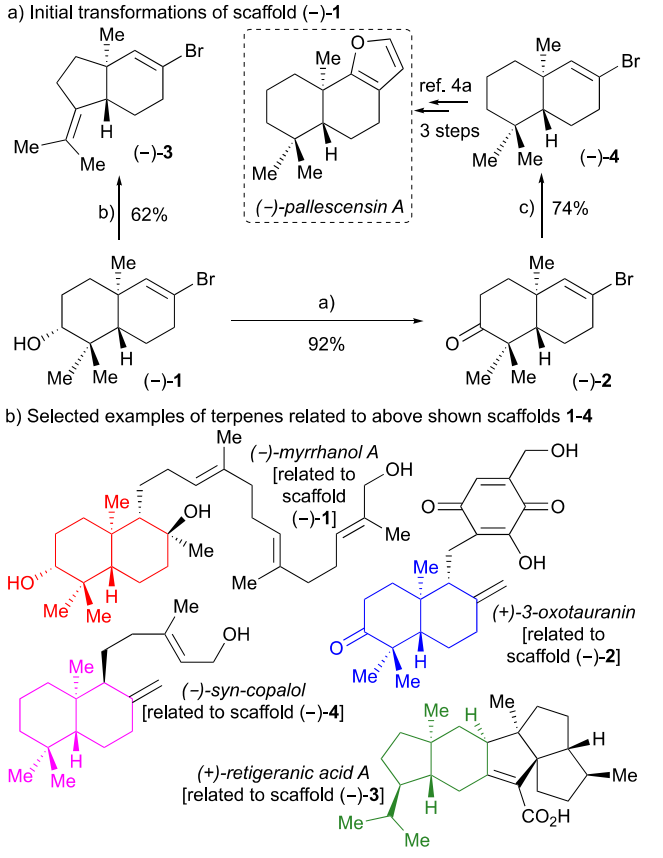
dimethyl substituted alkene of this molecule using AD-mix-α followed by selective mesylation of the secondary alcohol and subsequent intramolecular nucleophilic substitution led to the corresponding epoxide. The so-formed allylic alcohol was efficiently transformed into the bromide (+)-**12** that was coupled with a propargyl-lithium derivative to generate, after appropriate work-up, the enyne containing epoxide (+)-**13**. All this sequence could be performed at multigram scale as demonstrated by the synthesis of 4.8 grams of (+)-**13** in one batch (51% overall yield from geranyl acetate).



Scheme 1 Reagents and conditions: a) ADmix-α, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 ºC, 20 h; b) MsCl, pyridine, CH_2Cl_2, 0 ºC, 3 h, then K_2CO_3, MeOH, 0 ºC to RT, 12 h; c) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 30 min, then LiBr, THF, 0 ºC, 2,5 h; d) $TMSCCCH_3$, *n*BuLi, THF, –60 ºC, 1 h; then (+)-**12**, 0 ºC, 2.5 h; then K_2CO_3, MeOH, RT, 16 h; e) $AlBr_3$ (0.33 equiv), CH_2Br_2 (0.1M), –40 ºC, 1 h.

Taking advantage of our recent studies on cationic cyclization reactions,[4,6] we considered that a biomimetic cationic cyclization reaction of (+)-**13** initiated by the ring opening of the epoxide and performed in dibromomethane (as solvent and source of bromide) could render our desired enantiomerically pure scaffold **1**. After some experimentation, we found that aluminium bromide was an appropriate promoter for this process (see the ESI for experiments performed to demonstrate that the bromine comes from the solvent). Thus, when epoxide (+)-**13** was reacted with aluminium bromide (0.33 equiv) in dibromomethane (0.1 M) at –40 ºC, decalin (–)-**1** could be isolated in high overall yield (42% from geranyl acetate) and excellent enantiomeric excess (97%). The arrangement shown in **I** could explain the formation of the observed isomer (–)-**1.** Remarkably, 5.5 grams of decalin (–)-**1** could be prepared in one batch without problems. It is important to note that the enantiomer (+)-**1** could be easily obtained by using AD-mix-β in the first step of the sequence. The overall yield and enantiopurity was similar to that observed for (–)-**1.**

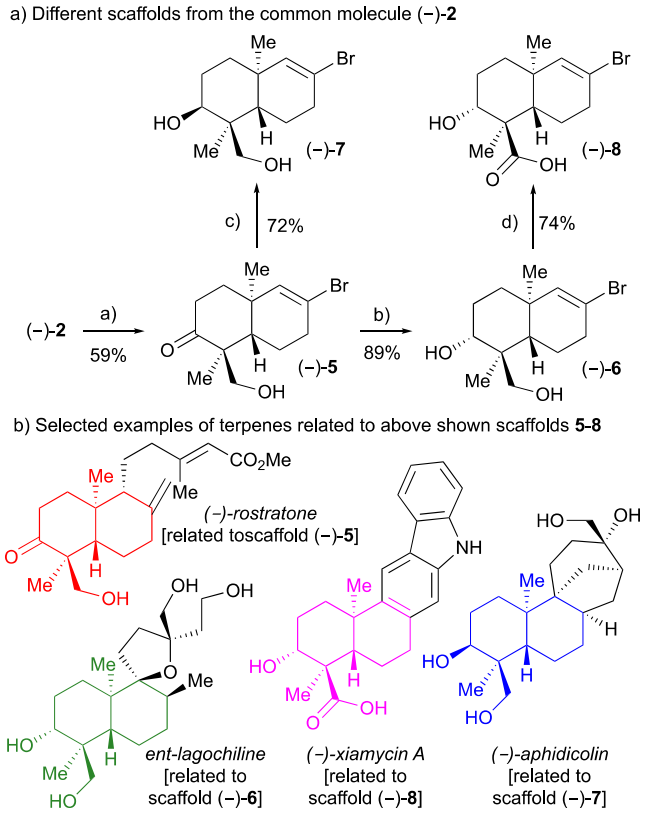
At this point, the cyclization of enyne-containing epoxide (+)-**13** to decalin (–)-**1** deserves some comment. Thus, it should be noted that in the context of biomimetic cyclizations,[7] reactions with starting materials containing an epoxide as initiating group in combination with different terminating groups are well documented.[8] Also, reactions with starting materials combining an alkyne as terminating group and different initiating groups have been widely reported.[9] But surprisingly, biomimetic cyclization reactions of substrates such as (+)-**13** with the particular combination of an epoxide as initiating group and an alkyne as terminating group have been scarcely reported and they are limited to examples where the alkyne acts as a masked ketone.[10] It seems that, despite its apparent potential, this gap in the context of biomimetic cyclization reactions have passed somewhat unnoticed by the synthetic community because no progresses have been reported since those early works published long time ago. Thus, we are herein reporting the first example of a biomimetic cationic cyclization reaction of an epoxide-containing enyne derivative to get a functionalized bicyclic alkenyl bromide.[11] It should be noted that the use of an epoxide as initiating group is particularly interesting because it allows the synthesis of enantiomerically pure cyclic compounds. This fact supposes a tremendous advantage over our previously developed biomimetic cyclization reactions with alkenes as initiating groups where only racemic products could be obtained.[4,6] The use of the alkyne as terminating group in this new biomimetic cyclization is also highly beneficial because it allows getting a product with a new functionality, an alkenyl bromide, that may be easily elaborated.[12] Other traditional biomimetic cyclization reactions with epoxides as initiating groups but with conventional terminating groups, such as alkenes or arenes, lead to final products synthetically less versatile than the alkenyl bromide. Hence, the new biomimetic cyclization reaction exemplified in the transformation of epoxide-containing enyne (+)-**13** into decalin (–)-**1** seems to be a powerful synthetic tool.



Scheme 2 Reagents and conditions: a) PCC, CH_2Cl_2, RT, 2 h; b) PCl_5, toluene, 25 ºC, 1h; c) (i) $TsNHNH_2$, MeOH, RT, 18 h; (ii) catecholborane, CH_2Cl_2, RT, 3 h; (iii) NaOAc, MeOH, 60 ºC, 16 h.

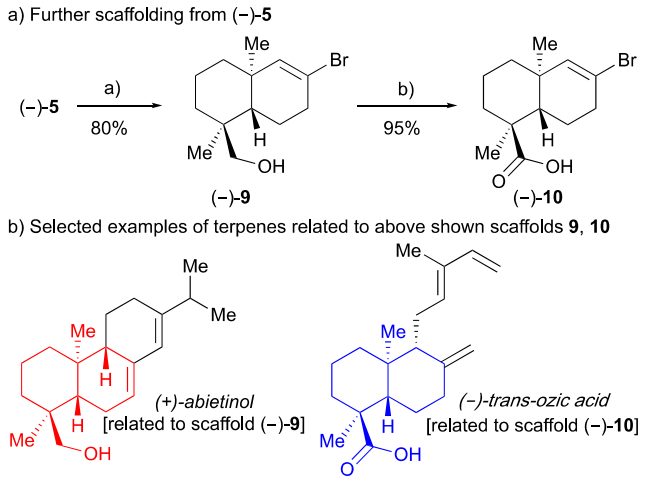
With a substantial quantity of enantiomerically pure scaffold (–)-**1** in hand, we turned our attention to demonstrate its utility as precursor of a diverse set of frameworks with ubiquitous presence in terpenoids and related molecules. Some simple initial transformations of decalin (–)-**1** to get interesting new chemical entities are shown in Scheme 2a. Thus, oxidation of the alcohol under conventional conditions delivered the ketone (–)-**2**. Otherwise, treatment of (–)-**1** with phosphorus pentachloride (PCl_5) induced a ring contraction process to get the new enantiomerically pure bicyclic product (–)-**3**. Furthermore, the deoxygenated decalin derivative (–)-**4** could be efficiently obtained by transformation of ketone (–)-**3** into the corresponding tosylhydrazone derivative and subsequent reduction with catecholborane. Remarkably, all these synthetic transformations were chemoselective, and thus, the alkenyl bromide functionality remained always intact. This is an important point because this is the functionality that allows further elaboration and construction of target molecules.[12] In this sense, it should be noted that the synthesis of compound (–)-**4** supposes a formal asymmetric synthesis of the natural product (–)-pallescensin A and demonstrates that the alkenyl bromide moiety can be easily transformed.[4a] Not only (–)-pallescensin A but other natural products such as (+)-retigeranic acid, (–)-myrrhanol A, (+)-3-oxotauranin, and (–)-*syn*-copalol could be available from products (–)-**1**, (–)-**2**, (–)-**3** and (–)-**4** (Scheme 2b).

The next challenge was the introduction of additional functionality around the decalin core (Scheme 3a). Selective hydroxylation of just one of the methyl substituents was easily achieved from ketone (–)-**2** through a sequence involving the initial formation of the corresponding oxime derivative. Subsequent palladium-catalysed selective C-H acetoxylation followed by hydrolysis gave rise to the new enantiomerically pure hydroxy ketone (–)-**5** (Scheme 3a). Interestingly, the bicyclic core of the natural product (–)-rostratone possesses an arrangement similar to that of hydroxy ketone (–)-**5** (Scheme 3b). Additionally, this ketone (–)-**5** could be selectively reduced to give the new diols (–)-**6** or (–)-**7**. More precisely, conventional reduction of (–)-**5** with sodium borohydride exclusively led to (–)-**6** (the new hydroxyl-group in an equatorial position). However, the diastereoisomeric diol (–)-**7** was selectively obtained when ketone (–)-**5** was reacted with L-selectride (the new hydroxyl-group in an axial position). It should be noted that both diastereoisomeric structural arrangements can be found in natural products. For example, while (–)-aphidicolin has a structure similar to (–)-**7**, the core assembly of lagochiline resembles that of (–)-**6** (Scheme 3b). The structure of many other terpenes is characterized by a decalin skeleton decorated with a carboxylic acid. An example of this type of natural products is xiamicyn A (Scheme 3b). This core was easily synthesized from (–)-**6** by reaction with TEMPO to get the corresponding aldehyde that was further oxidized to get the carboxylic acid derived scaffold (–)-**8** (Scheme 3a). Again, all these synthetic transformations did not affect the alkenyl bromide moiety and thus, this functionality could be used for the introduction of the additional decoration usually found around the decalin core of natural products.[12]



Scheme 3 Reagents and conditions: a) (i) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, H_2O, 85 ºC, 2 h; (ii) $Pd(OAc)_2$ (15 mol%), $PhI(OAc)_2$, AcOH, Ac_2O, 65 ºC, 6 h; (iii) K_2CO_3, MeOH, RT, 18 h; then $NaHSO_3$, MeOH, H_2O, 40 ºC, 36h; b) $NaBH_4$, MeOH, RT, 2 h; c) L-Selectride, THF, –30 ºC, 22 h; then H_2O_2, NaOH (aq, 4M), THF, RT, 1 h; d) TEMPO (15 mol%), $PhI(OAc)_2$, CH_2Cl_2, 5h, RT; then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, RT, 30 min.

In order to access additional scaffolds with potential application in the synthesis of terpenoids, the ketone functionality of compound (–)-**5** was fully reduced to get the alcohol (–)-**9** in high overall yield (80%; Scheme 4a). Interestingly, this scaffold is widespread in natural products being (+)-abietinol a representative example (Scheme 4b).



Scheme 4 Reagents and conditions: a) (i) $TsNHNH_2$, MeOH, RT, 16 h; (ii) catecholborane, CH_2Cl_2, RT, 3 h; (iii) NaOAc, MeOH, 60 ºC, 16 h; b) Jones' reagent, acetone, RT, 5 h.

Similar natural products containing a carboxylic acid instead of an alcohol are also prevalent in Nature (i.e. (–)-*trans*-ozic acid; Scheme 4b). This motif was easily obtained from alcohol (–)-**9** by a conventional oxidation reaction. Thus, carboxylic acid (–)-**10** was isolated in 95% yield as single enantiomer.

In summary, we have developed an unprecedented cationic cyclization reaction of a substrate containing an epoxide as initiating group and an alkyne as terminating functionality. This reaction closes a gap in the context of biomimetic cyclizations and we anticipate that it will find wide utility in the field of natural product total synthesis. Particularly, we have applied this new reaction to the synthesis of a decalin derivative that comprises all the features of an *enantiomeric scaffold*: its structure overlaps many common motifs in target molecules, both enantiomers are easily available in a scalable way in a minimum number of synthetic steps, and it contains additional functionalities for subsequent elaborations. More precisely, the enantiomerically pure decalin derivative here presented contains an alcohol in one of the rings and an alkenyl bromide in the other one. Interestingly, these two functionalities could be orthogonally transformed.

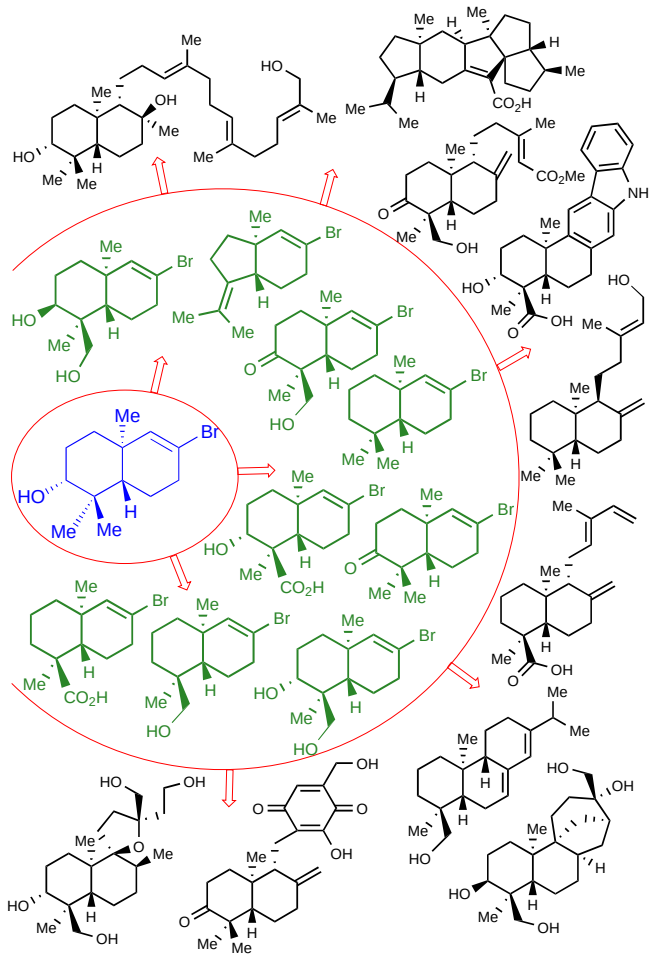


Figure 2 Summary of the enantiomeric scaffolding herein presented.

Thus, by one hand, the cycle containing the alcohol could be easily transformed into a variety of new enantiomerically pure scaffolds widespread found in terpenoids (Figure 2). In the other hand, the synthetic versatility of the alkenyl bromide functionality offers the opportunity for further elaboration of the decalin core as demonstrated with the formal synthesis of (–)-pallescensin A.[12] Noteworthy, this work constitutes one of the very few examples where the concept of enantiomeric scaffolding is disclosed in the context of terpene synthesis. However, not only target products, but also libraries of enantiomerically pure natural-product-inspired molecules for drug discovery could be easily available from the new molecules herein presented.

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