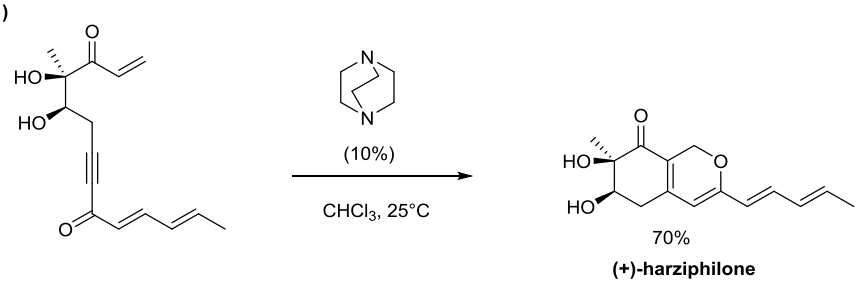
Exercise meeting (03/05/2017)

Submitted by Camilo M.

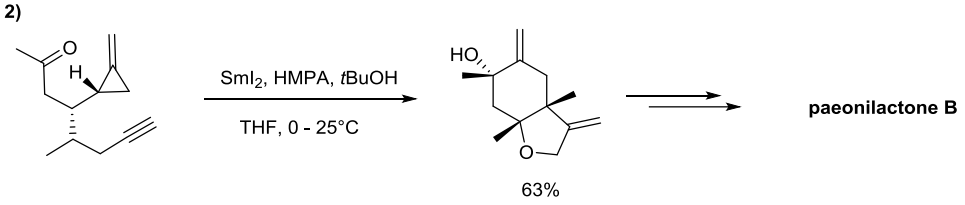
The following are examples of cascade reactions applied in total synthesis of natural products.

a) Propose a plausible mechanism for the reactions depicted.
b) Discuss the kinetic and/or thermodynamic effects accounting for these transformations to proceed smoothly.
c) Explain the observed stereoselectivity (if applicable)

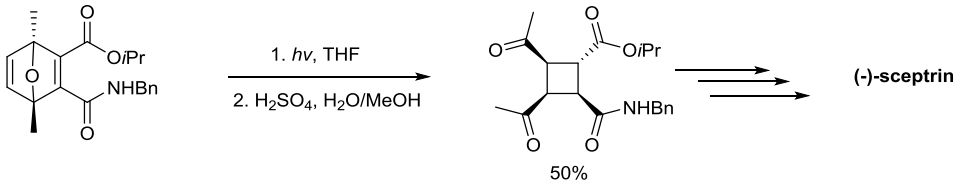
1)



2)



<u>Bonus (if there is enough time)</u>

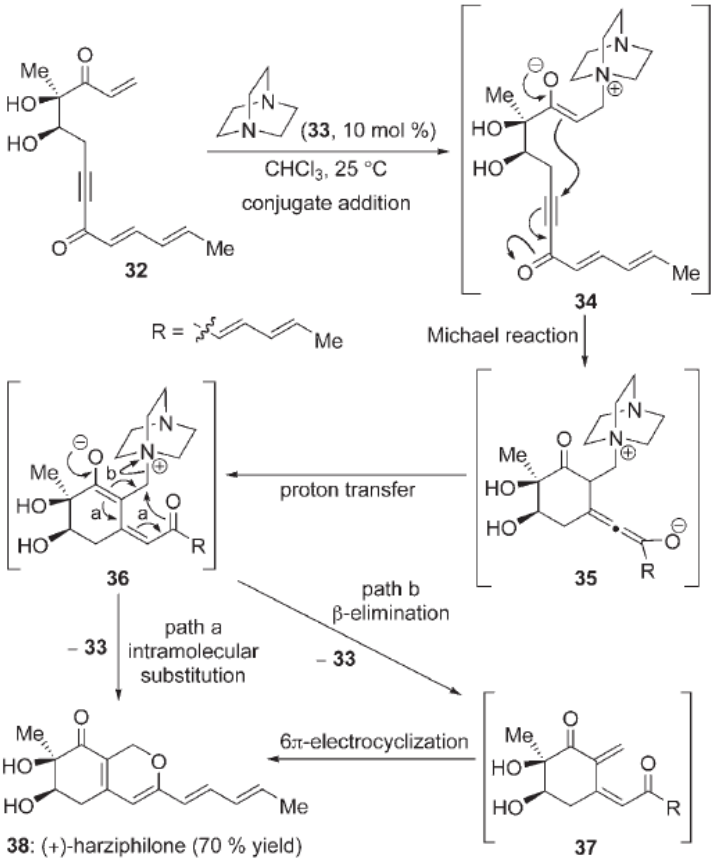


Exercise meeting (03/05/2017)

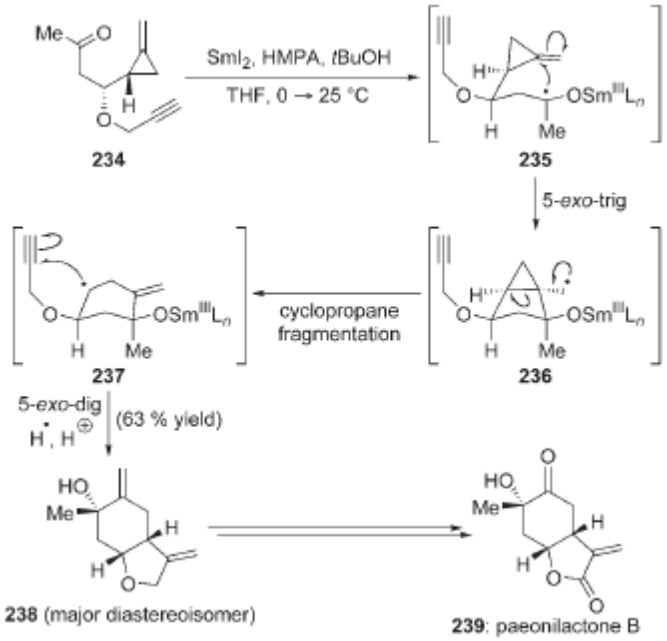
Submitted by Camilo M.

Solution

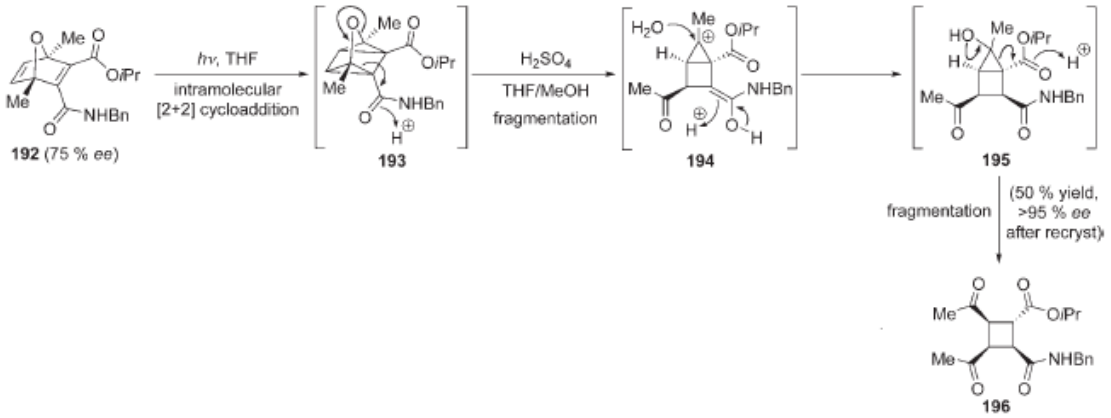
1)



2)


SmI2, HMPA, tBuOH
THF, 0 → 25 °C
234
235
5-exo-trig
236
cyclopropane fragmentation
237
5-exo-dig
(63 % yield)
238 (major diastereoisomer)
239: paeonilactone B

Bonus


192 (75 % ee)
hν, THF
intramolecular
[2+2] cycloaddition
193
H2SO4
THF/MeOH
fragmentation
194
195
fragmentation
(50 % yield,
>95 % ee
after recryst)
196

A nucleophile-catalyzed cycloisomerization permits a concise synthesis of (+)-harziphilone

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Edited by Kyriacos C. Nicolaou, The Scripps Research Institute, La Jolla, CA, and approved May 6, 2004 (received for review April 9, 2004)

Substantial structural transformations of much use in complex chemical synthesis can be achieved by channeling the reactivity of highly unsaturated molecules. This report describes the direct conversion of an acyclic polyunsaturated diketone to the HIV-1 Rev/Rev-responsive element inhibitor harziphilone under mild reaction conditions.

nucleophilic catalysis | Baylis–Hillman reaction | conjugate additions | electrocyclizations | domino reactions

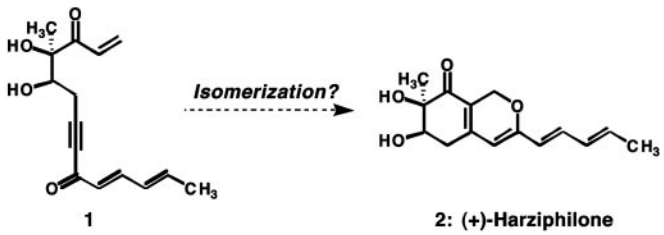
The reactivity of activated polyenes is the basis for some of the most impressive structural transformations in nature and chemical synthesis. The biosyntheses of the complex structures of the polycyclic triterpenes from squalene and 2,3-oxidosqualene may be viewed as paragons for processes that build polycyclic molecular complexity directly from reactive polyenes (1–3). In connection with our efforts to channel the reactivity of activated polyunsaturated molecules, we sought mild reaction conditions under which compound **1** could be isomerized to the bicyclic structure of harziphilone (**2**), a naturally occurring inhibitor of the binding interaction between the HIV-1 Rev protein and the Rev-responsive element (RRE) of viral mRNA (4) (Scheme 1). This report describes an enantioselective synthesis of (+)-harziphilone based on the general idea expressed in Scheme 1.

The structure of (+)-harziphilone (**2**) comprises fifteen carbon atoms, two six-membered ring systems, one carbocyclic and the other heterocyclic, a keto group, two contiguous hydroxyl-bearing stereocenters, and a pentadienyl side chain. All of the polar groupings of harziphilone are confined to the six-membered carbocycle, whereas the hydrophobic pentadienyl moiety is displayed as a side chain on the α-pyran ring. Our approach to the problem of synthesizing this natural product was guided by the retrosynthetic analysis shown in Scheme 2.

The independent early investigations of Büchi (5) and Marvell (6, 7) provided a sound basis for the proposal that the oxacyclic ring of harziphilone, with its particular arrangement of alkenes, could arise by a 6π-electrocyclization of a compound of type **3** (for selected examples of this type of valence isomerization in synthesis see refs. 8–11). With several electrophilic sites and a high degree of unsaturation, **3** was perceived to be a challenging objective for synthesis, and we elected to explore the possibility of producing this potentially transient intermediate *in situ* from a doubly activated, polyunsaturated acyclic compound of type **1**. To implement this concept, we would seek a suitable heteroatom nucleophile that could attack the unsubstituted enone moiety in **1**. Although almost certainly reversible, such a site-selective, intermolecular conjugate addition reaction could trigger an intramolecular conjugate addition (see arrows in **4**), resulting in the production of a key carbon–carbon bond and the carbocyclic ring of (+)-harziphilone (for selected tandem conjugate addition/Michael cyclization reactions see refs. 12–17). A β-elimination of the heteroatom nucleophile might then generate **3** and set the stage for a final cycloisomerization to (+)-harziphilone (**2**; P = H).

Materials and Methods

Experimental procedures and characterization data for the compounds described in this article are provided in the supporting text, which is published as supporting information on the PNAS web site.



Scheme 1. Can (+)-harziphilone (**2**) be formed by a cycloisomerization of acyclic diketone **1**?

Results and Discussion

Aspects of our design for synthesis call to mind the Morita–Baylis–Hillman reaction (18, 19), and we reasoned that nucleophiles known to be effective at instigating this useful reaction might also bring about the type of bicyclization we were seeking. In the course of searching for a mild method for transforming doubly activated acyclic compounds to the bicyclic architecture of harziphilone, we reacted enone ynone **5**[†] with 10 mol % 1,4-diazabicyclo[2.2.2]-octane (DABCO) in chloroform at room temperature (Scheme 3). After 10 days, compound **5** was completely converted into the harziphilone-like compound **6**. By contrast, when acyclic diol **7** was treated with 10 mol % DABCO under the same conditions, bicyclic diol **8** was produced in nearly quantitative yield after only 20 h. On steric grounds, the unsubstituted enone β-carbons of compounds **5** and **7** are both susceptible to nucleophilic attack; however, it may well be that an internally hydrogen-bonded carbonyl in **7** heightens the reactivity of the enone β-carbon toward the nucleophilic catalyst and is the origin of the 12-fold difference in rate between the cycloisomerizations of compounds **5** and **7** (for examples of intramolecular catalysis through hydrogen bonding see refs. 21–24).

With these promising preliminary results reinforcing our confidence in the concepts shown in Schemes 1 and 2, we turned our attention to the problem of synthesizing compound **1**. Our preferred pathway commences with an asymmetric reduction of commercially available 2-methyl-2-cyclopenten-1-one (**9**) (Scheme 4) by the powerful method of Corey, Bakshi, and Shibata (CBS) (25). Silylation of the resulting secondary alcohol was then followed by an efficient and highly diastereoselective dihydroxylation (26) of the ring alkene to give diol **10**. After protection of the vicinal diol system in the form of an acetonide,

This paper was submitted directly (Track II) to the PNAS office.

Abbreviations: RRE, Rev-responsive element; DABCO, 1,4-diazabicyclo[2.2.2]octane; rt, room temperature.

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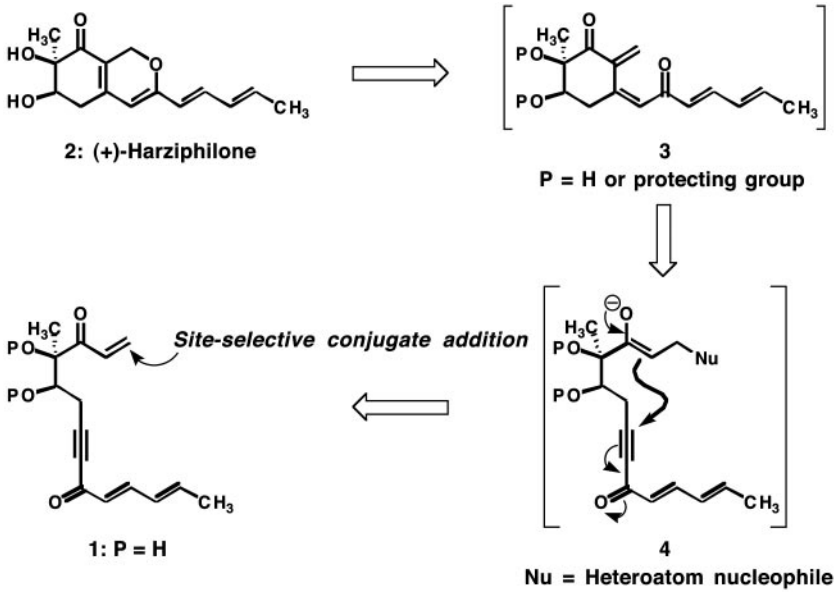
[†]See supporting information for a scheme showing a synthesis of compound **5** from propargyl alcohol by a pathway featuring a Sharpless asymmetric dihydroxylation reaction. For a review on the Sharpless asymmetric dihydroxylation see ref. 20.

www.pnas.org/cgi/doi/10.1073/pnas.0402563101



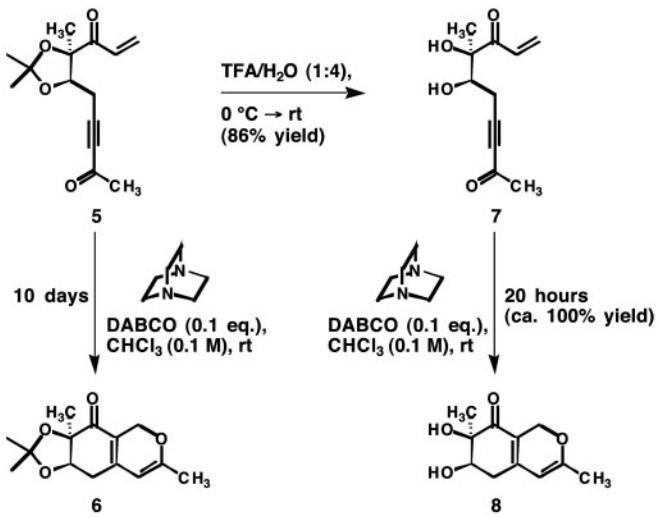
Scheme 2. A retrosynthetic analysis of harziphilone (**2**).

the silyl ether was cleaved with fluoride ion and the resulting alcohol was oxidized to optically active cyclopentanone **11**.

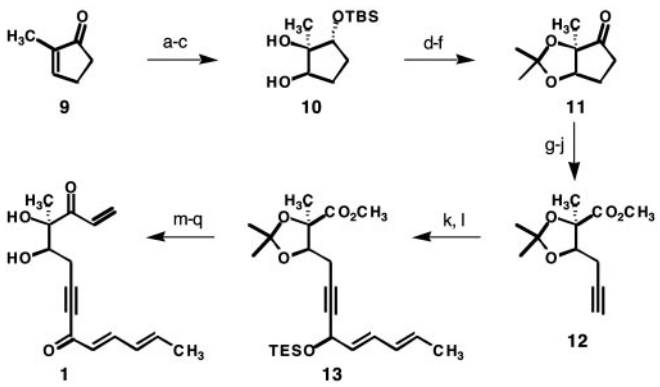
Our aim was to transform **11** to a bifunctional acyclic structure with differentiated oxidation states at the terminal carbons through an oxidative ring cleavage. To this end, **11** was enolized and acetylated on oxygen. Oxidative cleavage of the intermediate enol acetate afforded an aldehyde carboxylic acid, which was esterified with (trimethylsilyl)diazomethane to give the corresponding aldehyde methyl ester. A chemoselective reaction of the aldehyde group with Ohira's diazoketophosphonate (27) in basic methanol then gave rise to alkynyl ester **12**.

The lithium acetylide formed by a low-temperature deprotonation of alkyne **12** was then reacted with commercially available sorbaldehyde, after which silylation of the resulting secondary alcohol afforded compound **13** in 61% overall yield. To construct the required enone moiety, the methyl ester of **13** was converted to a Weinreb amide (28), which reacted smoothly with vinylmagnesium bromide to give the corresponding enone. After cleavage of the triethylsilyl ether with fluoride ion, a Dess–Martin oxidation (29) yielded the desired diketone. Finally, an acidic hydrolysis of the acetonide protecting group afforded compound **1** and set the stage for the pivotal bicyclization reaction.

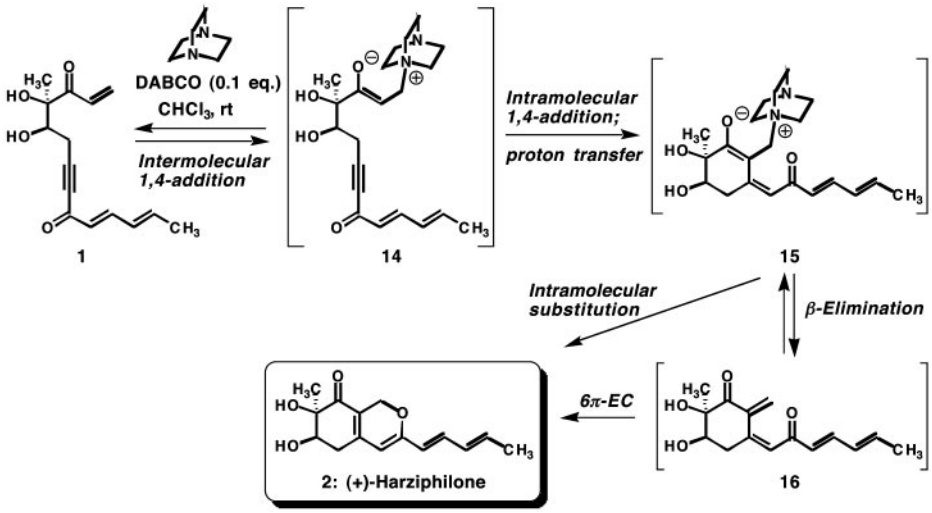
In relation to compounds **5** and **7** (Scheme 3), compound **1** possesses two additional electron-deficient carbon atoms that could predispose it toward undesired reactivity. Fortunately, however, it was possible to transform **1** directly to (+)-harziphilone (**2**) under the conditions shown in Scheme 5 in 70%



Scheme 3. Cycloisomerizations of compounds **5** and **7** catalyzed by DABCO. TFA, trifluoroacetic acid; rt, room temperature.



Scheme 4. Step a: (*S*)-2-methyl-CBS-oxazaborolidine (0.2 eq), $BH_3{\cdot}SMe_2$ (0.6 eq), tetrahydrofuran (THF), 0°C, enantiomeric excess = 90%. Step b: *t*-$BuMe_2SiCl$, imidazole, 4-dimethylaminopyridine (4-DMAP), CH_2Cl_2, 73% yield over two steps. Step c: OsO_4 (0.03 eq), 4-methylmorpholine *N*-oxide (2.5 eq), *i*-PrOH, 0°C, 86% yield, diastereomeric excess = 98%. Step d: 2-methoxypropene, 10-camphorsulfonic acid (0.1 eq), CH_2Cl_2, 98% yield. Step e: *n*-Bu_4NF, THF, 99% yield. Step f: $SO_3{\cdot}$pyridine, DMSO, Et_3N, CH_2Cl_2, 85% yield. Step g: Ac_2O, pyridine, 4-DMAP, 80°C, 84% yield. Step h: $K_2OsO_2(OH)_4$ (0.1 eq), $NaIO_4$, *t*-BuOH/H_2O. Step i: Me_3SiCHN_2, MeOH/benzene, 56% yield over two steps. Step j: K_2CO_3, MeOH, $CH_3COC(N_2)PO(OMe)_2$, 62% yield. Step k: lithium diisopropylamide, THF, −78°C; sorbaldehyde, −78°C to rt, 65% yield. Step l: Et_3SiCl, imidazole, CH_2Cl_2, rt, 94%. Step m: LiN(OMe)Me, THF, −78°C, 80% yield. Step n: vinylMgBr, THF, 68% yield. Step o: *n*-Bu_4NF, AcOH, THF, 80% yield. Step p: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 72% yield. Step q: 1:1 vol/vol trifluoroacetic acid/H_2O, 0°C, 85% yield. TBS, *t*-$BuMe_2Si$; TES, Et_3Si.



Scheme 5. A DABCO-catalyzed cycloisomerization of compound **1** to (+)-harziphilone (**2**). Conditions: Compound **1** (0.1 M in $CHCl_3$), DABCO (0.1 eq), rt, 24 h, 70% yield of compound **2**. EC, electrocyclization.

yield. To rationalize the course of this assisted bicycloisomerization, we suggest that DABCO adds reversibly to the unsubstituted and potentially activated enone system of **1**, affording a Baylis–Hillman-like zwitterion **14**. An intramolecular carbon–carbon bond formation could then generate an allenolate ion and subsequently the putative zwitterion **15** through a proton transfer. A simple β-elimination reaction could then return the nucleophilic catalyst to the reaction medium and afford **16**, thus enabling a final 6π-electrocyclization to (+)-harziphilone (**2**).‡ Alternatively, the oxacyclic ring of **2** could arise from zwitterion **15** by an intramolecular displacement of a neutral molecule of DABCO.

Under mild reaction conditions, the nucleophilic catalyst DABCO is capable of inducing unsaturated acyclic diketones to convert directly into the bicyclic architecture of the naturally occurring HIV-1 Rev/RRE inhibitor harziphilone. The total synthesis and DABCO-catalyzed bicyclizations described herein are the basis for an effort to create manifold side-chain variants of this natural product. Efforts are also underway to elucidate the binding interactions between harziphilone and HIV-1 constructs by NMR spectroscopy.

We thank Drs. D.-H. Huang and L. Pasternack for NMR assistance and Dr. G. Siuzdak for mass spectrometric assistance. This work was supported by National Institute for General Medical Sciences Grant GM65483 (to E.J.S.), The Skaggs Foundation at The Scripps Research Institute, the Deutscher Akademischer Austauschdienst (K.P.), a Skaggs Predoctoral Fellowship (to L.M.S.), the Achievement Rewards for College Scientists Foundation (L.M.S.), a Beckman Young Investigator Award (to E.J.S.), AstraZeneca, Eli Lilly, Pfizer, Merck Research Laboratories, Bristol–Myers Squibb, and a Camille Dreyfus Teacher–Scholar Award (to E.J.S.).

‡An optical rotation for naturally occurring harziphilone was not reported in ref. 4. Our sample of synthetic (+)-harziphilone (**2**) showed an $[\alpha]_D^{23}$ of +67° (c = 1.1 mg/ml, $CHCl_3$). The spectroscopic data (^{1}H NMR, ^{13}C NMR, and IR) obtained for **2** matched the data reported for natural harziphilone in ref. 4. We also synthesized (−)-harziphilone by the chemistry described herein for evaluation of both enantiomers of harziphilone in an HIV-1 Rev/RRE-binding assay.

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Diastereoselective SmI_2-mediated cascade radical cyclisations of methylenecyclopropane derivatives—a synthesis of paeonilactone B

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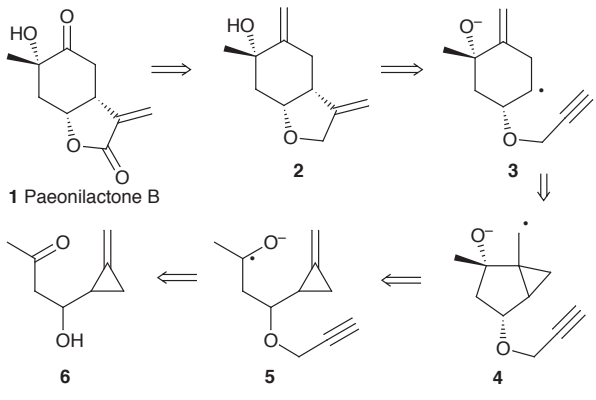
The SmI_2-mediated cascade reaction of methylenecyclopropyl ketone 9 proceeds with high diastereoselectivity, which is critically dependent on the presence of HMPA, and provides a short route to paeonilactone B.

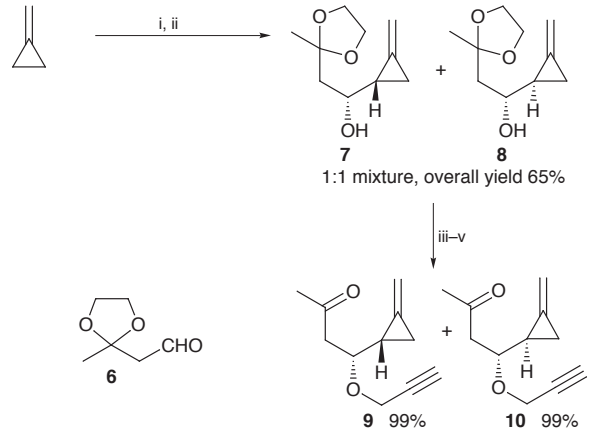
Cascade radical cyclisation reactions have proved to be very popular as a synthetic strategy as they allow the construction of several C–C bonds in one step and can provide elegant synthetic routes to complex polycyclic compounds and natural products.[1] Tandem reactions, initiated in particular by the versatile lanthanide reagent SmI_2, have also been a focus of recent attention.[2] We now report that SmI_2-promoted cascade cyclisations of methylenecyclopropyl ketone derivatives lead to bicyclic products in good yield and with excellent diastereoselectivity. This approach provides a short synthetic route to (±)-paeonilactone B **1**, one of several structurally related monoterpenes isolated from paeony roots,[3] all of which feature a highly oxygenated cyclohexane nucleus.[4]

A retrosynthetic analysis of paeonilactone B (Scheme 1) suggested that the *cis*-fused bicyclic methylenecyclohexane **2** could be prepared by a 5-*exo* cyclisation of methylenecyclohexyl radical **3** onto a pendant alkyne, and **3** could, in turn, arise from cyclisation of ketyl radical **5** onto a methylenecyclopropane unit with subsequent '*endo*' ring opening of **4**.[5] Whether such a sequence would prove to be diastereoselective and provide the correct relative stereochemistry of the tertiary alcohol required for the natural product remained to be tested by experiment.

Addition of lithiated methylenecyclopropane to aldehyde **6**,[6] produced the desired alcohols as a readily separable mixture of diastereoisomers **7** and **8** (Scheme 2).[7] The relative stereochemistry for the two diastereoisomers was established by X-ray crystallographic structure analysis of the *p*-nitrobenzoate ester derived from alcohol **8**.[8] Alkylation of the alcohols gave the corresponding prop-2-ynyl ethers, and subsequent ketal deprotection provided the two diastereomeric cyclisation precursors, **9** and **10** respectively, in essentially quantitative yield.



Scheme 1

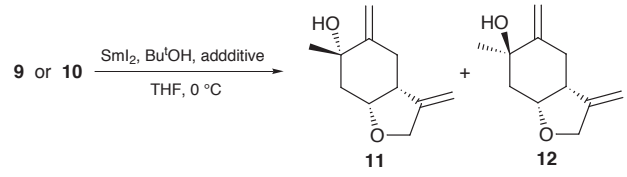


Scheme 2 *Reagents and conditions*: i, BuLi, THF, −78 °C; ii, compound **6**; iii, NaH, DMPU, THF; iv, $HC{\equiv}CCH_2Br$; v, TsOH, acetone, H_2O

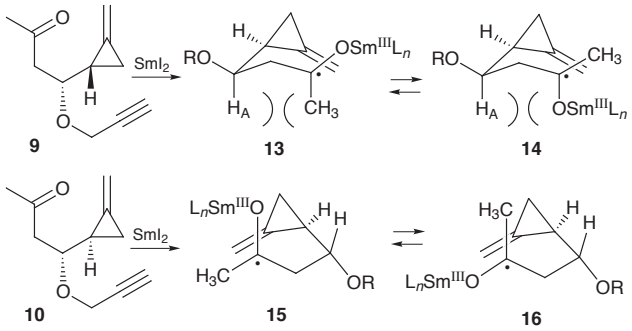
Treatment of ketone **9** with SmI_2, under standard conditions[9] (slow addition of **9** to 2.2 equiv. SmI_2, Bu^tOH, HMPA, THF, 0 °C) gave the desired bicyclic products as a readily separable mixture of diastereoisomers, **11** and **12**, in 57 and 6% isolated yields respectively (ratio **11**:**12** = 10 : 1 by analysis of the ^1H NMR spectrum of the crude reaction mixture) (Table 1). In contrast, treatment of diastereoisomeric ketone **10** with SmI_2, under identical conditions, gave the bicyclic product **12** in 73% isolated yield, and only a trace of the diastereoisomer **11** (ratio **12**:**11** > 30 : 1).

In order to rationalise the observed diastereoselectivity we repeated the cyclisations under identical conditions, but replacing HMPA with the less effective chelator DMPU.[10] These cyclisation reactions gave the bicyclic products with reduced overall yields and required a larger excess of SmI_2 (~6 equiv.) for consumption of starting material.[2b] Notably, for the cyclisation of **9**, the diastereoselectivity was reduced (ratio **11**:**12** = 1.5 : 1), whereas for the cyclisation of **10** the

Table 1 Reaction of **9** or **10** with different additives



Starting material	Additive	Yield (%)	**11** : **12**
9	HMPA	63	10:1
9	DMPU	40	1.5:1
9	—	~20	1:1.3
10	HMPA	79	<1:30
10	DMPU	62	<1:30
10	—	0	—



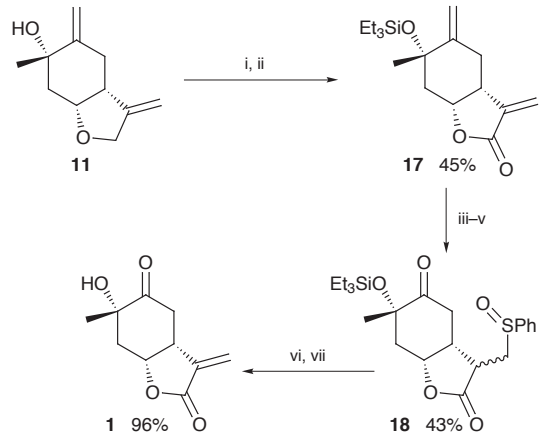
Scheme 3

diastereoselectivity was seemingly unaffected (ratio **12**:**11** > 30 : 1). In the absence of either DMPU or HMPA the cyclisation was, as expected, a poor reaction. Thus **9** gave an overall yield of ~20% of **11** and **12**, but with a reversal of stereoselectivity (ratio **11**:**12** = 1 : 1.3), while cyclisation of **10** yielded none of the desired bicyclic compounds.

The selectivity for the cyclisation of **9** in favour of **11**, in which the tertiary alcohol and ether oxygen are *cis* in the bicyclic product, might be the consequence of chelation control from the weakly basic prop-2-ynylic ether oxygen to the samarium(III) bound to the ketyl radical. However, the decrease in selectivity for the cyclisation of **9** as HMPA is replaced by the weaker chelator DMPU, and reversal of selectivity when neither is present, effectively rules out this possibility. It seems probable that the first step of the cyclisation of **9**, which effectively sets the relative stereochemistry of the product, proceeds through a chair-like transition state, allowing the prop-2-ynyl ether substitutent to adopt a pseudo-equatorial position (Scheme 3). As a consequence of the bond angles of the methylenecyclopropyl group, the alkene appears to be essentially staggered between the ketyl radical oxygen and the ketyl methyl group. Thus the preference for conformer **13** over **14** may largely result from the preference for the bulky $OSm^{III}(HMPA)_n$ moiety to also adopt a pseudo-equatorial position and avoid a 1,3-diaxial interaction with H_A. Replacement of HMPA with DMPU may effectively reduce the steric bulk of the $OSm^{III}L_n$ moiety,[10] leading to a lower selectivity for conformer **13**. In the absence of either HMPA or DMPU the ketyl methyl becomes sterically dominant, leading to a reversal in selectivity.

In contrast, the first step of the cyclisation of **10** may well proceed through a boat-like transition state, since a chair-like transition state would force the prop-2-ynyl ether substituent into a severely hindered axial orientation. In the boat-like transition state the alkene now appears to be largely eclipsed with either the ketyl methyl group (**15**) or the ketyl radical oxygen (**16**). Conformer **15** may now be preferred over **16** since it alleviates the electronic repulsion between the ketyl oxygen functionality and the alkene π-system,[11] and this preference is unaffected by replacing HMPA with DMPU.

Completion of the synthesis of paeonilactone B firstly required protection of the tertiary allylic alcohol as the triethylsilyl ether,[12] followed by oxidation of the allyl ether to the desired α-methylene lactone **17** using CrO_3 and pyridine (Scheme 4).[13] The selective oxidation of the ostensibly more electrophilic cyclohexyl alkene of **17** proved to be impossible with both alkenes reacting rapidly with ozone at −110 °C in EtOH in almost quantitative yield. Even more frustratingly, treatment of **17** with OsO_4 led to dihydroxylation of just the the α-methylene lactone, presumably due to steric congestion around the cyclohexyl alkene. Instead, base-mediated Michael addition of PhSH to **17** gave the thioether which was then successfully ozonolysed to give the desired ketone, with concomitant oxidation of the thioether to the corresponding sulfoxide **18**. Thermal elimination of phenylsulfenic acid[14] then reinstalled the α-methylene lactone and deprotection of the silyl



Scheme 4 *Reagents and conditions*: i, Et_3SiOTf, Et_3N, CH_2Cl_2, 0 °C; ii, CrO_3, pyridine, CH_2Cl_2, room temp.; iii, PhSH, Et_3N, MeOH; iv, O_3, MeOH, −78 °C; v, Me_2S; vi, CCl_4, reflux; vii, HF·pyridine, THF

ether was successfully achieved using pyridine·HF,[15] to give (±)-paeonilactone B, whose structure was confirmed by comparison of its NMR and IR spectroscopic data to those reported previously for the natural paeonilactone.[3]

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Asymmetric Synthesis

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Short, Enantioselective Total Synthesis of Sceptrin and Ageliferin by Programmed Oxaquadricyclane Fragmentation**

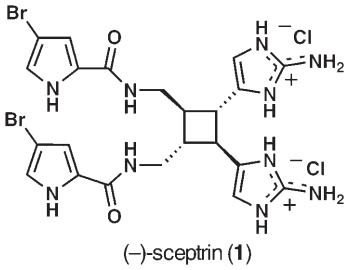
Phil S. Baran, Ke Li, Daniel P. O'Malley, and Christos Mitsos*

Dedicated to Professor David I. Schuster on the occasion of his 70th birthday.

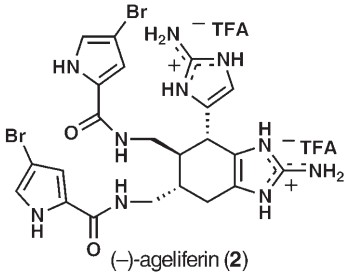
The marine-derived dimeric pyrrole-imidazole alkaloids sceptrin (**1**) and ageliferin (**2**) are endowed with intriguing molecular architectures and a range of useful bioactivities (Scheme 1).[1] The enantioselective synthesis of a dimeric pyrrole-imidazole alkaloid has yet to be reported, partly because of the intrinsic difficulty associated with handling multiply charged nitrogen-containing intermediates.[2]

We recently described practical syntheses of both **1** and **2** in their racemic form[3,4] by the use of an oxaquadricyclane fragmentation to generate the cyclobutane core of **1**. Since the mechanism of this reaction remained ill-defined,[5] it was unclear how, or even if, stereochemical information in an oxaquadricyclane could be transferred to the product cyclobutane. Indeed, preliminary screens using numerous enantioenriched oxaquadricyclanes (**3**, Scheme 2) under a variety of acidic conditions led to cyclobutanes which were either racemic or showed a considerable loss of optical activity. Racemic oxaquadricyclanes were also evaluated with chiral acids and auxiliaries, but to no avail. Further investigation was warranted because of the lack of viable alternatives for the enantioselective synthesis of tetrasubstituted cyclobutanes.[6]

Herein, we report the details of a unique method for the enantioselective synthesis of tetrasubstituted cyclobutanes by programmed fragmentation of an oxaquadricyclane, and the application of this method to the first asymmetric synthesis of both enantiomers of sceptrin and ageliferin.

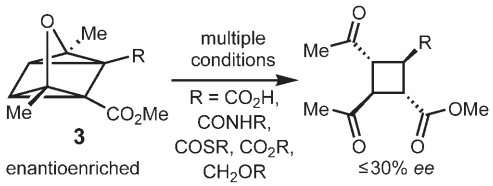


(–)-sceptrin (**1**)



(–)-ageliferin (**2**)

Scheme 1. The structures of sceptrin (**1**) and ageliferin (**2**). TFA=trifluoroacetate.



Scheme 2. Unsuccessful attempts at enantioselective fragmentation of an oxaquadricyclane.

The synthesis commenced with the enzymatic desymmetrization[7] of *meso*-diester **4**[3a] using pig liver esterase (PLE) to provide monoester **5** in quantitative yield and 75% *ee* (Scheme 3). The *ee* value was determined by ^{1}H NMR spectroscopic analysis of the amide derived from (*S*)-α-methylbenzylamine (absolute configuration determined by X-ray analysis of the ammonium salt derived from the same amine and **5**). Formation of a benzylamide using DMT-MM[8] afforded the monobenzylamide **6** in 92% yield. Remarkably, *cis,trans,trans*-cyclobutane **10** was formed in 50% overall yield and 75% *ee* when amide **6** was irradiated to form oxaquadricyclane **7** and directly treated with H_2SO_4 in THF/MeOH (1:1). Amide (–)-**10** is nearly enantiopure (> 95% *ee*) after a single recrystallization. The use of a benzylamide was critical to achieve complete transfer of chirality. A mild and chemoselective debenzylation/esterification of the robust secondary amide in **10** and epimerization to the all-*trans* stereochemistry were necessary to access (–)-**13**. Treatment of **10** with TsOH and MeOH in toluene at 105 °C[9] accomplished all three tasks in a single pot to afford (–)-**13** in 90% yield. The ease with which this amide is hydrolyzed is likely due to assistance by the nearby *cis*-methyl ketone, as depicted in structure **12** (simple secondary amides are not converted into methyl esters under these conditions).

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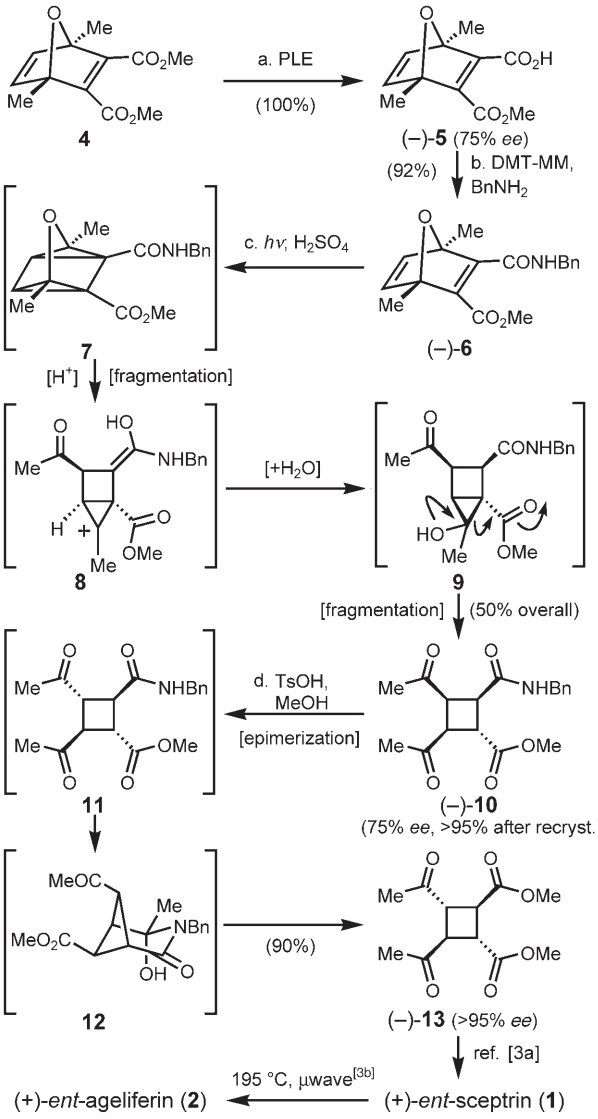
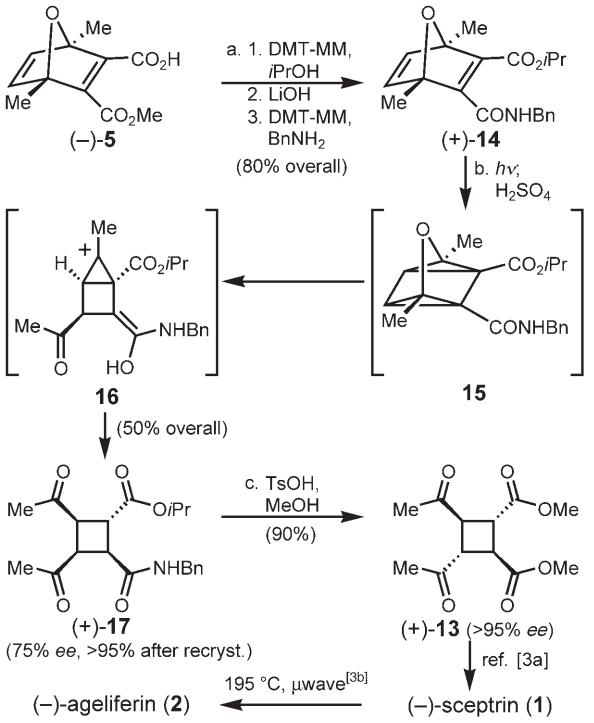
Supporting information for this article (detailed experimental procedures, copies of all spectral data, and full characterization) is available on the WWW under http://www.angewandte.org or from the author.



Scheme 3. Enantioselective Synthesis of *ent*-**1** and *ent*-**2**. Reagents and conditions: a) PLE (50 unit mmol^{-1}), acetone/phosphate buffer (pH 8), 23 °C, 1 week, 100%, 75% *ee*; b) $BnNH_2$ (1.05 equiv), DMT-MM (1.05 equiv), THF, 3 h, 92%; c) *hν*, THF, 72 h, then H_2SO_4, THF/MeOH (1:1), 3 h, 45–50%; d) recrystallization from hexanes/EtOAc (1:1), then TsOH (4.0 equiv), MeOH (20 equiv), toluene, 105 °C, sealed tube, 12 h, 50%. Bn = benzyl, THF = tetrahydrofuran; TsOH = toluenesulfonic acid, DMT-MM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride.



Scheme 4. Enantioselective Synthesis of *nat*-**1** and *nat*-**2**. Reagents and conditions: a) 1. DMT-MM (1.05 equiv), DMAP (0.05 equiv), *i*PrOH, 55 °C, 3 h; 2. LiOH (1.2 equiv), THF/H_2O (1:1), 2 h; 3. DMT-MM (1.05 equiv), $BnNH_2$ (1.05 equiv), THF, 3 h, 80% (3 steps); b) *hν*, THF, 72 h, then H_2SO_4, THF/MeOH (1:1), 3 h, 45–50%; c) recrystallization from hexanes/EtOAc (1:1), then *p*TsOH (4.0 equiv), MeOH (20 equiv), toluene, 105 °C, sealed tube, 12 h, 50%. DMAP = 4-dimethylaminopyridine.

The absolute configuration of (−)-**13** was verified by conversion into sceptrin[3a] and comparison with a natural sample, which revealed that *ent*-sceptrin (**1**) had been synthesized ($[\alpha]_D = +16.0$ (MeOH, $c = 0.25$, HCl salt), lit. [1] $[\alpha]_D = -7.4$ (MeOH, $c = 1.2$, HCl salt)). Exposure of *ent*-sceptrin (**1**) to microwave irradiation[3b] led to *ent*-ageliferin (**2**; $[\alpha]_D = +8.0$ (MeOH, $c = 0.05$, TFA salt), natural product $[\alpha]_D = -10.0$ (MeOH, $c = 0.1$, TFA salt)).[3] The absolute configuration of **2** can now be assigned as depicted in Scheme 1.

The naturally occurring forms of **1** and **2** could be prepared as outlined in Scheme 4. Thus, monoacid **5** was directly converted into the amide **14** in 80% overall yield, without purification, by sequential formation of an ester, selective saponification of the methyl ester, and formation of an amide. Amide **14** was amenable to the same reaction sequence used for **6** (Scheme 3) and furnished cyclobutane **17** with complete conservation of optical activity. Following recrystallization (> 95% *ee*), epimerization, and transesterification to (+)-**13**, the synthesis of *nat*-(−)-sceptrin ($[\alpha]_D = -11.7$ (MeOH, $c = 0.12$, HCl salt)) and (−)-ageliferin ($[\alpha]_D = -10.0$ (MeOH, $c = 0.03$, TFA salt)) was completed. Both the sign and magnitude of the optical rotation of sceptrin changes depending on the counteranion (synthetic *ent*-sceptrin bishydrochloride had $[\alpha]_D = +16.0$ (MeOH, $c = 0.25$, HCl salt), while the bistrifluoroacetate salt had $[\alpha]_D = -23.5$ (MeOH, $c = 0.75$, no literature value available). This unusual reversal of optical rotation and the fact that the literature measurements for **1** and **2** are variable necessitated the use of circular dichroism to verify the assignments (Figure 1). The fact that (−)-**2** can be derived from (−)-**1** is consistent with the suggestion that the former may be produced from the latter in nature or that they share common intermediates in the biosynthetic pathway.[2,3b]

The cascade rearrangement of oxaquadricyclanes to cyclobutanes was initially discovered by McInnes and coworkers,[5a] who proposed a mechanism involving the initial fragmentation of the oxa bridge with water. The cascade was

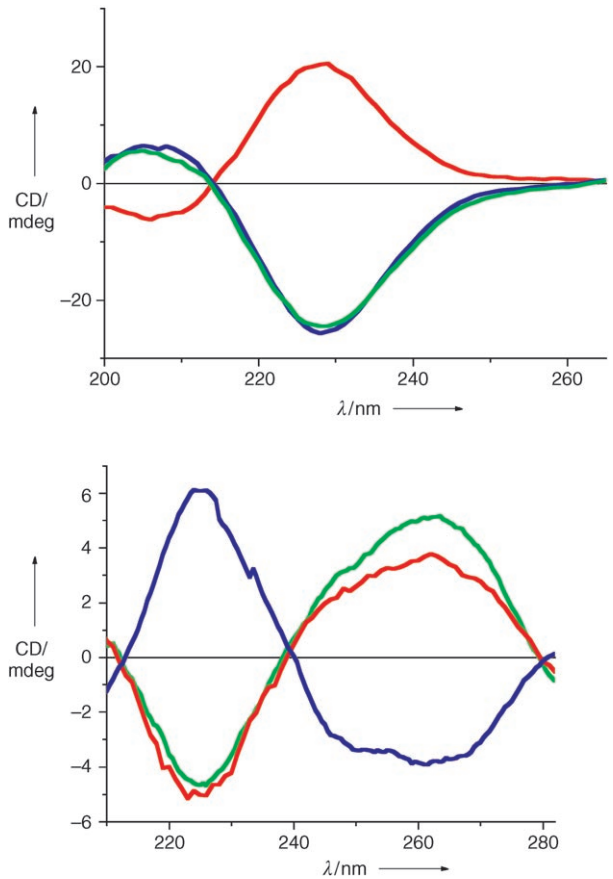


Figure 1. Top: Circular dichroism (CD) spectra of natural (−)-sceptrin (green), synthetic (−)-sceptrin (blue), and synthetic (+)-sceptrin (red) in water (0.2 mM). Bottom: Circular dichroism (CD) spectra of natural (−)-ageliferin (green), synthetic (−)-ageliferin (red), and synthetic (+)-ageliferin (blue) in water (0.35 mM). All measurements were recorded at 25 °C.

later studied by Nelsen and Calabrese,[5b] who posited an alternative mechanism initiated by fragmentation of a cyclopropyl ring to form an oxocarbonium ion (see **8** and **16**). After the work of Nelsen and Calabrese, little notice was taken of this reaction until it was adopted in the synthesis of sceptrin.[3] Success of an enantioselective variant relied on the assumption that the configuration of the final product is controlled by the order of the enolization (or protonation) of the carbonyl groups in the first fragmentation. For example, the major enantiomer (**10**) resulting from the fragmentation of **7** is produced by initial enolization of the benzylamide (Scheme 3), whereas the minor enantiomer (*ent*-**10**) would be produced by initial enolization of the ester. This result fits with the results of theoretical predictions that have found that enols of amides are more stable than those of carboxylic acids or esters.[10] The selective fragmentation of **7** to amide enol **8** is followed by tautomerization (protonation from the convex face) and capture by water to furnish **9**. Immediate fragmentation leads to the stable *cis*,*trans*,*trans*-cyclobutane **10**. The efficiency and complete transfer of chirality observed in these reactions (**6**→**10** and **14**→**17**) is surprising given the complexity of this mechanism, the difficulties encountered at the outset (see above), and the fact that oxaquadricyclanes are prone to a variety of other rearrangements under acidic conditions.[5c] This method proceeds in an operationally simple, scalable, and direct manner and represents the first solution for the nontrivial problem of the enantioselective construction of a tetrasubstituted cyclobutane which does not rely upon chiral auxiliaries.[6,11]

In summary, the first enantioselective syntheses of the dimeric pyrrole-imidazole alkaloids sceptrin (**1**) and ageliferin (**2**) have been accomplished (18% overall for (−)-**1** from commercially available compounds). Notably, column chromatography (on **10** and **17**) and HPLC (to separate **1** from **2**) only need to be performed once during the entire sequence. These syntheses have enabled the assignment of the absolute configuration of **2**, provided insight into the mechanism of the remarkable oxaquadricyclane→cyclobutane rearrangement, and opened up an enantioselective route to other complex alkaloids in this family.[12]

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Keywords: asymmetric synthesis · cascade reactions · enantioselectivity · natural products · rearrangement

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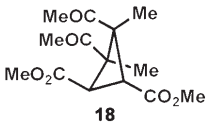

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[12] CCDC-281469 (chiral ammonium salt of **5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

