EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201500208

Collective Synthesis of Natural Products Sharing the Dihydro-γ-Ionone Core

Alexis Castillo,[a] Lucia Silva,[b] David Briones,[c] José F. Quílez del Moral,*[a] and Alejandro F. Barrero*[a]

Keywords: Natural products / Organocatalysis / Molecular diversity / Chiral pool

We decided to follow the so-called "collective total synthesis" approach to synthesize several structurally different molecules from a common intermediate possessing appropriate stereochemistry and functionalities. As the common precursor for the efficient preparation of these bioactive molecules, we chose (+)-3,4-dihydro-γ-ionone (**1**), a natural compound present in minor quantities in ambergris and in the plant *Bellardia trixago*. Thus, we report herein the enantioselective synthesis of siccanochromene F (**2**), metachromins U (**3**) and V (**4**), and bicyclic squalene derivative **5** as well as the formal syntheses of ambrein (**6**), phenazinomycin (**7**), and (–)-siccanin (**8**).

Introduction

Nature provides an almost endless source of impressive structural diversity. However, it is also recognized that the myriad of complex and diverse natural products is ultimately derived from a limited number of common precursors. Inspired by this concept[1] and to mimic the action of nature, we used natural (+)-3,4-dihydro-γ-ionone (**1**) as a common precursor[2] for the syntheses of **2**–**8** (Figure 1).[3–8] The significant decrease in the total number of steps is one of the main advantages of this methodology.

Siccanin (**8**) is a mold metabolite isolated from the cultured broth of the pathogenic plant fungus *Helminthosposium siccans*, a parasitic organism of rye grass.[8a] Siccanin possesses remarkable antifungal activity against some pathogenic fungi of the genera *Trichophyton* (the cause of the skin infection trichophytosis), *Epidermophyton*, and *Microsporum*.[8b] Thus, clinical tests showed that siccanin was effective against superficial fungal infections,[8c] including those of the opportunistic fungus *Candida albicans*.[8d] It has been reported recently by Mogi that siccanin is a species-selective succinate dehydrogenase (SDH) inhibitor.[8e] These studies have renewed interest in this molecule. Siccanin inhibits bacterial SDH from *Pseudomonas aeruginosa* (one of the leading causes of hospital-acquired infections, mainly owing to innate and acquired resistance to antimicrobial drugs) and *P. putida* but not SDH from *Escherichia coli* or *Corynebacterium glutamicum*. Species-selective inhibition is unique among SDH inhibitors, and this makes siccanin a potential lead compound for new chemotherapeutics. To date, only one enantioselective and two racemic total syntheses of siccanin have been reported.[8f–8i] Together with siccanin, siccanochromenes were also isolated from *H. siccans*. One of these molecules is siccanochromene F (**2**).[3] Metachromins U and V (**3** and **4**) were isolated from the marine sponge *Thorecta reticulata*. The cytotoxicities of these compounds were assessed against a panel of human tumor cell lines (SF-268, H460, MCF-7, and HT-29) and a mammalian cell line (CHOK1). Both compounds are cytotoxic against all of these cell lines, and metachromin V is the most active [50% growth inhibition (GI_{50}) 2.1–10 μM].[4] Compound **5** is a bicyclic squalene derivative, isolated from an anoxic sulfur-rich sediment in Lake Cadagno, Switzerland.[5] This triterpene possesses a hydrocarbon skeleton not reported in living organisms. Phenazinomycin (**7**), isolated from *Streptomyces sp.* WK-2057, belongs to the group of phenazine antibiotics.[7a] This compound is also active against P 388 leukemia cells and also shows in vivo activity against murine tumors.[7b] Phenazinomycin also possesses antitrypanosomal activities both in vitro and in vivo.[7c]

Ambrein (**6**) is a major constituent of ambergris, which is a concretion formed by sperm whales that has been highly valued since ancient times and is currently used in the fabrication of expensive perfumes.[6a] Recently, the antioxidant and antiinflammatory activities of ambrein were also reported.[6b,6c] The total synthesis of this triterpene was previously achieved,[6d–6f] and this compound was very recently obtained enzymatically.[6g]

[a] Department of Organic Chemistry, University of Granada, Avda. Fuentenueva, 18071 Granada, Spain
E-mail: jfquilez@ugr.es, afbarre@ugr.es
http://www.ugr.es/~sinmobio/
[b] Department of Chemistry, University of Beira Interior, Rua Marquês d'Ávila e Bolama, 6200 Covilhã, Portugal
[c] Department of Chemical and Energy Technology, Rey Juan Carlos University, C/ Tulipán s/n, 28933 Móstoles, Spain

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500208.

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

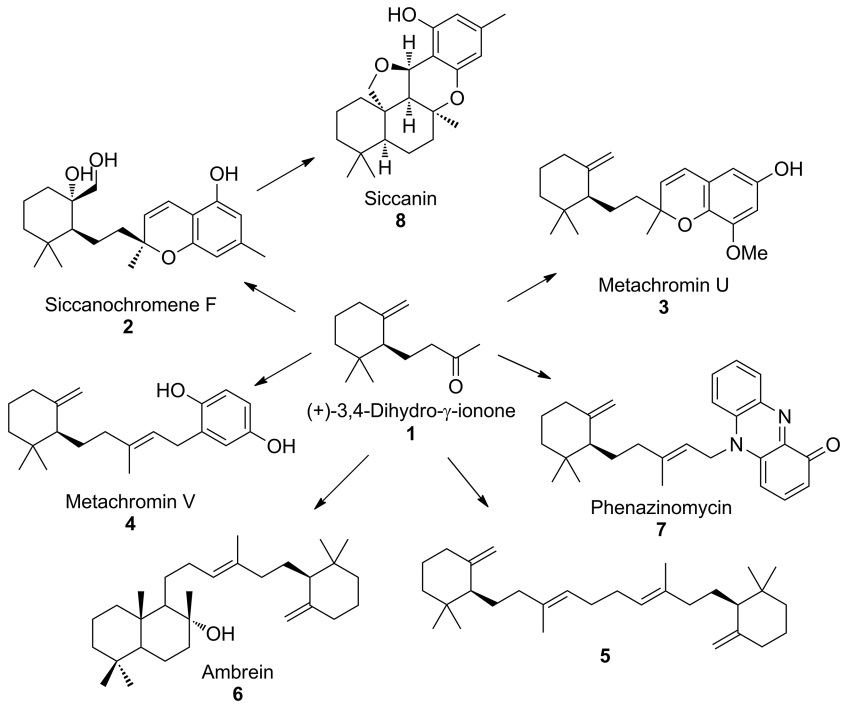


Figure 1. Natural products sharing the dihydro-γ-ionone core.

Results and Discussion

Our first aim was to find a protocol that gave access to (+)-3,4-dihydro-γ-ionone (**1**) on a multigram scale as quickly and straightforwardly as possible. 3,4-Dihydro-γ-ionone is present only in minor amounts in the aerial parts of *Bellardia trixago*.[9b,2a] However, in this plant, the TRIX chemotype contains significant proportions of trixagol (**9a**), an adequate precursor of **1** through degradative oxidation.[2] Thus, when dried aerial parts (1 kg) were extracted with a Soxhlet system with hexane as the solvent, **9a** (5.4 g per kg of plant) was obtained after acid–base fractionation, defatting, and chromatographic purification.[2a] Further experimentation was then required to avoid the time-consuming isolation of **9a**. If dry leaves, stems, and flowers are extracted separately with hexane by using a Soxhlet apparatus, the monomalonyl ester of trixagol (**9b**) is only found in the flowers in up to 24.8 g per kg.[2b,2c]

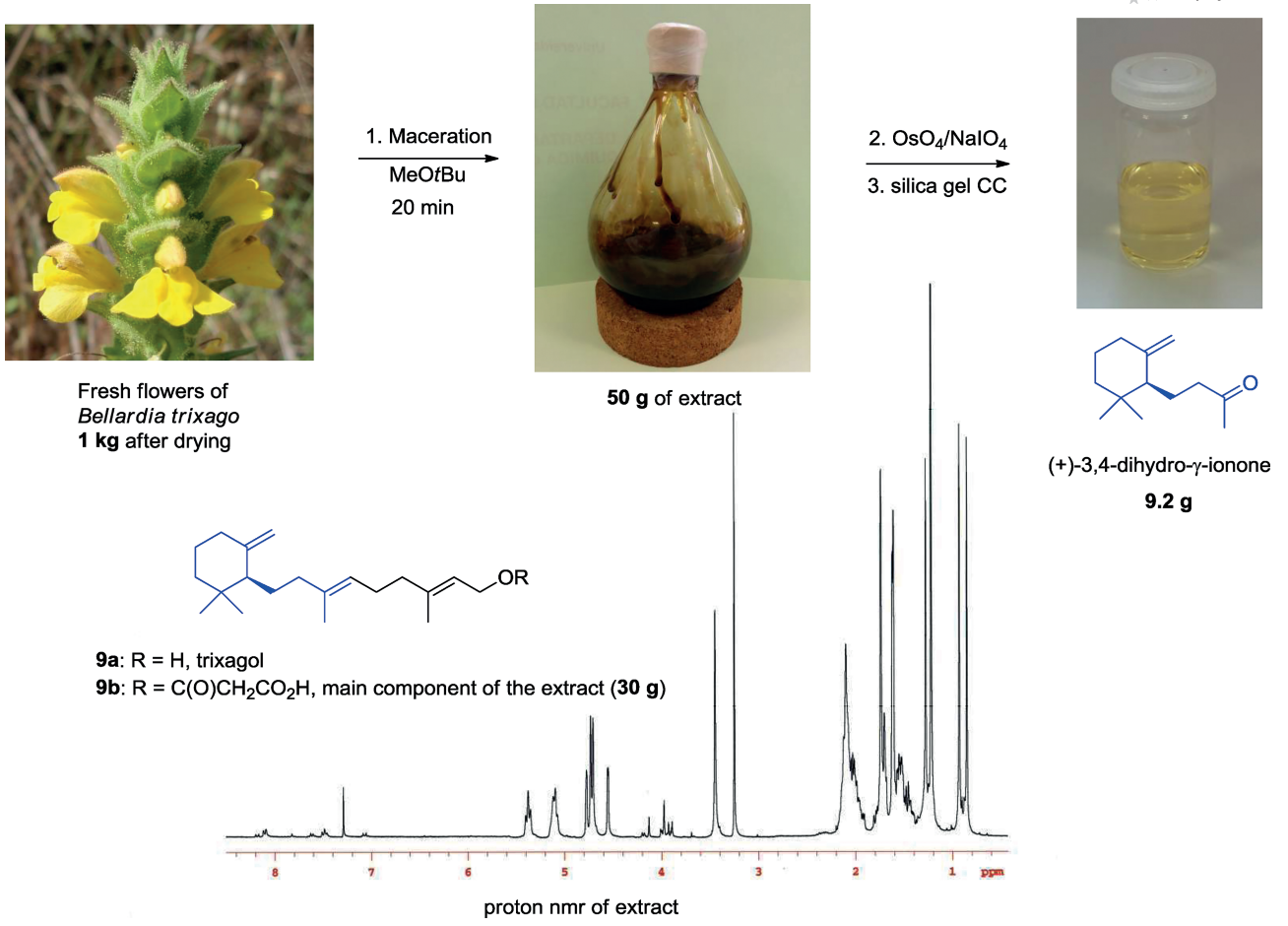
The observation that the inflorescence is covered by hairs and resin glands led us to try a selective extraction of **9** by macerating the fresh flowers in different solvents. Good results were found for methyl *tert*-butyl ether (MTBE) at room temperature, and the ^{1}H NMR spectrum of the extract showed a high proportion of the monomalonyl ester of trixagol, together with minor quantities of benzoic acid and fats (Scheme 1). By this method, the monomalonyl ester of trixagol (**9b**) was obtained (up to 30 g per kg of plant material, which corresponds to 23 g of trixagol). Standard oxidative degradation of the crude extract with catalytic OsO_4 and excess $NaIO_4$ in *t*BuOH afforded pure **1** (9.2 g per kg of flowers, after one column chromatography purification, weighed after drying).

We started our study into the feasibility of using **1** as a common intermediate for transformation into a collection of natural products with the synthesis of siccanochromene F (**2**) and siccanin (**8**). In designing a synthetic route toward siccanochromene F (**2**), we envisioned a convergent approach based on the coupling of the chiral natural synthon **1** with commercially available 2,6-dihydroxy-4-methylacetophenone (**10**) by an organocatalytic cascade reaction (Scheme 2).

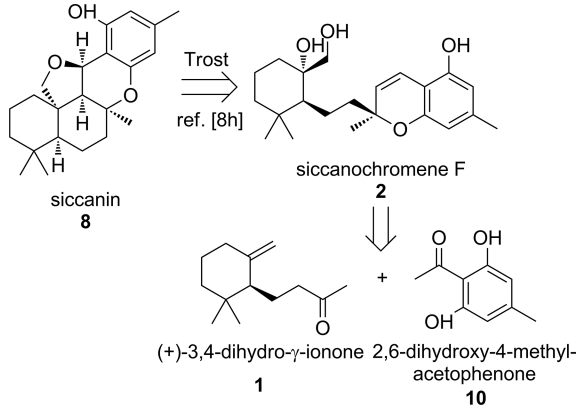
This coupling process is based on the protocol described by Kabbe for the syntheses of these kinds of products.[10] Despite the amazing advances in organocatalysis in the last decade,[11] it should be noted that this field did not exist as we know it now when Kabbe reported this process, which could be considered as one of the first examples of an organocatalyzed reaction.

To evaluate the feasibility of our approach, including the development of an asymmetric version, we chose the commercially available 2-decanone (**11**) as a model starting methyl ketone. Different parameters that could determine the outcome of the reaction were considered, namely, the presence of an acid, the influence of molecular sieves, and the quantity of pyrrolidine required. Thus, after some experimentation, we found the best experimental conditions. Although the presence of acid is not required, molecular sieves are essential for the completion of the reaction. Excellent yields (96%) were obtained when 1.5 equiv. of pyrrolidine were used, although acceptable yields (80%) were also produced when the amount of amine was reduced to 0.3 equiv. The use of only 0.15 equiv. of pyrrolidine increased the reaction time excessively (up to a week) and also reduced the efficiency of the process (60%).

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

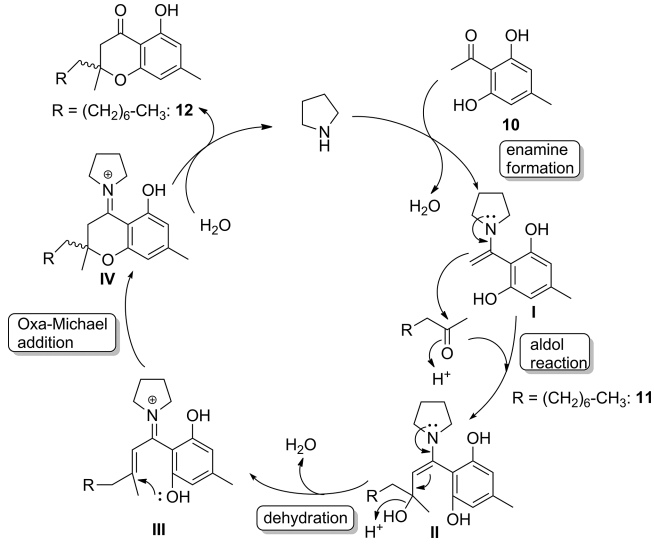


Scheme 1. Selective multigram production of **1** from its natural source *B. trixago*.



Scheme 2. Retrosynthetic analysis for siccanochromene F and (–)-siccanin.

Mechanistically, this pyrrolidine-based protocol consists of a cascade aldol–dehydration–oxa-Michael organocatalytic reaction that proceeds via enamine intermediates and is favorable towards enamine–iminium catalysis.[11a] However, as the relative tendency of both linear ketones and acetophenone to form enamines has been recently reported to be similar,[12a] the mechanism for this transformation could be initiated by two different amine activations as proposed by Kabbe in his original report.[10] The first one would involve the initial formation of the enamine–imine derived from the acyclic methyl ketone. The second would assume the generation of the enamine produced by the reaction of the acetophenone with pyrrolidine (Scheme 3). At this point, it should be noted that the mechanism would



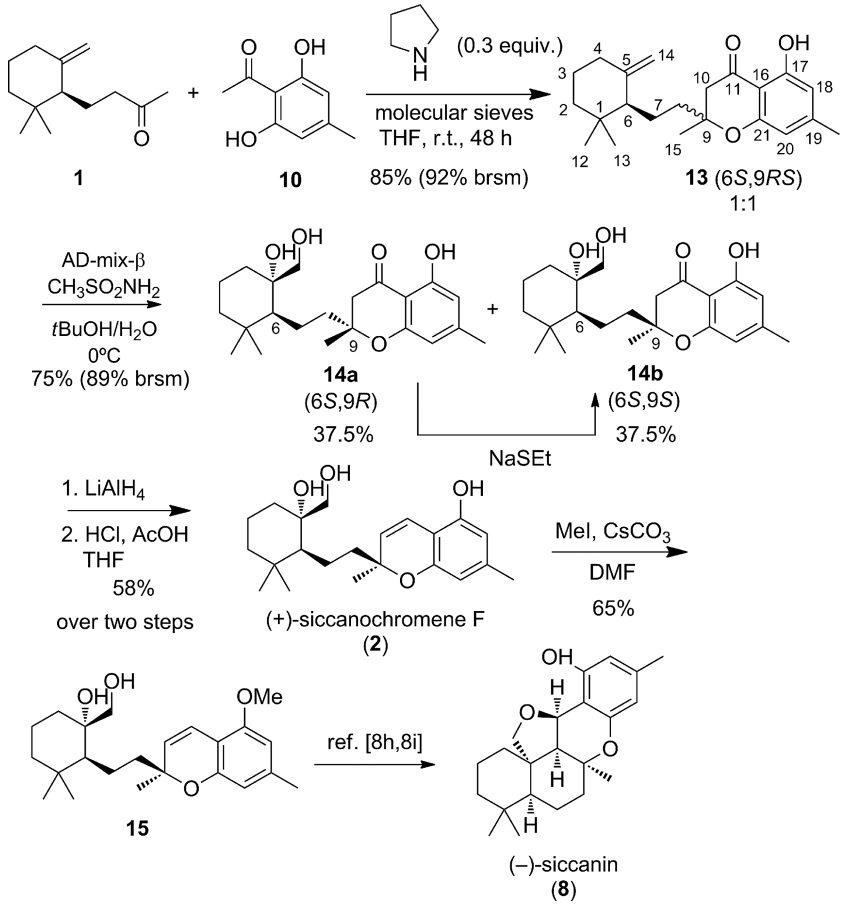
Scheme 3. Mechanism proposed for the Kabbe reaction.

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

involve the use of only 1 equiv. of ketone donor in either case (in reported aldolization reactions, the ketone donor is generally used in large excess) and also 1 equiv. of a second unactivated ketone acceptor (only activated ketone acceptors as α-keto acids, α-keto esters, or α-keto phosphonates were reported to act as ketone acceptors in proline-catalyzed intermolecular aldolization reactions).[13]

To obtain some data to help us to discern between both mechanistic proposals, we reacted **10** with pyrrolidine in toluene under reflux by using a Dean–Stark apparatus. As the reaction of the thus-generated enamine **I** with **11** produced chromanone **12**, we postulate that the second initiation step is the one most likely to occur (Scheme 3).[12b] Through the proposed mechanism, the employment of a chiral amine could result in the asymmetric generation of the chiral center created by a stereoselective oxa-Michael addition to the α,β-unsaturated iminium **III**. In this regard, there is ample evidence of the involvement of pyrrolidine-based secondary amines in the reversible formation of enamine–imine intermediates.[14] Thus, chiral pyrolidine derivatives, namely, proline, proline methyl ester, and diphenylprolinol methyl ether,[11] were tested for the enantioselective synthesis of chromanone **12**. Unfortunately, in all cases, the yields were negligible (≤5%) even after several days of reaction, and no enantiomeric excesses were detected. As this lack of reactivity could be due to the high steric demand hampering the nucleophilic attack of the enamine of the methyl ketone and bearing in mind the proven reactivity of primary amines in aldol reactions,[15] we decided to use this kind of amine to generate the desired diastereoselectivity. However, neither the use of chiral amino acids such as tryptophan[15c] nor the use of primary amines such as 1-phenylethylamine produced any diastereoselectivity.

Once the conditions for the chromanone generation had been optimized, we addressed the synthesis of siccanochromene F and consequently that of siccanin (Scheme 4). Thus, the reaction of **1** with **10** in the presence of 0.3 equiv. of pyrrolidine led to desired chromanone **13** in 85% yield [92% based on recovered starting material (brsm)] as an epimeric mixture at C-9. The Sharpless asymmetric dihydroxylation[16] of ketoolefin **13** with AD-mix β generated the readily separable mixture of diols **14** with complete diastereoselectivity. At this point, the efficiency of the approach was significantly improved as the chromanone moiety of the undesired epimer **14a** could be epimerized to form **14b** in 50% yield by treatment with NaSEt in *N*,*N*-dimethylformamide (DMF) under reflux.[8i] The same quantity (50%) of unaltered **14a** was also recovered. This process meant that, practically, the mixture of epimers at C-9 generated in the formation of chromanone **13** could be derived into the desired 9*S* diastereomer. (+)-Siccanochro-



Scheme 4. Synthesis of (+)-siccanochromene F: Formal synthesis of (–)-siccanin.

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

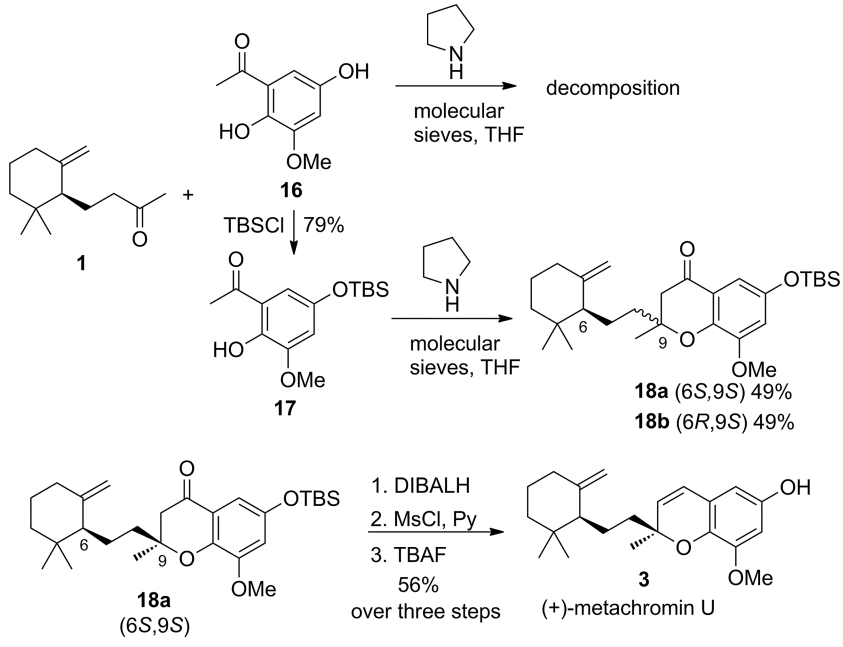
mene F was finally generated by acid treatment of the benzylic alcohol obtained after the lithium aluminium hydride (LAH) reduction of **14b** (Scheme 4).

Once the synthesis of siccanochromene F was achieved, the formal synthesis of (–)-siccanin only required the chemoselective protection of the aromatic hydroxyl to produce diol **15**, which was reported to be an intermediate in the enantioselective synthesis of siccanin by Trost et al.[8h,8i] This transformation was achieved in acceptable yield by the treatment of **2** with MeI in the presence of Cs_2CO_3 (Scheme 4). A noteworthy fact is that intermediate **15** was generated after 17 steps in the seminal work of Trost et al.,[8g] a number that is considerably reduced in our approach (only five steps).

By continuing with our collective approach with (+)-3,4-dihydro-γ-ionone (**1**) as a common precursor and taking advantage again of the Kabbe reaction, the synthesis of cytotoxic metachromin U (**3**) was performed as depicted in Scheme 5. It should be noted at this point that none of the configurations of the stereogenic centers in this molecule were assigned when this natural product was described.[4]

The appropriate acetophenone, **16**, for the synthesis of metachromin U can be obtained by persulfate oxidation of commercially available 2-hydroxy-3-methoxyacetophenone, as described by Simpson.[17] However, an attempted condensation of γ-ionone (**1**) with 2,5-dihydroxy-3-methoxyacetophenone (**16**) in the presence of pyrrolidine resulted in the total degradation of the aromatic scaffold. We attributed this change of reactivity to the new electronic distribution caused by the presence of the hydroquinone moiety and decided to try to overcome this situation by protecting the new aromatic hydroxyl as its silyl ether, **17**. Gratifyingly, the exposure of a mixture of acetophenone **17** to the presence of pyrrolidine led to the targeted epimeric mixture of chromanones **18a** and **18b** in excellent yields, and the epimers could be separated by standard silica gel chromatography. At this point, we were unable to determine the configuration of ketones **18a** and **18b** at C-9 either by NMR spectroscopy or by circular dichroism studies. Fortunately, we obtained appropriate crystals of the less-polar diastereomer **18a**. The molecular structure of **18a** was obtained from single-crystal X-ray diffraction data.[18] The structure of **18a** was solved and refined in the monoclinic space group P_{21}. Details of the data collection and structure refinement are summarized in Table S1 in the Supporting Information. The unit cell contains two identical molecules of **18a** in the asymmetric unit, as can be observed in Figure 2.

To continue with our synthetic approach, we chose randomly the less-polar isomer **18a**, as Motti et al. did not assign any configuration in their report of the isolation of metachromin U.[4] To conclude the synthesis of metachromin U from **18a**, the generation of the chromene was required. However, when we subjected the benzylic alcohol derived from **18a** to the same acidic conditions that generated the chromene scaffold in the synthesis of siccanochromene F, only the decomposition of the starting materials was observed, and this suggested that milder conditions would be required for this transformation. Thus, the diisobutylaluminium hydride (DIBALH) reduction of ketone **18a** and the subsequent treatment of the corresponding crude reaction mixture with mesyl chloride in pyridine led to the direct elimination of the mesylate group to produce chromene **3** after tetra-*n*-butylammonium fluoride (TBAF) induced silyl ether deprotection. The MS as well as the ^1H and ^{13}C NMR spectroscopy data of our synthetic metachromin U match completely those of the natural product. In addition, the sign of the optical rotation for the natural ($[\alpha]_D$ = +20.1, CH_2Cl_2) and synthetic metachromin U ($[\alpha]_D$



Scheme 5. Synthesis of (+)-metachromin U.

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

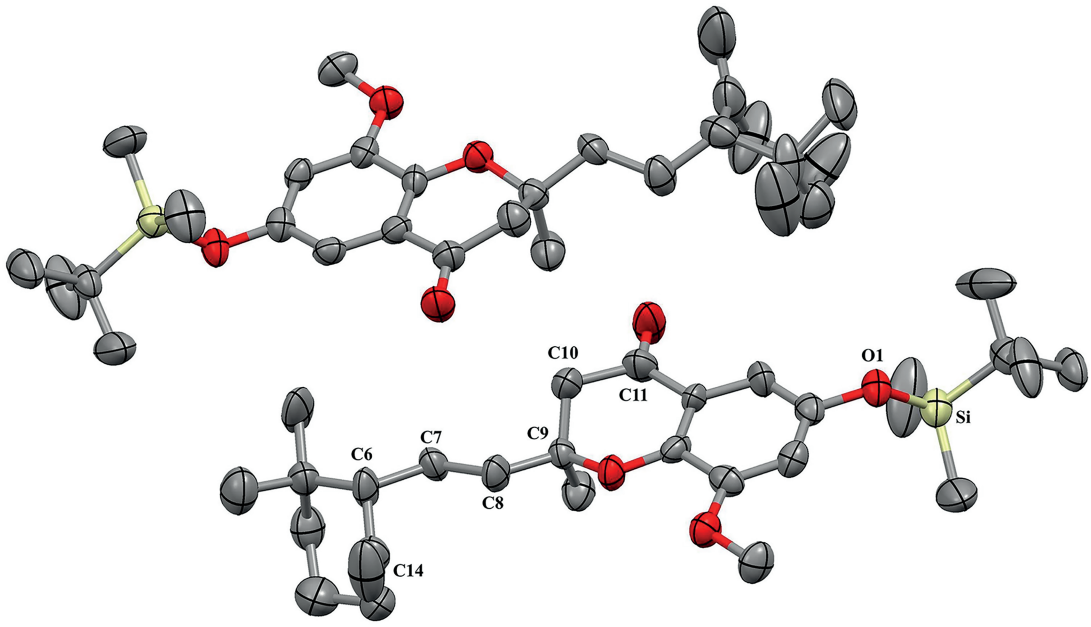
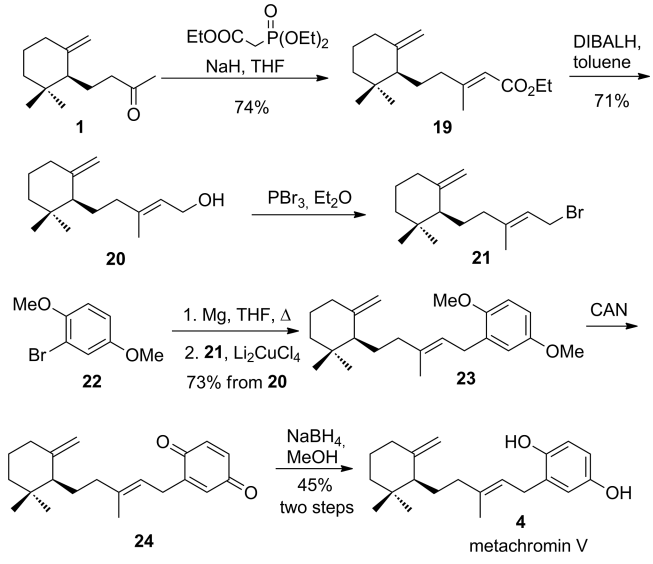


Figure 2. ORTEP perspective of **18a**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been removed for more clarity. Selected atoms have been labeled.

= +28, MeOH) coincide; therefore, the assignment of both the relative and the absolute configuration of the natural product is that shown in Scheme 5.

Metachromin V was the third of the molecules that we planned to expediently access from our common precursor **1** (Scheme 6). The application of the Horner–Wadsworth–Emmons protocol to **1** furnished the required two-carbon homologation. The corresponding unsaturated ester **19** was reduced with DIBALH to give **20** (74% in two steps). Alcohol **20** was treated with PBr_3 to give the allylic bromide **21**. The synthesis of the merosesquiterpene scaffold of metachromin V was attempted through the copper-catalyzed coupling of bromide **21** and the Grignard reagent derived from bromide **22** (Scheme 6). The bromide **22** was reacted with magnesium metal in THF under reflux for 30 min, and a solution of allylic bromide **21** and Li_2CuCl_4[19] was transferred into this mixture to afford the target coupling product **23** in an acceptable yield. The direct demethylation of **23** with sodium thiolate afforded partial deprotection and partial degradation of the starting material. Finally, demethylation to natural metachromin **4** was performed by ceric ammonium nitrate (CAN) oxidation of **23** to quinone **24** and subsequent reduction.[20] The spectroscopic data of synthetic **4** agree with those reported for the natural compound. As we were in the final phase of the drafting of this article, Serra et al. reported the enantioselective synthesis of metachromin V by a closely related protocol.[21]

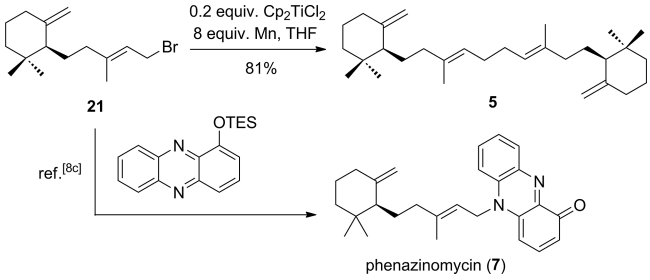
Continuing with our idea of proving the versatility of (+)-3,4-dihydro-γ-ionone as a precursor for the expedient synthesis of natural products, we addressed the synthesis of cyclosqualene dimer **5**. The key step in our approach to **5** was the Ti^{III}-catalyzed regioselective α,α′-homocoupling of allylic halide **21** through a protocol developed in our



Scheme 6. Synthesis of metachromin V.

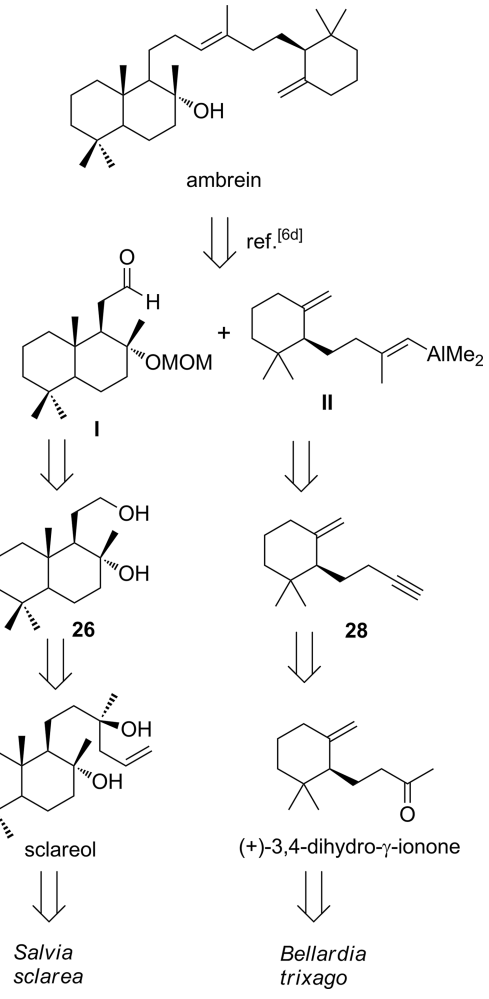
laboratories (Scheme 7).[22] The homocoupling reaction of allylic bromide **21** in the presence of catalytic quantities of Ti^{III} and an excess of Mn afforded **5** (54%), accompanied by the corresponding α,γ′ isomer (27%). Thus, compound **5** was synthesized from **1** in only three steps. The preparation of allylic bromide **21** in only three steps could also be applied to the formal synthesis of the antitumor antibiotic phenazinomycin (**7**), as Kitahara reported that the coupling of bromide **21** with the silyl ether derivative of the natural compound 1-hydroxyphenazine afforded phenazinomycin (**7**), although in low yields.[7d] It must be highlighted that the synthesis of allylic bromide **21** from (+)-3,4-dihydro-γ-ionone was achieved in only three steps, whereas Kitahara reported the generation of **21** in 23 steps.

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



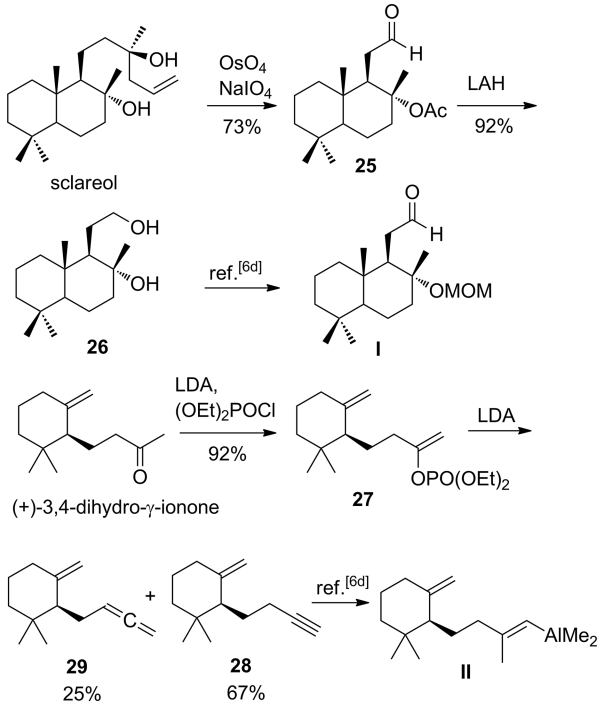
Scheme 7. Formal synthesis of phenazinomycin.

Finally, ambrein (**6**) was the last molecule to be prepared from (+)-3,4-dihydro-γ-ionone. Remarkably, the formal synthesis of ambrein was planned to involve the use of two renewable chiral starting materials (Scheme 8).



Scheme 8. Retrosynthetic analysis of ambrein.

Thus, although **1** would be the origin of the monocyclic part of ambrein, the bicyclic moiety of this triterpene was anticipated to originate from sclareol, a diterpenic natural product isolated from cultivated *Salvia sclarea* or recently produced by genetic engineering.[23] In our retrosynthetic analysis, the formal synthesis of ambrein required the interception of intermediates **24** and **26**, from which Mori[6d] generated the mono- and bicyclic synthons **I** and **II** in his convergent synthesis of ambrein (Scheme 9). It should be noted that this plant was successfully cultivated by some of us; thus, the sustainable availability of this compound is guaranteed.



Scheme 9. Formal synthesis of ambrein.

The synthesis of **26** from sclareol could be straightforwardly achieved by following a OsO_4-mediated catalytic protocol previously described by some of us[24] to degrade the sclareol lateral chain and afford acetoxyaldehyde **25**. The LAH reduction of **25** produced optically pure **26** in two steps from sclareol (Scheme 9). The monocyclic moiety needed for the synthesis of ambrein, that is, is terminal alkyne **28**, could be prepared from (+)-3,4-dihydro-γ-ionone by the protocol described by Negishi for the conversion of methyl ketones into terminal acetylenes.[25] However, the application of this one-step protocol failed to deliver the terminal alkyne and invariably led to the isomerization of the exocyclic double bond. The generation of the desired **28** was accomplished after the isolation of the corresponding enol phosphate intermediate **27** and the reaction of this derivative with only 1.1 equiv. of lithium diisopropylamide (LDA). Under these conditions, acetylene **28** was obtained in 67% yield, together with a 25% yield of allene **29**.

It should be remarked at this point that Mori employed 14 steps in the construction of intermediate **26** from geranylacetone (one separation of enantiomers included) and 17 steps to produce **28** from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone.

Conclusions

We have described an expedient process for the multigram production of (+)-3,4-dihydro-γ-ionone (**1**) from its natural source *B. trixago*. The capability of **1** to achieve

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

different natural products has been shown with the synthesis of siccanochromene F (**2**, four steps, 18.9% yield; 23.7% brsm), metachromins U (**3**, five steps, 22.0%) and V (**4**, six steps, 17.3% yield), and bicyclic squalene derivative (**5**, four steps, 28.2% yield) as well as the formal synthesis of ambrein (**6**; intermediate **24**: two steps, 67% yield; intermediate **26**: two steps, 61.6% yield), siccanin (**7**; intermediate **15**: four steps, 12.3% yield, 15.4% brsm), and phenazinomycin (**8**; intermediate **20**: two steps, 52.5% yield). Other elements of interest of this work include the optimization and mechanistic proposal for the organocatalyzed Kabbe reaction, the Ti^{III}-catalyzed homocoupling of allylic alcohol **19**, and the use of a second natural renewable source and enantiopure starting material in addition to **1** for the formal synthesis of ambrein.

Experimental Section

Full experimental data as well as characterization and NMR spectra of new compounds are given in the Supporting Information.

Acknowledgments

Financial support for this work was provided by the Junta de Andalucia (grant number P08-FQM-3596) and Ministerio de Economía y Competitividad (MEC) (grant number CTQ-2010-16818).

[1] a) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183; b) J. Wang, S.-G. Chen, B.-F. Sun, G.-Q. Lin, Y.-J. Shang, *Chem. Eur. J.* **2013**, *19*, 2539; c) H. Li, X. Wang, B. Hong, X. Lei, *J. Org. Chem.* **2013**, *78*; d) E. E. Anagnostaki, A. L. Zografos, *Chem. Soc. Rev.* **2012**, *41*, 5613; e) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nature Commun.* **2010**, *1*, 80; f) G. Valot, J. García, V. Duplan, C. Serba, S. Barluenga, N. Wissinger, *Angew. Chem. Int. Ed.* **2012**, *51*, 5391–5394; *Angew. Chem.* **2012**, *124*, 5487–5490; g) K. Foo, I. Ussi, D. C. G. Götz, E. W. Werner, D. Holte, P. Baran, *Angew. Chem. Int. Ed.* **2012**, *51*, 1–6; *Angew. Chem.* **2012**, *124*, 1.

[2] a) J.-T. de Pascual, E. Caballero, C. Caballero, M. Medarde, A. F. Barrero, M. Grande, *Tetrahedron* **1982**, *38*, 1837; b) A. F. Barrero, M. M. Herrador de Pino, P. Arteaga, H. J. Rodriguez Dieguez, WO 2010103145 A1, **2009**; c) A. F. Barrero, M. M. Herrador, P. Arteaga, A. Castillo, A. F. Arteaga, *Nat. Prod. Commun.* **2011**, *6*, 1.

[3] K. Hirai, K. T. Suzuki, S. Nozoe, *Tetrahedron* **1971**, *27*, 6057.

[4] S. P. B. Ovenden, J. L. Nielson, C. H. Liptrot, R. H. Willis, D. M. Tapiolas, A. D. Wright, C. A. Motti, *J. Nat. Prod.* **2011**, *74*, 1335.

[5] A. Behrens, P. Schaeffer, S. Bernasconi, P. Albrecht, *Geochim. Cosmochim. Acta* **2000**, *64*, 3327.

[6] a) G. Ohloff, in: *Fragrance Chemistry* (Ed.: E. T. Theimer), Academic Press, New York, **1982**, p. 535; b) M. Raza, M. S. Alorainy, A. A. Alghashm, *Food Chem. Toxicol.* **2007**, *45*, 1614; c) S. A. Taha, *Med. Sci. Res.* **1994**, *22*, 97; d) K. Mori, H. Tamura, *Liebigs Ann. Chem.* **1990**, 361; e) H. Tanimoto, T. Oritani, *Tetrahedron* **1997**, *53*, 3527; f) N. Fujiwara, M. Kinoshita, H. Akita, *Tetrahedron: Asymmetry* **2006**, *17*, 3037; g) D. Ueda, T. Hoshino, T. Sato, *J. Am. Chem. Soc.* **2013**, *135*, 18335.

[7] a) S. Funaama, S. Eda, K. Komiyama, S. Omura, T. Tokunaga, *Tetrahedron Lett.* **1989**, *30*, 3151; b) S. Omura, S. Eda, S. Funayama, K. Komiyama, Y. Takahashi, H. B. Woodruff, *J. Antibiot.* **1989**, *42*, 1037; c) S. Omura, S. Eda, S. Funayama, K. Komiyama, Y. Takahashi, H. B. Woodruff, *J. Antibiot.* **2010**, *63*, 579; d) Y. Kinoshita, T. Kitahara, *Tetrahedron Lett.* **1997**, *38*, 4993–4996.

[8] a) K. J. Ishibashi, *J. Antibiot., Ser. A* **1962**, *15*, 161; b) M. G. Belloti, L. Riviera, *Chimioterapia* **1985**, *4*, 431; c) N. Kitano, F. Kondo, K. Kusano, K. Ishibashi, US 3974291, **1976**; d) M. Matsuki, H. Hanatsu, T. Watanabe, A. Ogasawara, T. Mikami, T. Matsumoto, *Biol. Pharm. Bull.* **2006**, *29*, 919; e) T. Mogi, T. Kawakami, H. Arai, Y. Igarashi, K. Matsushita, M. Mori, K. Shiomi, S. Omura, S. Harada, K. Kita, *J. Biochem.* **2009**; *146*, 383; f) M. Kato, K. Heima, Y. Matsuma, A. Yoshikoshi, *J. Am. Chem. Soc.* **1981**, *103*, 2434; g) B. M. Trost, F. J. Fleitz, W. J. Watkins, *J. Am. Chem. Soc.* **1996**, *118*, 5146; h) B. M. Trost, H. C. Shen, J. P. Surivet, *Angew. Chem. Int. Ed.* **2003**, *42*, 3943; *Angew. Chem.* **2003**, *115*, 4073; i) B. M. Trost, H. C. Shen, J. P. Surivet, *J. Am. Chem. Soc.* **2004**, *126*, 12565.

[9] a) L. Ružička, C. F. Seidel, M. Pfeiffer, *Helv. Chim. Acta* **1948**, *31*, 827; b) A. F. Barrero, J. F. Sanchez, F. G. Cuenca, *Phytochemistry* **1988**, *27*, 3676.

[10] a) H. J. Kabbe, *Synthesis* **1978**, 886; b) H. J. Kabbe, A. Widdig, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 247; *Angew. Chem.* **1982**, *94*, 254.

[11] a) For reviews, see: C. Grondal, M. Jeanty, D. Enders, *Nature Chemistry* **2010**, *2*, 167; b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[12] a) D. Sánchez, D. Bastida, J. Burés, C. Isart, O. Pineda, J. Vilarrasa, *Org. Lett.* **2012**, *14*, 536; b) although the rates of enamine formation of acetophenone and alkyl ketones are similar according to ref.[12a], the fact that **10** is electronically different to acetophenone could account for the observed selective enamine formation.

[13] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 541.

[14] a) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; *Angew. Chem.* **2006**, *118*, 8042; b) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248; c) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354 and references cited therein.

[15] a) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047; b) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807; c) Z. Jiang, Z. Liang, X. Wua, Y. Lu, *Chem. Commun.* **2006**, 2801.

[16] a) G. A. Crispino, K. B. Sharpless, *Tetrahedron Lett.* **1992**, *33*, 4273; b) E. J. Corey, M. C. Noe, S. Lin, *Tetrahedron Lett.* **1995**, *36*, 8741; c) E. J. Corey, J. Zhang, *Org. Lett.* **2001**, *3*, 3211.

[17] T. H. Simpson, *J. Org. Chem.* **1963**, *28*, 2107.

[18] CCDC-980367 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. For additional X-ray data, see Supporting Information.

[19] M. Lang, W. Stieglich, *Synthesis* **2005**, *5*, 1019.

[20] T. Yoshimura, H. Kisyuku, T. Kamei, K. Takabatake, M. Shindo, K. Shishido, *ARKIVOC (Gainesville, FL, U.S.)* **2003**, 247.

[21] a) S. Serra, A. A. Cominettia, V. Lissoni, *Nat. Prod. Commun.* **2014**, *9*, 303.

[22] A. F. Barrero, M. M. Herrador, J. F. Quílez del Moral, P. Arteaga, J. Arteaga, M. Piedra, E. M. Sánchez, *Org. Lett.* **2005**, *7*, 2301.

[23] M. Schalk, L. Pastore, M. A. Mirata, S. Khim, M. Schouwey, F. Deguerry, V. Pineda, L. Rocci, L. Daviet, *J. Am. Chem. Soc.* **2012**, *134*, 18900.

[24] A. F. Barrero, E. A. Manzaneda, J. Altarejos, S. Salido, J. M. Ramos, M. S. Simmonds, W. M. Blaney, *Tetrahedron* **1995**, *51*, 7435.

[25] E. Negishi, A. O. King, J. M. Tour, *Org. Synth.* **1986**, *64*, 44–49.

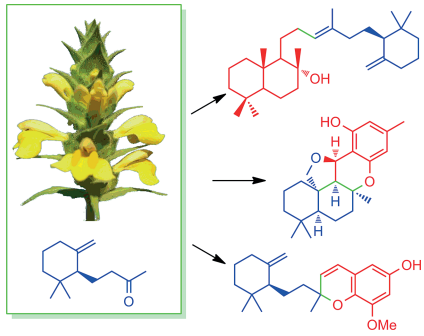
Received: February 12, 2015
Published Online: ■

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

EurJOC European Journal of Organic Chemistry

Natural Products

The expedient enantioselective synthesis of several natural products from a common precursor, (+)-3,4-dihydro-γ-ionone, is described. The production of this natural compound in multigram scale from the extract *Bellardia trixago* is the basis of this approach.



A. Castillo, L. Silva, D. Briones, J. F. Quílez del Moral,* A. F. Barrero*

Keywords: Natural products / Organocatalysis / Molecular diversity / Chiral pool

 © 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim