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Biomimetic Synthesis of (+)-Ledene, (+)-Viridiflorol, (−)-Palustrol, (+)-Spathulenol, and Psiguadial A, C, and D via the Platform Terpene (+)-Bicyclogermacrene

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Abstract: (+)-Bicyclogermacrene is a strained bicyclic and common sesquiterpene found in several essential oils. A short and good yielding synthesis of bicyclogermacrene proceeding in seven steps is reported. This terpene is used as key platform intermediate for a biomimetic access to several aromadendrene sesquiterpenoids, such as ledene, viridiflorol, palestrol, and spathulenol. Furthermore, bicyclogermacrene is shown to be the terpene component in the synthesis of the meroterpenoids psiguadial A, C, and D.

Introduction

Terpenoids constitute one of the largest natural product families,[1] with an important economic value, for example, as flavours, fragrances, spices, and drugs.[2] The biosynthesis of terpenoids is commonly divided into two phases: the cyclase and the oxidase phase.[3] The cyclase phase converts a linear precursor into the particular cyclic scaffold. During the oxidase phase, sequential C=C and C–H bond oxidations transform the hydrocarbon into the individual terpenoid accounting for the functional group diversity within a terpenoid family. Meroterpenoids belong to a large subgroup of natural products with a mixed polyketide terpenoid origin.[4] Recently, a family of meroterpenoids, the psiguadials A (**1**), C (**2**), and D (**3**) were isolated from *psidium guajava*, an important food crop (fruits) and medicinal plant (leaves and bark) in the tropical and subtropical regions (Figure 1).[5] The psiguadials are structurally related to the macrocarpals that were isolated from *eucalyptus globulus*,[6] pointing towards a similar biosynthetic origin. Several members of these meroterpenoids are associated with interesting biological properties, such anti-HIV[6b] and antibacterial activity,[6a,c] as well as inhibition of aldol reductase[6e,f] and glucosyl transferase.[6h] However, their mode of action and potential molecular targets so far have remained elusive. Biosynthetically, they are hypothesized to derive from phloroglucinol derivatives and the terpene bicyclogermacrene (**4**) (Scheme 1).[6b,7]

Moreover, a wide range of terpenoids are postulated to originate biosynthetically from bicyclogermacrene.[7–9] The aromadendranes are a family of hydroazulene compounds that occur at different oxidation levels (Figure 2). These compounds are found in plants and show cytotoxic,[10a] antiviral,[10b,c] antibacterial,[10d,e] and antifungal[10f] properties. A point to note is that aromadendrenes with opposite absolute configurations have been isolated from corals.[11]

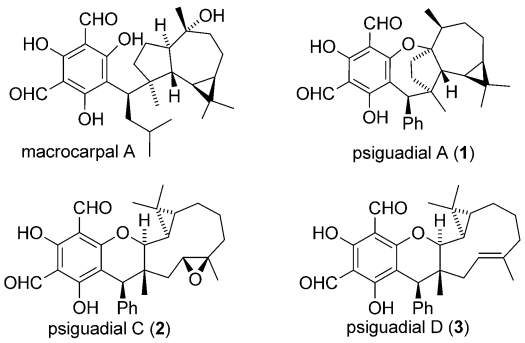

Figure 1. Selected meroterpenoids built from a phloroglucine and a sesquiterpene unit.

We reasoned that an access to substantial amounts of bicyclogermacrene would constitute an ideal platform to initiate synthetic efforts based on biomimetic strategies. Such bioinspired synthesis would not only constitute an efficient access to individual natural products but would also allow us to confirm their proposed biosynthetic pathway for this terpenoid family. Herein, we report a concise synthesis of (+)-bicyclogermacrene and its use as a platform intermediate to access a range of terpenoids and meroterpenoids.

Synthesis of (+)-bicyclogermacrene

Although bicyclogermacrene (**4**) is a rather frequently occurring constituent of essential oils from various plants,[8] it is neither commercially available nor has received significant attention in the synthetic community. So far, there is only a single

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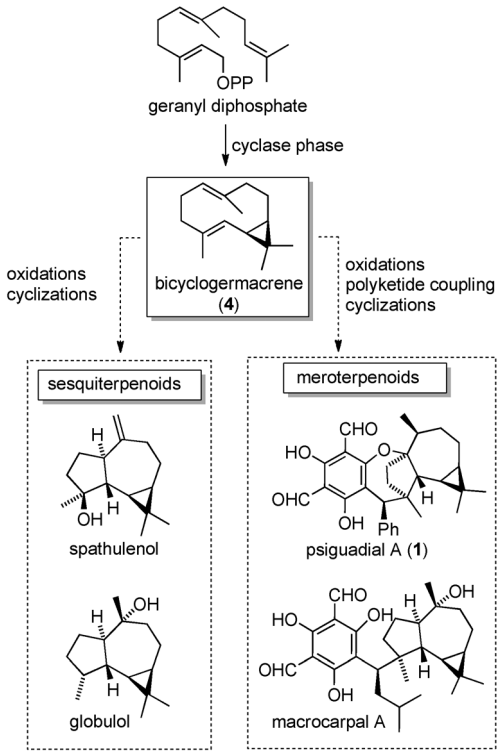


Scheme 1. Bicyclogermacrene as a potential platform intermediate for macrocarpals/psiguadials meroterpenoids and aromadendrane sesquiterpenoids.

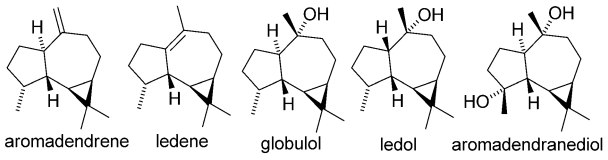
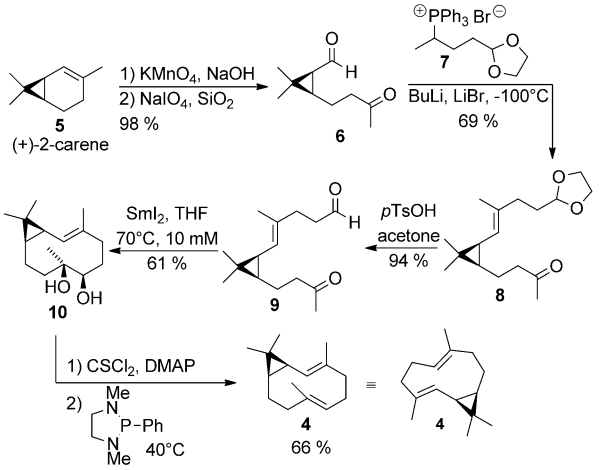


Figure 2. Selected aromadendrene terpenes and terpenoids.

racemic synthesis reported by McMurry, which has both diastereoselectivity and scalability shortcomings.[9] Thus any exploration of terpenoid and meroterpenoid synthesis such as the psiguadials requires first an efficient synthesis securing reliably sufficient quantities of bicyclogermacrene. Despite being a rather small hydrocarbon, bicyclogermacrene bears several noteworthy synthetic challenges. The molecule consists of a strained 10-membered ring that contains two *trans*-olefins and a highly substituted *cis*-cyclopropane, which makes a selective ring-closure a demanding task. Our initial approaches involving different ring-closing metathesis or intramolecular cyclopropanation strategies failed without giving any traces of cyclized products. The successful route started from commercially available (+)-2-carene (**5**), which was smoothly converted to ketoaldehyde **6** by $KMnO_4$-mediated dihydroxylation and subsequent oxidative diol cleavage by periodate (Scheme 2). Subsequently, Wittig olefination with the ylide derived from phosphonium salt **7** gave ketone **8** in 69% yield under carefully controlled conditions. A point to note is that the ylide needs to be generated with butyl lithium in the presence of lithium bromide to assure reproducible results. The olefination itself



Scheme 2. Synthesis of (+)-bicyclogermacrene **4**. DMAP = 4-dimethylaminopyridine.

has to be conducted at −100 °C to be stereoselective. Higher reaction temperatures, or an alteration of the base or solvent, compromised the *E*/*Z* ratio. For instance, a higher reaction temperature of −78 °C gave an inseparable *E*/*Z* 5:1 mixture. Furthermore, double olefinations, or base-promoted intramolecular aldol condensation, became an issue. Subsequently, the dioxolane moiety was cleaved under acidic conditions, revealing the aldehyde group and setting the stage for the critical cyclization step. While direct cyclization to the olefin by using McMurry or related couplings failed, a selective two-step procedure was successful. Under optimized conditions, reproducible results were obtained with 2.5 equivalents of freshly prepared samarium diiodide in THF, giving 10-membered cyclic diol **10** in 61% yield. The reaction is completely diastereoselective and X-ray crystallographic analysis confirmed a *syn*-relationship between the two newly formed OH groups (Figure 3).[12] The configuration of the two hydroxyl groups is favorable for the anticipated *syn*-elimination process providing the required *E*-olefin geometry. In this respect, the double bond was installed by a modified Corey–Winter protocol. Warming the formed thiocarbonate in neat 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine at 40 °C induced smooth fragmentation.[13] The acid labile and rather volatile (+)-bicyclogermacrene (**4**) was obtained in 66% yield by rapid elution of the adsorbed reaction mixture on Florisil with pentane. The use of

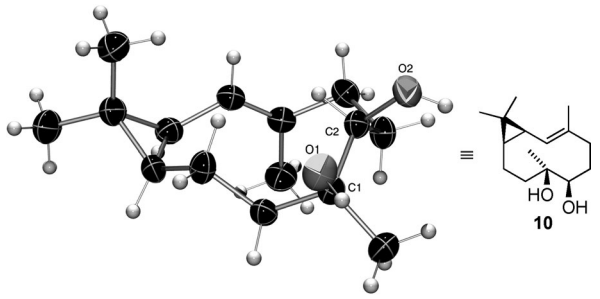
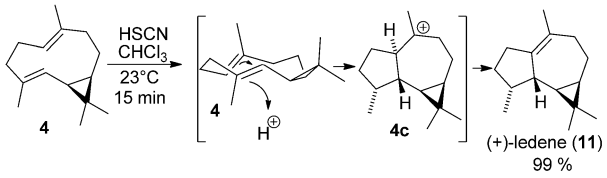


Figure 3. ORTEP representation of diol intermediate **10** (ellipsoids at 50%).

standard silica gel purification techniques rapidly decomposes **4**. Finally, the synthesis could be scaled to give 600 mg batches of **4** in 25% overall yield and in seven steps.

Synthesis of (+)-ledene and the terpenoids (+)-viridiflorol, (−)-palustrol and (+)-spathulenol

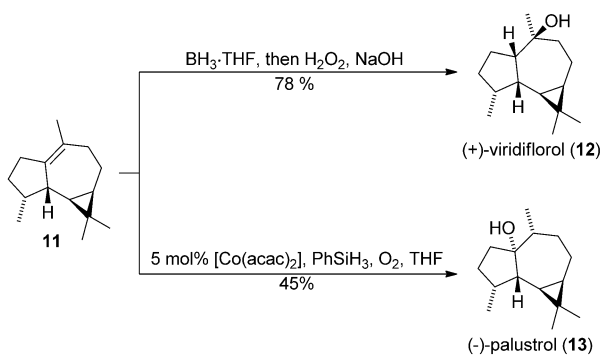
Earlier work[8] and modelling of bicyclogermacrene conformations[14] clearly indicate a higher accessibility and reactivity of the olefin moiety proximal to the cyclopropyl group towards electrophilic reagents. A brief exposure of bicyclogermacrene (**4**) to mildly acidic conditions induced a fast cyclization (Scheme 3). For instance, the terpene (+)-ledene (**11**)[15] is



Scheme 3. Cationic cyclization of bicyclogermacrene (**4**) to (+)-ledene (**11**).

formed in a virtually quantitative manner upon exposure to diluted hydrothiocyanic acid (a wider range of other acids provides **11** as well). The intermediate carbenium ion **4c** undergoes exclusive *endo*-elimination forming the tetrasubstituted olefin.

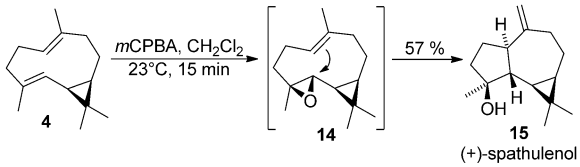
Ledene **11** was next exposed to different hydration strategies to access different aromadendranols. For instance, hydroboration of **11** with borane followed by oxidative workup provided (+)-viridiflorol (**12**) with a *cis*-configured ring junction in 78% yield (Scheme 4). The reaction is completely regio- and diastereoselective resulting from an approach of BH_3 from the more accessible convex face and an orientation of the borane away from the ring junction. To alter the diastereoselectivity of the hydration event, we exposed **11** to Mukaiyama's cobalt-catalyzed phenylsilane/O_2 hydration method.[16] Intriguingly, these conditions reverse the regiochemistry providing the hydroxyl group at the ring junction. Presumable due to the inter-



Scheme 4. Selective hydration of (+)-ledene provides (+)-viridiflorol (**12**) and (−)-palustrol (**13**). acac = acetylacetonate.

mediary radical species,[18] the addition is *trans*-selective and the product could be identified as (−)-palustrol (**13**).[18]

Next, we evaluated direct oxidative cyclization modes of bicyclogermacrene which should provide a manifold to further rearranged terpenoids. Indeed, exposure of **4** to *m*CPBA at ambient temperature led to a very fast consumption of starting material (Scheme 5). Putative epoxide **14** could not be detected. Instead, its tricyclic compound **15**, identified as (+)-spathulenol,[19] was isolated as a sole product in 57% yield. Conformationally enforced selective epoxidation triggers the intramolecular cyclization and subsequent elimination to give the *exo*-double bond of **15**. With the often observed simultaneous presence of both spathulenol and bicyclogermacrene in their



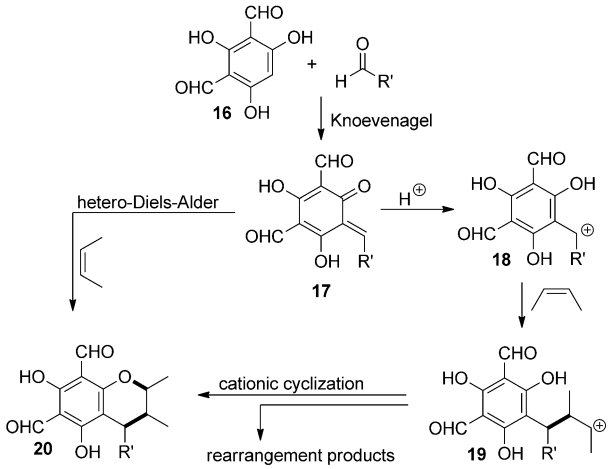
Scheme 5. Oxidative cyclization of bicyclogermacrene (**4**) to (+)-spathulenol (**15**). *m*CPBA = *meta*-chloroperbenzoic acid.

natural sources, a similar oxidative pathway probably occurs in the spathulenol biosynthesis.[20]

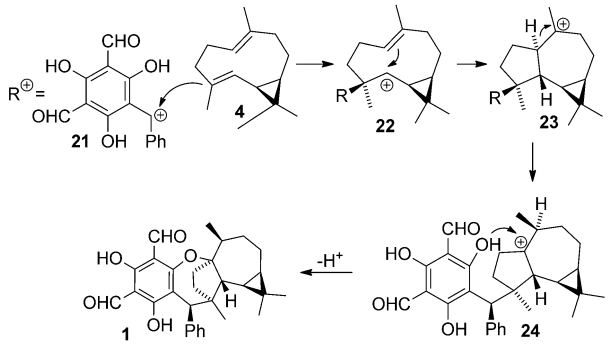
Biomimetic approach to meroterpenoids: Synthesis of psiguadial A, C and D

We next turned our focus towards meroterpenoids that are potentially built from a coupling process involving a bicyclogermacrene unit and an electron-rich aromatic phloroglucinol part. The aromatic part derives from the polyketide metabolism and constitutes a condensation product between doubly formylated phloroglucinol **16** and an aliphatic or aromatic aldehyde. Knoevenagel-type condensation gives *o*-quinone methide **17** (Scheme 6). Such *o*-quinone methides are reactive substrates engaging in hetero-Diels–Alder reactions as previously shown for related meroterpenoids.[7,21] However, the highly stabilized carbenium ion **18** (generated by loss of water from the aldol intermediate or by protonation of **17**) might allow for alternative and divergent pathways. While such a cyclization pathway might be stereochemically less clean, it could allow for typical carbocation rearrangements providing additional products.

In this respect, members of the psiguadial and macrocarpal structural family could be targeted by using bicyclogermacrene **4** in the cationic cyclization cascade.[6b,7] For instance, psiguadial D could be reached by the direct hetero-Diels–Alder pathway and psiguadial A might originate from the electrophilic cascade cyclization (Scheme 7). After the initial cyclization step leading to tertiary carbenium **23**, either direct Wagner–Meerwein shift or elimination similar to the aforementioned synthesis of ledene followed by a protonation would give carbenium ion **24**. Subsequent intramolecular attack of the phenolic OH group would give psiguadial A (**1**).

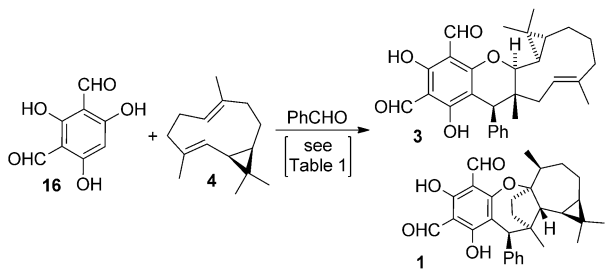


Scheme 6. Potentially diverging reaction pathway of *o*-quinone methide coupling with olefins.



Scheme 7. Proposed biosynthesis of psiguadial A (**1**).

The required *o*-quinone methide species is commonly prepared in situ by a Knoevenagel condensation between phenol **16** and benzaldehyde (Scheme 8).[21] However, when the reported conditions by Bharate and Singh for the robustadial A and B synthesis were employed,[22] no traces of any meroterpenoid product were detected and only unspecific decomposition occurred (Table 1, entry 1). A similar non-productive outcome was observed with the modified conditions (water and a surfactant) that were used by Lee and co-workers for the synthesis of psidial A and guajadial (entry 2).[23] We attribute this failure to the significantly more sensitive nature of bicyclogermacrene relative to the previously employed more robust terpenes β-pinene and caryophyllene. Therefore, milder reaction conditions and lower reaction temperatures would be required to utilize bicyclogermacrene as the nucleophilic terpene component for this three-component coupling.



Scheme 8. Three-component coupling between bicyclogermacrene (**4**), benzaldehyde and phloroglucinol **16**.

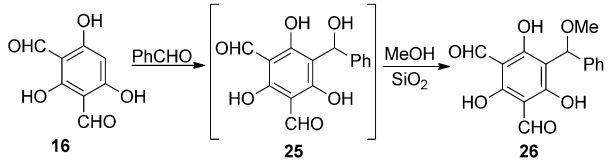
Table 1. Selected optimization studies for the meroterpenoid assembly.[a]

Entry	Solvent (*T* [°C], *t* [h])	Cat.	Yield of **3**[b]	Yield of **1**[b]
1	AcOH (80 °C, 2 h)	NaOAc	0	0
2	H_2O (100 °C, 15 h)	PTS	0	0
3	HFIP (25 °C, 1 h)	DMEDA	7	1
4	TFE (25 °C, 1 h)	DMEDA	10	0
5	none (25 °C, 1 h)	DMEDA	0	0
6	HFIP (25 °C, 1 h)	EDDA	0	0

[a] Reaction conditions: **20** (6.0 μmol), catalyst (20 mol%), PhCHO (3 equiv), **4** (3 equiv), 0.5 M in the indicated solvent. [b] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the standard. DMEDA = dimethylethylenediamine; PTS = PEG-600/R-Tocopherol-based diester of Sebacic acid.

Further extensive screening of the reaction conditions revealed that a combination of the highly polar protic solvent hexafluoroisopropanol (HFIP) with a secondary diamine catalyst provided, for the first time, the desired products. In this respect, a reaction of compound **16** in the presence of three equivalents of benzaldehyde and bicyclogermacrene gave, with 20 mol% dimethylethylene diamine catalyst at ambient temperature, two cycloadducts (Table 1, entry 3). Subsequent purification by silica gel chromatography followed by reversed-phase HPLC gave psiguadial D (**3**) (7%) and A (**1**) (1%). Switching the solvent to trifluoroethanol (TFE) gave psiguadial D in slightly higher yield, but with no formation of psiguadial A (entry 4). Solvent-free conditions or the use of EDDA (ethylenediammonium diacetate) as a condensation catalyst completely inhibited the reaction (entries 5–6). The very low yield of psiguadial A obtained in this transformation is not suitable for a practical synthetic purpose, but its appearance only with the most polar and acidic solvent can be seen as a first experimental evidence for the biosynthetic assembly of psiguadial A by the hypothesized bicyclogermacrene cationic cyclization cascade.

The complexity of the cascade reaction and the resulting modest yields caused by the lability of **4** under the requisite reaction conditions required a further adaption of the coupling strategy. Therefore, we anticipated that a separation of the *o*-quinone methide formation step and the following hetero-Diels–Alder reaction might mitigate this problem. However, the high reactivity of *o*-quinone methides generally precludes their isolation. We hypothesized that omitting the dienophile and running the initial condensation reaction in methanol might convert the transient *o*-quinone methide into ether **26** by 1,4-addition. However, the elimination of water from alcohol **25** to give **17** proceeded only in contact with silica gel. Addition of methanol provided in turn the desired ether **26** after chromatographic purification (Scheme 9). The nature of species **26** could be confirmed by X-ray crystallographic analysis (Figure 4).[24]



Scheme 9. Generation of *o*-quinone methide precursor (**26**).

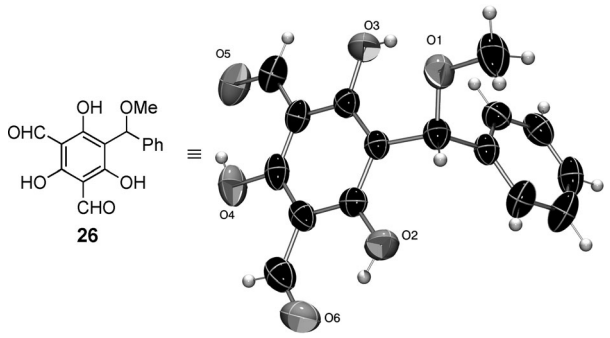
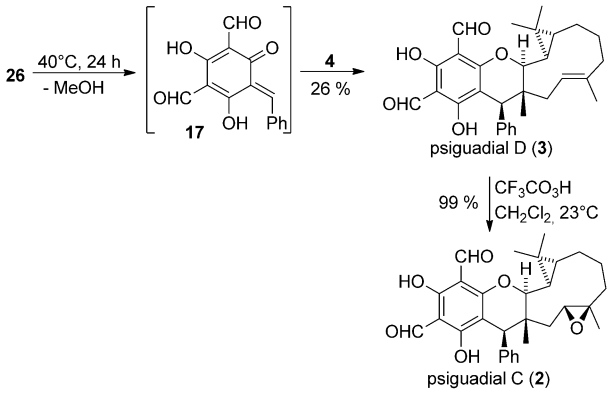


Figure 4. ORTEP representation of *o*-quinone methide precursor **26** (ellipsoids at 50%).

Although compound **26** is isolable and reasonably stable, warming it at 40 °C for a prolonged time without any catalyst prompted elimination of methanol to the *ortho*-quinone methide, which in turn reacted in the presence of bicyclogermacrene to psiguadial D (Scheme 10). With these reaction conditions, psiguadial D is the only formed product that is obtained in an improved 26% yield. Subsequently, exposure of psiguadial D (**3**) to trifluoroperacetic acid at ambient temperature resulted in complete diastereoselective epoxidation and provided psiguadial C (**2**) in an excellent yield. The observed diastereoselectivity can be rationalized by an approach of the peracid epoxidation reagent from the peripheral face of the 10-membered ring of **3**.



Scheme 10. Synthesis of psiguadial D (**3**) and C (**2**).

Conclusion

We have devised a brief seven-step synthesis of the terpene (+)-bicyclogermacrene and demonstrated its utility as a platform intermediate for the biomimetic syntheses of several terpenoids and members of phloroglucinol terpene adducts. These findings provide a solid support for the biosynthetic origin of this class of natural products. The accessibility of these compounds enables new studies of their pharmacological activity profile and molecular targets.

Acknowledgements

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Keywords: bicyclogermacrene · biomimetic synthesis · cyclization · natural products · terpenes

[1] F. Chen, D. Tholl, J. Bohlmann, E. Pichersky, *Plant J.* **2011**, *66*, 212 – 229.
[2] a) E. Breitmaier in Terpenes: Flavors, Fragrances, Pharmaca, Pheromones WILEY-VCH, Weinheim, **2006**; b) P. M. Dewick, Medicinal natural products: a biosynthetic approach, 3rd ed., Wiley, Hoboken, **2008**.
[3] a) E. M. Davis, R. Croteau, *Top. Curr. Chem.* **2000**, *209*, 53 – 95; for examples of synthetic applications of this concept, see: b) K. Foo, I. Usui, D. C. G. Götz, E. W. Werner, D. Holte, P. S. Baran, *Angew. Chem.* **2012**, *124*, 11659 – 11663; *Angew. Chem. Int. Ed.* **2012**, *51*, 11491 – 11495; c) G. Valot, J. Garcia, V. Duplan, C. Serba, S. Barluenga, N. Winssinger, *Angew. Chem.* **2012**, *124*, 5487 – 5490; *Angew. Chem. Int. Ed.* **2012**, *51*, 5391 – 5394.
[4] a) T. J. Simpson, *Chem. Soc. Rev.* **1987**, *16*, 123 – 160; b) J. Stauntona, K. J. Weissmana, *Nat. Prod. Rep.* **2001**, *18*, 380 – 416; c) J. Achkar, M. Xian, H. Zhao, J. W. Frost, *J. Am. Chem. Soc.* **2005**, *127*, 5332 – 5333.
[5] a) M. Shao, Y. Wang, Z. Liu, D. M. Zhang, H. H. Cao, R. W. Jiang, C. L. Fan, X. Q. Zhang, H. R. Chen, X. S. Yao, W. C. Ye, *Org. Lett.* **2010**, *12*, 5040 – 5043; b) M. Shao, Y. Wang, Y. Q. Jian, X. J. Huang, D. M. Zhang, Q. F. Tang, R. W. Jiang, X. G. Sun, Z. P. Lv, X. Q. Zhang, W. C. Ye, *Org. Lett.* **2012**, *14*, 5262 – 5265.
[6] a) M. Murata, Y. Yamakoshi, S. Homma, K. Aida, K. Hori, Y. Ohashi, *Agr. Biol. Chem.* **1990**, *54*, 3221 – 3226; b) M. Nishizawa, M. Emura, Y. Kan, H. Yamada, K. Ogawa, N. Hamanaka, *Tetrahedron Lett.* **1992**, *33*, 2983 – 2986; c) Y. Yamakoshi, M. Murata, A. Shimizu, S. Homma, *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1570 – 1576; d) H. Satoh, H. Etoh, N. Watanabe, H. Kawagishi, K. Arai, K. Ina, *Chem. Lett.* **1992**, 1917 – 1920; e) M. Murata, Y. Yamakoshi, S. Homma, K. Arai, Y. Nakamura, *Biosci. Biotechnol. Biochem.* **1992**, *56*, 2062 – 2063; f) K. Osawa, H. Yasuda, H. Morita, K. Takeya, H. Itokawa, *Phytochemistry* **1995**, *40*, 183 – 184; g) I. P. Singh, H. Etoh, *Biosci. Biotechnol. Biochem.* **1995**, *59*, 2330 – 2332; h) K. Osawa, H. Yasuda, H. Morita, K. Takeya, H. Itokawa, *J. Nat. Prod.* **1996**, *59*, 823 – 827.
[7] For a biosynthetic proposal of macrocarpals, see: E. L. Ghisalberti, *Phytochemistry* **1996**, *41*, 7 – 22.
[8] a) K. Nishimura, N. Shinoda, Y. Hirose, *Tetrahedron Lett.* **1969**, *10*, 3097 – 3100; b) J. D. H. Connolly, R. A. Hill, *Dictionary of terpenoids.* Chapman and Hall, **1991**.
[9] a) J. E. Mcmurry, G. K. Bosch, *J. Org. Chem.* **1987**, *52*, 4885 – 4893; b) J. E. Mcmurry, G. K. Bosch, *Tetrahedron Lett.* **1985**, *26*, 2167 – 2170.
[10] a) Z.-S. Su, S. Yin, Z.-W. Zhou, Y. Wu, J. Diang, J.-M. Yue, *J. Nat. Prod.* **2008**, *71*, 1410 – 1413; b) M. Nishizawa, M. Emura, Y. Kan, H. Yamada, K. Ogawa, N. Hamanaka, *Tetrahedron Lett.* **1992**, *33*, 2983 – 2986; c) N. De Tommasi, C. Pizza, C. Conti, N. Orsi, M. L. Stein, *J. Nat. Prod.* **1990**, *53*, 830 – 835; d) C. Gaspar-Marques, M. F. Simoes, B. Rodriguez, *J. Nat. Prod.* **2004**, *67*, 614 – 621; e) Y. Yamakoshi, M. Murata, A. Shimizu, S. Homma, *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1570 – 1576; f) I. C. Moreira, J. H. G.

Lago, N. C. M. Young, N. F. Roque, *J. Braz. Chem. Soc.* **2003**, *14*, 828 – 831.
[11] C. M. Beechan, C. Djerassi, H. Eggert, *Tetrahedron* **1978**, *34*, 2503 – 2508.
[12] CCDC-997208 (**10**) 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.
[13] a) E. J. Corey, R. A. E. Winter, *J. Am. Chem. Soc.* **1963**, *85*, 2677 – 2678; b) E. J. Corey, B. Hopkins, *Tetrahedron Lett.* **1982**, *23*, 1979 – 1982.
[14] a) K. Takeda, I. Horibe, H. Minato, *J. Chem. Soc. D* **1971**, 308 – 308; b) K. Nishimura, I. Horibe, K. Tori, *Tetrahedron* **1973**, *29*, 271 – 274; c) F. Orsini, F. Pelizzoni, L. Verotta, *Theochem-J Mol. Struc.* **1993**, *284*, 67 – 74.
[15] R. Faure, A. R. P. Ramanoelina, O. Rakotonirainy, J. P. Bianchini, E. M. Gaydou, *Magn. Reson. Chem.* **1991**, *29*, 969 – 971.
[16] S. Isayama, T. Mukaiyama, *Chem. Lett.* **1989**, *18*, 1071 – 1074.
[17] T. Tokuyasu, S. Kunikawa, A. Masuyama, M. Nojima, *Org. Lett.* **2002**, *4*, 3595 – 3598.
[18] NMR spectroscopic studies on the structure of palustrol: C. J. Cheer, D. H. Smith, C. Djerassi, *Tetrahedron* **1976**, *32*. 1807 – 1810; Correction of the configuration of palustrol: J.-C. Braekman, D. Daloze, C. Stoller, *Bull. Soc. Chim. Belg.* **1989**, *11*, 869 – 875.
[19] a) R. C. Bowyer, P. R. Jefferies, *Chem. Ind.* **1963**, 1245 – 1246; b) F. Inagaki, A. Abe, *J. Chem. Soc. Perkin Trans. 2* **1985**, 1773 – 1778; c) F. P. Van Lier, T. G. M. Hesp, L. M. Vanderlinde, A. J. A. Vanderweerdt, *Tetrahedron Lett.* **1985**, *26*, 2109 – 2110.
[20] M. Toyota, H. Koyama, M. Mizutani, Y. Asakawa, *Phytochemistry* **1996**, *41*, 1347 – 1350.
[21] Recent review on *o*-quinone methides: N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160 – 9173.
[22] S. B. Bharate, I. P. Singh, *Tetrahedron Lett.* **2006**, *47*, 7021 – 7024.
[23] A. L. Lawrence, R. M. Adlington, J. E. Baldwin, V. Lee, J. A. Kershaw, A. L. Thompson, *Org. Lett.* **2010**, *12*, 1676 – 1679.
[24] CCDC-997209 (**26**) 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.

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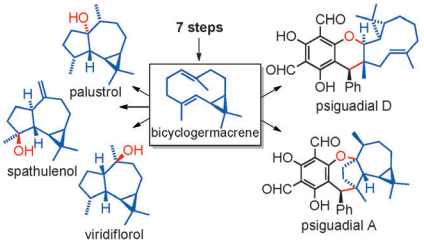
FULL PAPER

Let nature be your guide! A concise synthesis of the terpene (+)-bicyclogermacrene enables its use as a platform for a fast access to a range of different terpenoids of the aromadendrene family and meroterpenoids of the psiguadial family (see scheme).



Natural Products

*D. N. Tran, N. Cramer**

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Biomimetic Synthesis of (+)-Ledene, (+)-Viridiflorol, (−)-Palustrol, (+)-Spathulenol, and Psiguadial A, C, and D via the Platform Terpene (+)-Bicyclogermacrene