Synthesis of Phenolic Components of Grains of Paradise

By Hiroyuki Hattori,[a] Tohru Mitsunaga,[a] Derrick L. J. Clive*[b]

[a]*The United Graduate School of Agricultural Science, Gifu University, 1-1 Yanagido, 10 501-1193, Gifu, Japan*

[b]*Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada*

ABSTRACT: Two vanilloids, (5*E*)-8-(4-hydroxy-3-methoxyphenyl)oct-5-en-4-one (**1**) and 4-[3-hydroxydecyl]-2-methoxyphenol (**2**), isolated from the dried seeds of Grains of Paradise (*Aframomum melegueta*), were synthesized; the latter compound was made as the *S*-enantiomer and the material derived from the seeds was found to be a 1:1.7 mixture of the *R* and *S* isomers. The synthetic route used should allow the preparation of analogs having extended alkyl chains and consequently different lipophilicity, and **3**, a homolog of **2**, was also prepared.

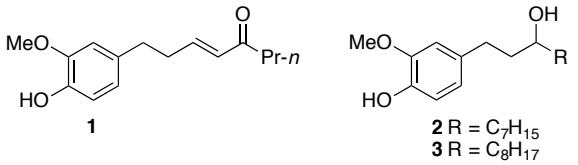
Keywords:
Grains of Paradise
anti-obesity
malic acid
Wittig reaction
Horner-Wadsworth Emmons olefination
Hydrogenolyis

*Corresponding author.
E-mail address: derrick.clive@ualberta.ca

Introduction

Grains of Paradise is one of the names given[1] to the dried seeds of the tropical plant *Aframomum melegueta*, which is widely distributed throughout West Africa. The seeds have long been used in folkloric herbal remedies[2] and are known to have, among other properties, antioxidant,[3] antibacterial[4] and antinociceptive[1] activity. In preliminary studies[5] it was found that intake of a methanol extract of Grains of Paradise has an anti-obesity effect in mice and lowers hepatic and serum fats. A reduction in visceral fat has also been observed in humans, using an ethanol extract.[6] Some of the phenolic compounds present in the seeds[7] were also isolated[8] and found to

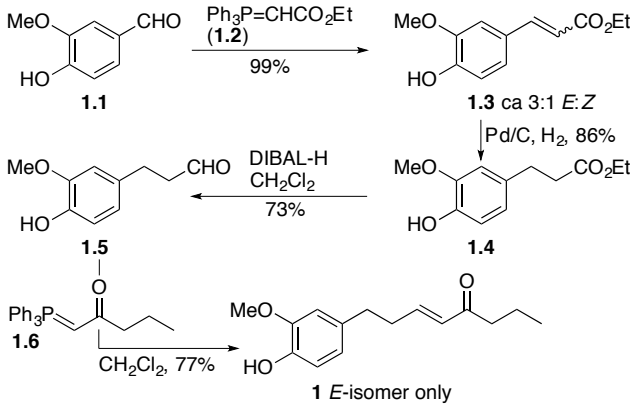
share structural features with vanilloids that were already known[9] to have anti-obesity properties. Consequently, it was of interest to establish if the vanilloids from *Aframomum melegueta* were responsible for the anti-obesity effect. Most of the compounds could be isolated in adequate quantities and several were found to possess anti-obesity properties,[10] but the isolated amounts of the vanilloids **1**[8] and **2**[8,11] were insufficient for biological evaluation in mice. For this reason we have synthesized both **1** and **2**, as well as the homolog **3**, and the synthetic work is described below. Independently of the initial report of **1**[8] the same compound was isolated from a different plant.[12] Compound **2** has been isolated as a *racemate* by hexane extraction from *Aframomum melegueta*;[13] and by supercritical CO_2 extraction from the rhizomes of ginger (*Zingiber officinale* Roscoe),[14] and has been prepared[15] in *racemic* form by $NaBH_4$ reduction of [6]-shogaol. Racemic **2** has been found to promote cholesterol efflux from THP-1-derived macrophages.[16] Our sample of natural **2**,[8,11] as isolated, contained a small impurity[8] and had $[\alpha]_D$ –0.46 (*c* = 0.29 g/100 mL). After we had prepared the *S*-enantiomer we established that the natural material was not racemic but was a 1:1.7 mixture of the *R* and *S* enantiomers.[17]



Results and discussion

Synthesis of compound 1

Compound **1** was synthesized by the method summarized in Scheme 1. Vanillin (**1.1**) underwent efficient Wittig reaction with ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate (**1.2**) to form a 3:1 mixture of *E* and *Z* esters **1.3**.[18] Hydrogenation afforded the saturated ester **1.4** and DIBAL-H reduction then gave aldehyde **1.5**.[18] This underwent Wittig reaction with the readily available



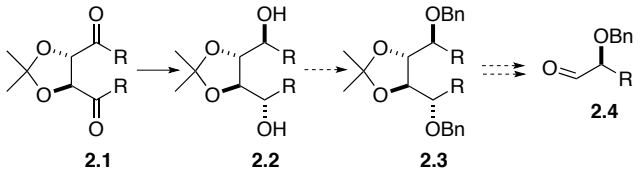
Scheme 1. Synthesis of compound 1

keto ylide **1.6**,[19] and the resulting enone **1** could be isolated in good yield as the desired *E* isomer which was spectroscopically identical with the compound extracted[8] from Grains of Paradise. Unlike the natural material which was an oil, the synthetic enone was obtained as a crystalline solid, mp 35–38 °C.

Synthesis of compound 3

We first developed a route to the unnatural homolog **3** before making the natural material **2**.

As the absolute configuration and optical purity of compound **2** was unknown at the time, we made the arbitrary decision to use tartaric acid for our work, along the lines shown in Scheme 2. This plan was based on a report[20] that the diketone **2.1** (R = *n*-C_5H_{11}) derived from D-(–)-tartaric acid could be reduced stereoselectively with K-Selectride to the diol **2.2** (R = *n*-C_5H_{11}). However, when we attempted to follow an analogous sequence to make **2.4** (R = *n*-C_8H_{17}), using *n*-octylmagnesium bromide instead of the reported pentyl reagent, we obtained low yields (ca

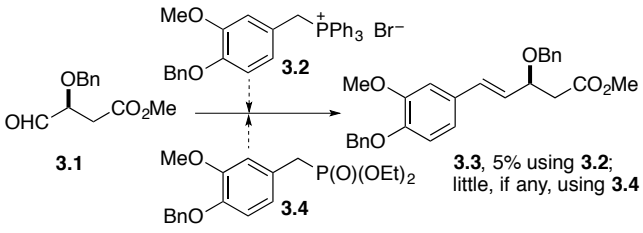


Scheme 2. Initial approach based on tartaric acid

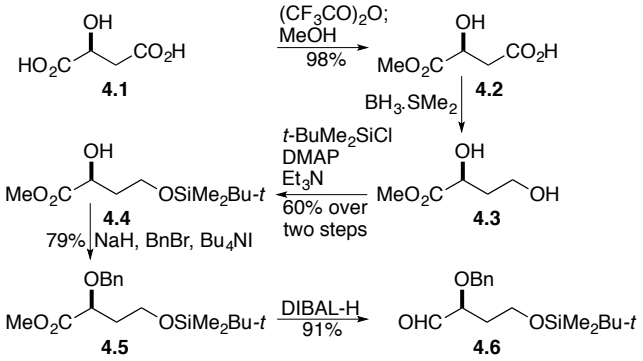
43%) of the desired diketone **2.1** (R = C_8H_{17}). This outcome prompted us to change to a route based on L-(–)-malic acid. The enantiomer is, of course, available, although it is more expensive, and there would also be an opportunity to invert the stereochemistry of the hydroxyl-bearing carbon at a suitable stage.

Initially, we converted malic acid into its *O*-benzyl dimethyl ester and reduced that selectively (Scheme 3) to methyl (2*S*)-4-oxo-3-(phenylmethoxy)butanoate (**3.1**),[21] but in our hands (working at –78 °C instead of the reported[21a] temperature of –90 °C) the yield in the reduction step (DIBAL-H) was low (47%). In addition, attempts to form the olefin **3.3** either by Wittig reaction with the phosphonium salt **3.2**[22] or by the Horner-Wadsworth-Emmons process, using phosphonate **3.4**,[23] were unsatisfactory (Scheme 3). Accordingly, we modified the route to

one that involves conversion of malic acid into aldehyde **4.6** (Scheme 4), followed by olefination with a benzylic phosphonate.

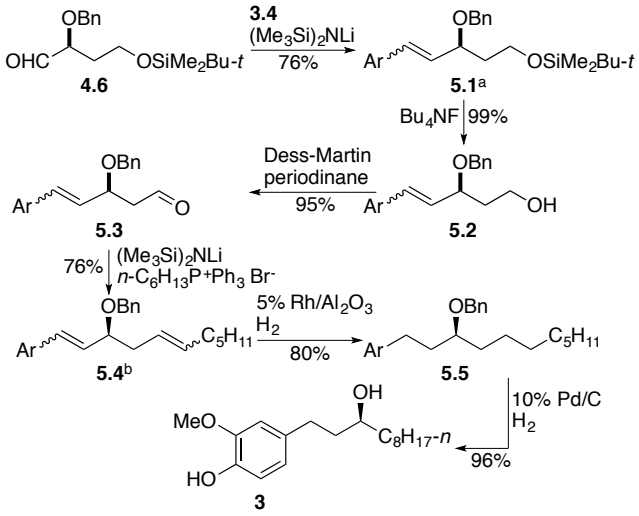


Scheme 3. Initial approach based on malic acid



Scheme 4. Synthesis of aldehyde 4.6

The aldehyde **4.6** was made by regioselective esterification of L-malic acid (**4.1**→**4.2**), following a literature procedure.[24] The remaining carboxyl group was then easily reduced[24] with $BH_3.SMe_2$ and the resulting primary hydroxyl was protected by silylation (**4.2**→**4.3**→**4.4**). The next step, *O*-benzylation of the secondary hydroxyl in **4.4** was tried by two methods. Use of freshly-prepared Ag_2O[25] and BnBr in CH_2Cl_2[26] gave the desired product in 30% yield, but the efficiency of the benzylation was improved (79% yield) by using NaH and BnBr in DMF in the presence[27] of Bu_4NI. Finally, DIBAL-H reduction afforded the aldehyde **4.6** needed as one of the components for the intended olefination.



[a]Ar = (4-benzyloxy-3-methoxy)phenyl. [b]A single isomer was obtained when starting from *E*-**5.3**.

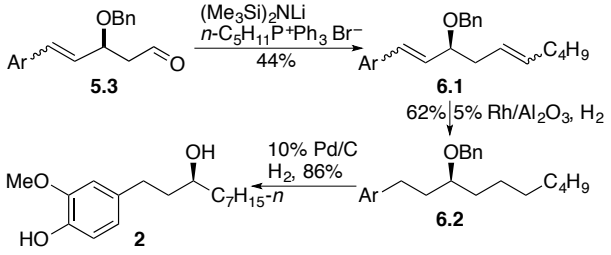
Scheme 5. Olefination of aldehyde 4.6 [Ar = (4-benzyloxy-3-methoxy)phenyl]

Deprotonation of phosphonate **3.4** with $(Me_3Si)_2NLi$ in a 4:1 (v/v) mixture of THF and HMPA,[28] followed by addition of aldehyde **4.6** gave the olefins **5.1**. In the first experiment the *E* and *Z* isomers were isolated in yields of 70% and 6%, respectively, but in subsequent work the isomer mixture was used. Use of HMPA in the olefination was essential; without it very low yields were obtained. Desilylation proceeded without incident, but oxidation of the resulting alcohols (**5.2**) with PCC gave a very low yield. Fortunately, the Dess-Martin periodinane was extremely effective in generating the desired aldehyde **5.3** (95% yield), and a Wittig reaction then took the route as far as **5.4**, which was obtained as a mixture of isomers. We had originally intended to subject **5.4** to hydrogenation of the double bonds over Pd/C and then in situ hydrogenolysis of the benzyloxy groups but, in the event, significant hydrogenolysis of the allylic C—O bond occurred. Therefore **5.4** was first reduced over 5% Rh-Al_2O_3 to saturate the double bonds (monitored by ^{1}H NMR and tlc), and then the benzyl groups were removed by hydrogenolysis (Pd/C) so as to obtain the target alcohol (**5.4**→**5.5**→**3**).

In order to establish the optical purity of **3** we needed a racemic sample. Several attempts to selectively oxidize the aliphatic hydroxyl of **3** were unsuccessful,[29] but the phenolic hydroxyl was easily benzylated (BnBr, K_2CO_3, 96%) and the remaining secondary hydroxyl could be oxidized with the Dess-Martin reagent. Then reduction ($NaBH_4$) and hydrogenolysis provided a reference sample of racemic **3**. Chiral HPLC analysis served to establish that the ee of (*S*)-**3** {$[\alpha]_D$ 8.35 (*c* = 1.233, $CHCl_3$)} was 90%.

Synthesis of compound 2

With a practical route to (*S*)-**3** we next diverted the advanced intermediate **5.3** to the natural product **2**. To this end, **5.3** was subjected to Wittig reaction with the ylide generated from pentyltriphenylphosphonium bromide (Scheme 6). The resulting dienes were first hydrogenated over Rh-Al_2O_3 and then subjected to hydrogenolysis over Pd/C to afford (*S*)-**2** as a crystalline solid (**6.1**→**6.2**→**2**). To make a racemic sample, the phenolic hydroxyl of (*S*)-**2** was benzylated, following our earlier procedure, and the secondary alcohol was oxidized to a ketone, which was then reduced ($NaBH_4$) and subjected to hydrogenolysis to liberate the phenol. With racemic and optically active samples in hand, chiral HPLC showed that synthetic (*S*)-**2** {$[\alpha]_D$ 6.31 (*c* = 1.049, $CHCl_3$)} had an ee of 68% and, surprisingly, that the natural sample was a 1:1.7 mixture of *R* and *S* isomers. We did not establish why the optical purity of (*S*)-**2** is lower than that of the homolog (*S*)-**3**, but suspect that the reason is due to the fact that in making (*S*)-**2** the epimerizable aldehyde **4.6** was not used *immediately* after its preparation. The negative value of the specific rotation of natural phenolic alcohol **2** must be due to a minor impurity, as the predominance of the *S*-isomer should result in a positive value.



Scheme 6. Conversion of 5.3 to 6.3

Conclusions

The two naturally occurring vanilloids **1** and **2**, isolated from the seeds of *Aframomum melegueta*, were synthesized by routes that provide adequate quantities for biological testing and that should allow variation in alkyl chain length with consequent alteration in the lipophilicity of the final vanilloid. Unlike other reports on the isolation of **2**, the natural material was not racemic but was a 1:1.7 mixture of *R* and *S* isomers, and the present synthetic route should allow biological evaluation of the individual enantiomers since both enantiomers of malic acid are available.

Acknowledgements

We thank NSERC and Gifu University (Head Office for Glocalization) for financial support and E. Fu (Chemistry Department, University of Alberta) for the chiral HPLC measurements.

Appendix A. Supplementary data

Supplementary data (copies of spectra and experimental procedures) related to this article can be found at https://doi.org/

References

(1) Umukoro, S.; Ashorobi, R. B. *J. Ethnopharmacol.* **2007**, *109*, 501–504.

(2) (a) Ilic, N.; Schmidt, B. M.; Poulev, A.; Raskin, I. *J. Ethnopharmacol*. **2010**, *127*, 352–356. (b) Dalziel, J. M. *The Useful Plants of West Tropical Africa*; The Crown Agents for the Colonies: London, 1937; pp 471–472.

(3) Onoja, S. O.; Omeh, Y. N.; Ezeja, M. I.; Chukwu, M. N. *J. Tropical Medicine* **2014**, Article ID 159343.

(4) Galal, A. M. *Int. J. Pharmacognosy* **1996**, *34*, 64–69.

(5) Hattori, H.; Yamauchi, K.; Onwona-Agyeman, S.; Mitsunaga, T. *Am. J. Plant Sci*. **2017**, *8*, 85–95.

(6) Sugita, J.; Yoneshiro, T.; Sugishima, Y.; Ikemoto, T.; Uchiwa, H.; Suzuki, I.; Saito, M. *J. Nutr. Sci. Vitaminol.* **2014**, *60*, 22–27.

(7) The seeds were obtained from Share Trade Inc., Tokyo, but were harvested in Ghana.

(8) Hattori, H.; Yamauchi, K.; Onwona-Agyeman, S.; Mitsunaga, T. *J. Sci. Food Agric*. **2018**, *98*, 4742–4748.

(9) (a) Saito, M. in *Advances in Food and Nutrition Research*; Henry, C. J., Ed.; **2015**, *76*, 1–28. (b) Luo, X.-J.; Peng, J.; Li, Y.-J. *Eur. J. Pharmacol*. **2011**, *650*, 1–7.

(10) Hiroyuki, H.; Mitsunaga, T. Unpublished observations.

(11) In the initial report (Reference 8) the structure of vanilloid **2** is incorrect and should be as shown here.

(12) Li, Z.; Wang, Y.; Gao, M.; Cui, W.; Zeng, M.; Cheng, Y.; Li, J. *Molecules* **2018**, *23*, 315–324.

(13) (a) Gröblacher, B.; Maier, V.; Kunert, O.; Bucar, F. *J. Nat. Prod*. **2012**, *75*, 1393–1399. (b) The country of origin of the seeds was not specified.

(14) Nievergelt, A.; Huonker, P.; Schoop, R.; Altmann, K.-H.; Gertsch, J. *Bioorg. Med. Chem*. **2010**, *18*, 3345–3351.

(15) (a) Zhu, Y.; Warin, R. F.; Soroka, D. N.; Chen, H.; Sang, S. *PLos One* **2013***, 8*: e54677. *(b)* Sang, S.; Chen, H.; Zhu, Y. US Patent 9,272,994 B1, March 1, 2016.

(16) Wang, D.; Hiebl, V.; Ladurner, A.; Latkolik, S. L.; Bucar, F.; Heiss, E. H.; Dirsch, V. M.; Atanasov, A. G. *Mol. Nutr. Food Res*. **2018**, *62*, 1800011.

(17) For examples of the isolation of unequal amounts of enantiomers from the same plant, see: Lee, S. T.; Molyneux, R. J.; Panter, K. E. In *Bioactive Natural Products: Detection, Isolation, and Structural Determination*; 2nd ed.; Colegate, S. M.; Molyneux, R. J. Eds.; CRC/Taylor and Francis: Boca Raton, FL, 2008, p 209.

(18) Cf Luo, D.; Sharma, H.; Yedlapudi, D.; Antonio, T.; Reith, M. E. A.; Dutta, A. K. *Bioorg. Med. Chem*. **2016**, *24*, 5088–5102.

(19) Ruijter, E.; Schültingkemper, H.; Wessjohann, L. A. *J. Org. Chem*. **2005**, *70*, 2820–2823.

(20) (a) Achmatowicz, B.; Wicha, J. *Tetrahedron Lett*. **1987**, *28*, 2999–3002. (b) Achmatowicz, B.; Wicha, J. *Bull. Polish Acad. Sci*. **1988**, *36*, 267–276.

(21) (a) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417–420. (b) Brimble, M. A.; Finch, O. C.; Heapy, A. M.; Fraser, J. D.; Furkert, D. P.; O'Connor, P. D. *Tetrahedron* **2011**, *67*, 995–1001.

(22) Made by the method reported for benzyltriphenylphosphonium bromide: Zheng, Y.; Song, W.-B.; Xuan, L.-J. *Tetrahedron* **2016**, *72*, 5047–5050.

(23) (a) Jang, H. Y.; Park, H. J.; Damodar, K.; Kim, J.-K.; Jun, J.-G. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 5438–5443. (b) Cf Harada, K.; Makino, K.; Shima, N.; Okuyama, H.; Esumi, T.; Kubo, M.; Hioki, H.; Asakawa, Y.; Fukuyama, Y. *Tetrahedron* **2013**, *69*, 6959–6968.

(24) Hayashi, Y.; Yamaguchi, J.; Shoji, M. *Tetrahedron* **2002**, *58*, 9839–9846

(25) Tanabe, M.; Peters, R. H. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 386–393.

(26) Cf Liu, D.-D.; Sun, T.-W.; Wang, K.-Y.; Lu, Y.; Zhang, S.-L.; Li, Y.-H.; Jiang, Y.-L.; Chen, J.-H.; Yang, Z. *J. Am. Chem. Soc.* **2017**, *139*, 5732–5735.

(27) Cf Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 1529–1531.

(28) Cf O'Connor, B.; Just, G. *Tetrahedron Lett*. **1986**, *27*, 5201–5202.

(29) Reddy, A. R.; Wadavrao, S. B.; Yadav, J. S.; Narsaiah, A. V. *Helv. Chim. Acta* **2015**, *98*, 1009–1017.