ORGANIC LETTERS

2008
Vol. 10, No. 6
1135−1138

Stereoselective Synthesis of Woody Fragrances Related to Georgyone and Arborone

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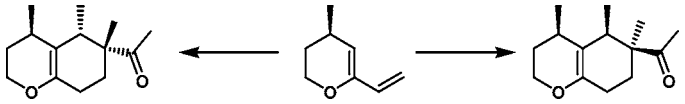
Received January 7, 2008

ABSTRACT



The synthesis of two very powerful and pleasant new odorants has been carried out from a common intermediate.

Recent research in our laboratory resulted in the enantioselective synthesis of a number of enantiomerically pure woody odorants related to the racemic commercial fragrances, "Georgywood" and "Iso E Super".[1] This work demonstrated the absolute configuration of the active principles as **1** ("georgyone") and **2** ("arborone"). In contrast to the very pleasant and powerful odors of **1** (Figure 1) and **2**, the odor of *ent*-**1** is disagreeable and that of *ent*-**2** is negligible.

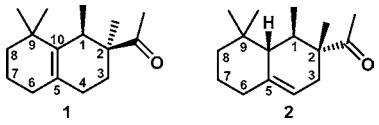


Figure 1. Georgyone and Arborone.

Given the importance of absolute configuration in this series to woody odor, it is perhaps surprising that the orientation of the acetyl group in **2** is opposite to that in **1**. The study of a number of stereoisomers and analogs of **1** and **2** revealed that, in contrast, the orientation of the methyl group at C(1) does not vary in the compounds that possess a strong woody odor. Further removal of the methyl group at C(1) also abolishes odor as does removal of both methyls at C(9). In addition, one of the methyl groups at C(9) is critical for odor, specifically that which is cis to the methyl group at C(1). A model of the olfactory receptor that is consistent with these and other results has been advanced.[1] In this model, binding takes place with at least two transmembrane α-helical domains of the olfactory receptor, resulting in a somewhat different binding pocket for **1** and **2**. In the present study, this model has been used as a guide to search for other molecules that might serve as potent woody fragrances.

We were interested in the series of analogs of **1** and **2** in which the C(6)-methylene group is replaced by oxygen (Figure 2). Among the reasons for considering this approach

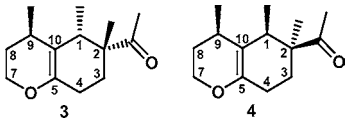


Figure 2. Synthetic targets of this study.

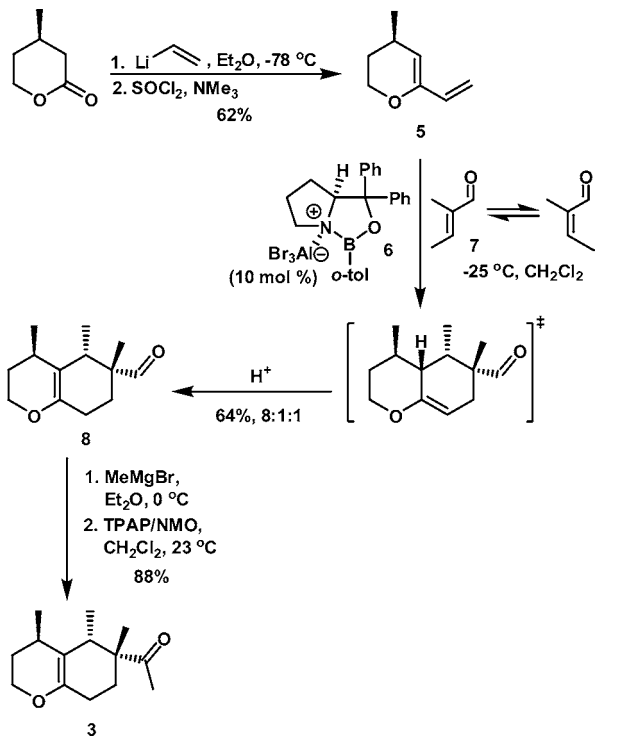
are: enhancement of positional selectivity using the Diels−Alder reaction as a key step, decreased substrate volatility, and increased water solubility/bioavailability at the olfactory receptors. The first of these analogs to be synthesized was

(1) Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 1346−1352.

10.1021/ol8000359 CCC: $40.75
Published on Web 02/28/2008

the ketone **3**. It was produced by a route that was originally intended to afford the isomer **4**, which can be considered to be a 6-oxy-georgyone lacking the non-essential methyl group at C(9).

Scheme 1



(*R*)-(+)-3-Methyl-5-valerolactone (Scheme 1)[2] was conveniently prepared from methyl (*R*)-(+)-3-methyl-glutarate[3] by a previously described three step sequence: (1) reaction with cyanuric fluoride-pyridine in CH_2Cl_2, (2) reduction with $NaBH_4$ in 1:1 CH_2Cl_2−CH_3OH, and (3) cyclization of the product, methyl (*R*)-3-methyl-5-hydroxyvalerate, with HCl on silica gel in $CHCl_3$ at 23 °C (94% overall yield).[4] Vinylation of (*R*)-(+)-3-methyl-5-valerolactone with 1 equiv of vinyllithium in ether at −78 °C and treatment of the resulting lithium alkoxide with 1 equiv of thionyl chloride and ca. 2.1 equiv of trimethylamine generated the volatile and acid-sensitive diene **5**, which was isolated by rapid filtration through a small pad of silica gel eluting with Et_2O/pentane and careful removal of solvent (62% yield).

Slow addition of **5** to a solution of the (*S*)-oxazaborolidine catalyst **6** (10 mol %)[5] and (*E*)-2-methyl-2-butenal (**7**) in CH_2Cl_2 at −25 °C over 7 h with further stirring at −25 °C for 17 h afforded the Diels−Alder adduct **8** in 64% yield as the predominating product with minor amounts of two isomeric products. The structure of the adduct **8** was proven by conversion to the crystalline semicarbazone (mp = 196−198 °C) and single-crystal X-ray diffraction analysis (Figure 3). It is evident that **8** must be formed through a minor amount of (*Z*)-2-methyl-2-butenal in equilibrium with the predominating *E*-isomer by Diels−Alder addition, followed by acid-catalyzed transposition of C=C.[6]

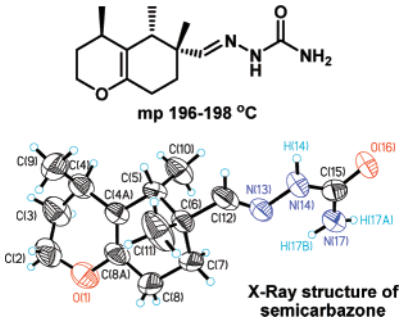


Figure 3. Absolute configuration of **8**.

Another interesting aspect of the Diels−Alder reaction **5** → **8** is apparent from our finding that this reaction does not occur with any of the standard achiral Lewis acids tested, for example Me_2AlCl, $BF_3(OEt_2)$, $MgBr_2(OEt_2)$, $Yb(OTf)_3$, $Sc(OTf)_3$, or $ZnCl_2$.[7] In addition, the conversion of **5** → **8** did not occur using the (*R*)-enantiomer of **6**. This fact provides a provocative example of a special ability of complex chiral catalysts to allow an otherwise inaccessible reaction pathway.[7]

The structure of aldehyde **8** was further confirmed by the straightforward synthesis of this same compound by the route shown in Scheme 2. Diene **5** and bromocrotonaldehyde particpated in a Diels−Alder addition at −78 °C in the presence of 10 mol % of the (*S*)-catalyst **6** to produce the aldehyde shown as a single isomer in 43% yield.[8] Sequential treatment of this aldehyde with lithium naphthalenide and MeI in THF produced **8**. Reaction of **8** with methylmagnesium bromide in ether at 0 °C followed by oxidation with tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide[9] gave the methyl ketone **3** as a colorless oil. The odor of **3** was intensely woody with a sweet floral overtone, very pleasant and not dissimilar from that of georgyone (**1**) or arborone (**2**).[10] The intensity of the odor

(2) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142−146.

(3) We are grateful to Genentech research and Dr. Travis P. Remarchuk for a generous gift of this chiral acid (produced by Sumitomo Chemical Co.).

(4) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2007**, *129*, 4148−4149.

(5) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498−1499.

(6) The equilibration of *E* and *Z* isomers in the reaction mixture is likely catalyzed by Lewis acid **6**. Other instances of this isomerization have previously been observed by Dr. S. Hong in this laboratory, details of which are found in ref 1.

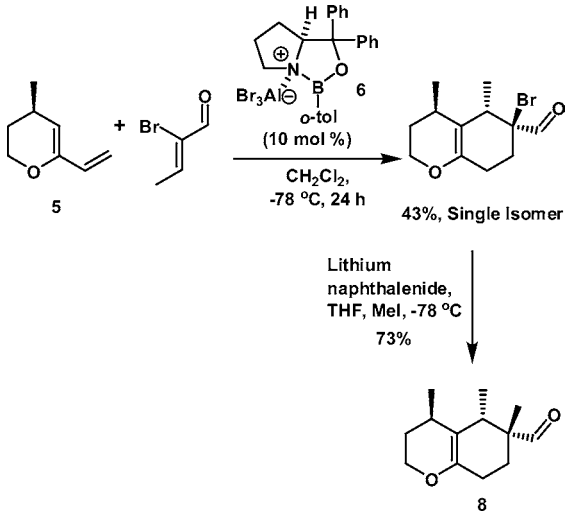
(7) For another interesting case of the sort, see Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740−742.

(8) The stereochemistry of the Diels-Alder adduct in Scheme 2 is assumed to be as shown due to the evidence found in Scheme 1 and ref 1. The C(2) epimer cannot be entirely ruled out as the reduction/alkylation sequence would provide the same product although it suggests an unfavorable exo-transition state.

(9) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(10) The odors of **3** and **4** were evaluated by several members of our laboratory whose perceptions of their odors were essentially the same.

Scheme 2. Alternative Synthesis of **8**



of **3** is comparable to that of **1** or **2**. The pleasant odor of **3** persisted for about 4 h when ca. 10 μg was applied evenly to the back of the hand over a 9 cm^2 area. This result came as a surprise because we had observed earlier that **9** (Figure 4), another of our synthetic analogs of arborone, possessed only a faint odor when compared to **1**.[1]

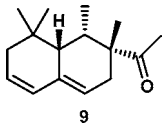
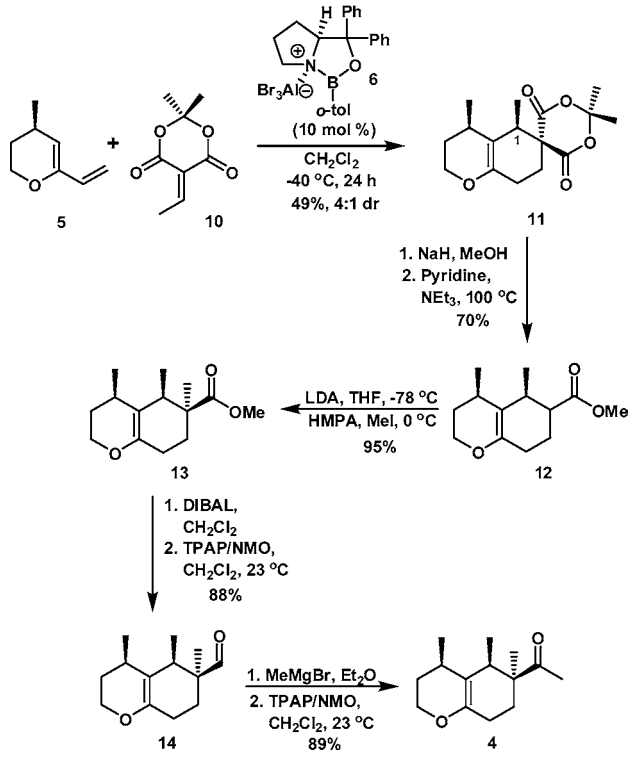


Figure 4. Non-fragrant analogue of arborone.

Despite the fact that the pathway outlined in Scheme 1 afforded **3** rather than **4**, we were able to synthesize **4** by the route that appears in Scheme 3. The diene **5** underwent Diels−Alder addition to the known dienophile **10**[11] at −40 °C in the presence of 10 mol % of the (*S*)-catalyst **6** to produce the C=C transposed adduct **11** as the major product along with ca. 20% of the C(1) diastereomer. Methanolysis and careful isolation of the crude intermediate was followed by decarboxylation of **11** in 1:1 pyridine/triethylamine to generate the ester **12**, which was converted to the enolate and α-methylated with complete stereoselectivity to form **13**. Reduction of the carboxymethyl group of **13** and TPAP oxidation gave the aldehyde **14** from which the desired methyl ketone **4** was formed by methylation and oxidation. The odor of **4** was very close to that of **3**.[10] Some of the evaluators noted a slight minty note for **4** in addition to the strong woody odor and sweet floral note.

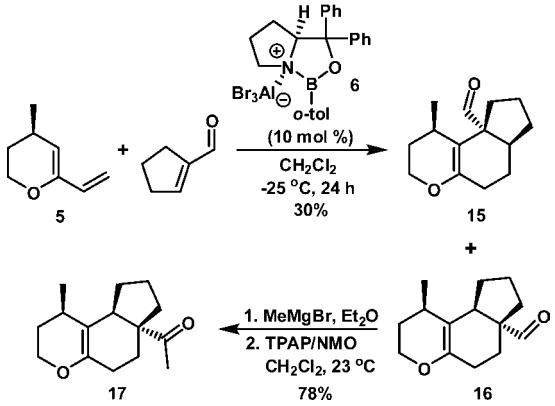
We have also synthesized a cyclopentane analog of **3** and **4** in which the methyl groups at C(1) and C(2) are bridged

Scheme 3



by a methylene group to enforce a cis arrangement, specifically the tricyclic methyl ketone **17**. The synthesis (outlined in Scheme 4) began with the Diels−Alder reaction of **5** and

Scheme 4



1-cyclopentene carboxaldehyde,[12] which produced a mixture of adducts **15** and **16** in a ratio of 1:1.2, respectively, with each found as single isomers. After separation, **16** was transformed into **17** by the methylation/oxidation sequence shown. The odor of **17** was neither woody nor floral-sweet but instead was unpleasant and reminescent of kerosene.

The findings of this research with the new woody odorants **3** and **4** are consistent with the general model proposed earlier

(11) (a) Akue-Gedu, R.; El-Hafidi, H.; Rigo, B.; Couturier, D. *J. Heterocyclic Chem.* **2006**, *43*, 365−369. (b) Ziegler, F. E.; Guenther, T.; Nelson, R. *Synth. Comm.* **1980**, *10*, 661−665.

(12) Wang, Z.-M.; Qian, X.-H.; Zhou, W.-S. *Tetrahedron* **1990**, *46*, 1191−1196.

for georgyone and arborone.[1] In this model, there is considerable mobility of the transmembrane α-helices relative to one another, and an individual receptor can provide a variety of different binding sites.[1] Thus, sensing receptors are differentiated from ligand-regulated receptors in that they have the capability to bind to multiple ligands. In addition, this feature helps to explain how a given ligand (e.g., **1** or **2**) can bind to several of the 340 or so known human receptors.[13−17] The perceived odor characteristics of any particular odorant are determined combinatorially by the set of olfactory receptors to which it binds.[1]

The research described herein has provided two very powerful and pleasant woody odorants that may be commercially interesting. The synthesis employs for the first time a Lewis-acid mediated Diels−Alder reaction of an unmodified vinyldihydropyran.[18] The use of the $AlBr_3$-activated catalyst **6** is critical. The analogous triflic acid- or triflimide-activated oxazaborolidine catalyst[1] appeared to favor destruction of the acid-sensitive diene **5**, resulting in much lower yields of Diels−Alder product. The strong fragrance of compounds **3** and **4** shows that the olfactory receptors responsible for their woody odor can accommodate a heteroatom in the C(6)−C(7) region of georgyone and also variable stereochemistry at C(2) (as between georgyone and arborone) and (surprisingly) either orientation of methyl at C(1) as compared to georgyone and arborone. The results provide additional support for our model[1] of conformational flexibility of olfactory receptors. The study of these woody odorants in the georgyone class has significant implications with regard to the complexity of structure activity correlations in the rational design of fragrances.

Supporting Information Available: Detailed experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Buck, L. B.; Axel, R. *Cell* **1991**, *65*, 175−187. (b) Malnic, B.; Godfrey, P. A.; Buck, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 2584−2589. (c) Godfrey, P. A.; Malnic, B.; Buck, L. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 2156−2161. (d) Malnic, B.; Hirono, J.; Sato, T.; Buck, L. B. *Cell* **1999**, *96*, 713−723. (e) Buck, L. B. *Cell* **2000**, *100*, 611−618. (f) Takahashi, Y. K.; Kurosaki, M.; Hirono, S.; Mori, K. *J. Neurophysiol.* **2004**, *92*, 2413−2427. (g) Uchida, N.; Takahashi, Y. K.; Tanifuji, M.; Mori, K. *Nat. Neurosci.* **2000**, *3*, 1035−1043. (h) Ronnett, G. V.; Moon, C. *Ann. Rev. Physiol.* **2002**, *64*, 189−222. (i) Vosshall, L. B. *Curr. Opin. Neurobiol.* **2000**, *10*, 498−503.

(15) Glusman, G.; Yanai, I.; Lancet, D. *Genome Res.* **2001**, *11*, 685−702 (the complete human olfactory subgenome).

(16) Serizawa, S.; Miyamichi, K.; Nakatani, H.; Suzuki, M.; Saito, M.; Yoshihara, Y.; Sakano, H. *Science* **2003**, *302*, 2088−2091 (regulation of OR gene expression).

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(18) In contrast, there are several examples of thermal Diels-Alder reactions with vinyldihydropyrans; see (a) Sun, K.-M.; Giuliano, R. M.; Frasier-Ried, B. *J. Org. Chem.* **1985**, *50*, 4774−4780. (b) Giuliano, R. M.; Buzby, J. H.; Marcopulos, N.; Springer, J. P. *J. Org. Chem.* **1990**, *55*, 3555−3562. (c) Giuliano, R. M.; Jordan, A. D.; Gauthier, A. D.; Hoogsteen, K. *J. Org. Chem.* **1993**, *58*, 4979−4988. (d) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Bouanou, H. *J. Org. Chem.* **2007**, *72*, 3332−3339.