Pergamon

Tetrahedron Letters 43 (2002) 6417–6420

TETRAHEDRON LETTERS

First total synthesis of (±)-helibisabonol A

Francisco A. Macías,* David Marín, David Chinchilla and José M. G. Molinillo

Grupo de Alelopatía, Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, C/República Saharaui s/n, Apdo. 40, 11510-Puerto Real (Cádiz), Spain

Received 10 May 2002; revised 1 July 2002; accepted 4 July 2002

Abstract—Helibisabonol A is a new sesquiterpene with phytotoxic activity isolated from *Helianthus annuus* leaves. (±)-Helibisabonol A has been synthesized as an approach to the natural product in the search for new herbicide models. Herein, we report the first total synthesis for this molecule from methylhydroquinone in six steps. The key steps of this synthesis are a Fries rearrangement, a Grignard reaction and a catalytic hydrogenation. The synthesis was carried out with high yield and in an easy to scale manner. © 2002 Elsevier Science Ltd. All rights reserved.

Helianthus annuus L. (sunflower) is a plant with a very high commercial importance and it is known for its high production of secondary metabolites, specially terpenes[1] and phenolic compounds.[2] Recently, a new phenolic sesquiterpene with the bisabolane skeleton, helibisabonol A (Fig. 1), has been isolated from *H. annuus* L. var. Peredovick©.[3]

Allelochemicals are an important potential source for new agrochemicals, and particularly herbicides, since they could offer new modes of action, more specific interactions with weed and less environmental damage.[4] These facts make very interesting the large scale synthesis of these products, in order to test them in suitable bioassays and propose them as new herbicide models.

There are no previous reports about the synthesis of helibisabonol A, but many sesquiterpenes with similar structures have been synthesized, including curcuphenol and curcudiol.[5] The main difference between the synthetic methods employed for these compounds is the way to link the side-chain with the aromatic moiety. Among the different alternatives for this purpose, we chose that shown in Scheme 1, in which the new C–C bond is formed by nucleophilic addition to the aromatic ketone **3** using a Grignard reagent.

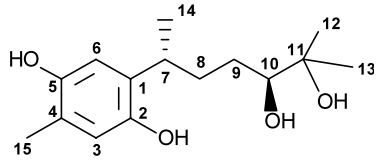


Figure 1. (±)-Helibisabonol A.

The low yields obtained in the electrophilic aromatic substitution reactions enforced us to look for alternative methods to get access to the starting aromatic ketone. Thus, a Fries rearrangement[6] provides the desired compound with quantitative yield in short time and mild conditions.

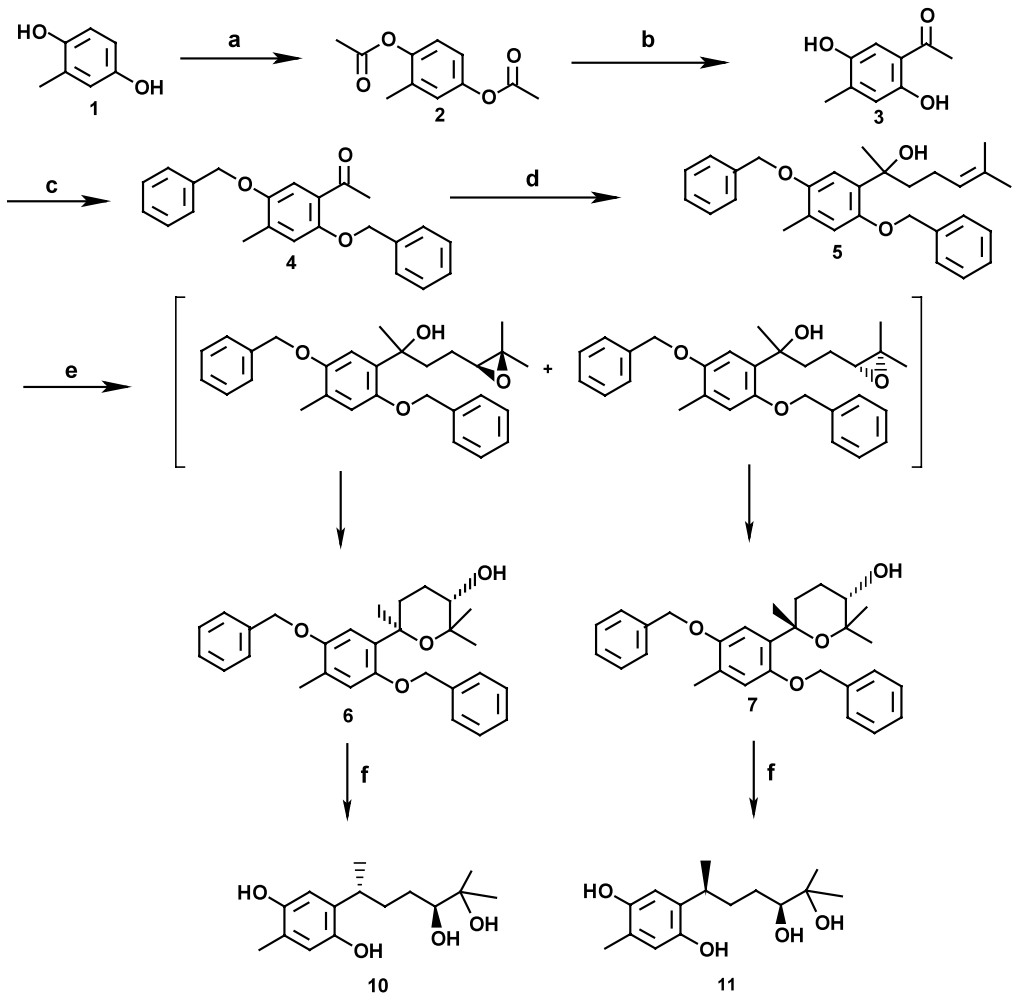
Firstly, an esterification reaction (Scheme 1) yields the diacetyl derivative **2** from methylhydroquinone (**1**) with a 99% yield. This compound (2,5-diacetoxitoluene) is heated at 120°C with 2 mol equiv. of aqueous boron trifluoride (step b) giving the *ortho* Fries rearrangement product, in which the ester in positions 2 and 5 are cleaved. 2,5-Dihydroxy-4-methylacetophenone (**3**) is obtained in 6 h (quantitative yield). Temperature control is extremely important at this point, since a lower temperature provides the *para* isomer.

After a double etherification with benzyl bromide in basic conditions (step c), we were ready to introduce the side-chain by Grignard reaction (step d). Good yields were not observed below +65°C, probably due to the high steric hindrance caused by the benzyl moiety at position 2.

After 1 h, the observed yield for **5** was 70%. Compound **5** had an unexpected evolution under epoxidation conditions. After reaction with MCPBA and sodium acetate at room temperature, no epoxide derivative could be isolated. The NMR and HREIMS spectra allowed

* Corresponding author. Tel.: +34-956-016370; fax: +34-956-016193; e-mail: famacias@uca.es

PII: S0040-4039(02)01381-3



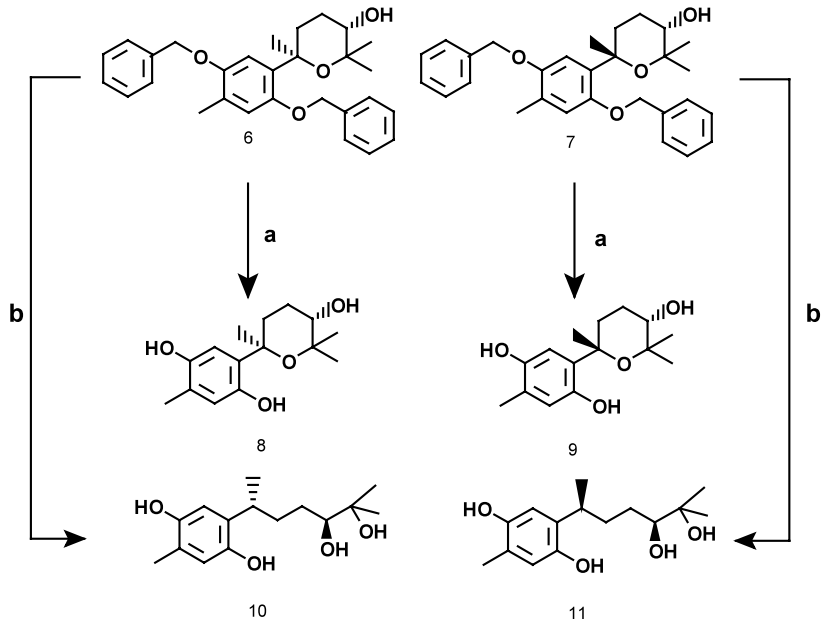
Scheme 1. *Reagents and conditions*: (a) Ac_2O, Py, rt, 12 h, 99%; (b) $BF_3{\cdot}2\ H_2O$, 120°C, 5 h, 99%; (c) BnBr, K_2CO_3, DMF, DME, 80°C, 12 h, 99%; (d) 5-Br-2-methyl-2-pentene, Mg, THF, 65°C, 1 h, 70%; (e) MCPBA, sodium acetate, $CHCl_3$, rt, 1 h, 99%; (f) H_2, Pd/C, AcOEt, rt, 1 h, 99%.

us to identify the main reaction products (85% yield) as the intramolecular cyclization products **6** and **7**. This couple of diastereomers could be separated easily using column chromatography (15% Et_2O/hexane) and HPLC methods (8% AcOEt/hexane), in order to continue the synthesis of both epimers of (±)-helibisabonol A and complete their activity profile separately.

The final steps illustrate the importance of the solvent choice to control the evolution of the catalytic hydrogenation reactions. As shown in Scheme 2, the hydroxyl groups at C-2 and C-5 are first deprotected, the pyrane ring opening occurring later. When ethyl acetate is used as a solvent, the second step proceeds very fast, and when the solvent used is DMF, products **10** and **11** are not observed before the complete transformation of **6** and **7** in **8** and **9**, respectively. Using both solvents the transformations are quantitative, so we can get products **10** or **11** as well as **8** and **9** after a simple work-up with no further purification. These facts allow us to get large quantities of the desired products in a short time. Products **8** and **9** were isolated as red oils. Differences in the [M^+] of compounds **8**–**9** and **10**–**11** in the HREIMS experiment confirm the pyrane ring opening. The structures were unequivocally confirmed using spectroscopic data,[7,8] and the relative configuration at the stereogenic centers C-7 and C-10 was proposed by correlation of bond angles for the most stable conformers (Fig. 2), found by PM3 calculations,[9] and experimental coupling constants (Table 1). In conclusion, this synthesis afforded the desired compound (±)-helibisabonol A with a 67% overall yield, in six steps. The structure of the compounds obtained was unequivocally determined by using spectral and computational techniques, and structural data for compound **10** match exactly with the natural compound isolated from *H. annuus* var. Peredovick©.[3]

Acknowledgements

This research was supported by the Dirección General de Investigación Científica y Técnica, Spain (DGICYT, Project # PB98-0575).



Scheme 2. *Reagents and conditions*: (a) H_2, 10% Pd/C, DMF, rt, 1 h, 99%; (b) H_2, 10% Pd/C, AcOEt, rt, 1 h, 99%.

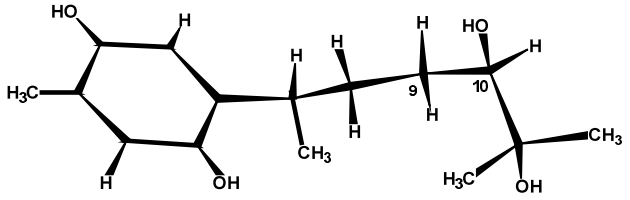


Figure 2. Most stable conformer for compound **10**.

Table 1. Observed coupling constants versus Φ obtained for the most stable conformer of **10**

Protons	Calculated Φ	Observed J
H9a-10	73.8	1.38
H9b-10	41.5	4.9

References

1. Macías, F. A.; Molinillo, J. M. G.; Torres, A.; Varela, R. M.; Castellano, D. *Phytochemistry* **1997**, *45*, 683–687.
2. Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. In *Allelopathy in Pests Management for Sustainable Agriculture*; Narwal, S. S.; Tauro, P., Eds.; Scientific Publishers: Jodhpur, India, 1996; Chapter 4, pp. 77–92.
3. Macías, F. A.; Varela, R. M.; Galindo, J. L. G.; Torres, A.; Molinillo, J. M. G. *Phytochemistry* **2002**, 60.
4. (a) Vyvyan, J. R. *Tetrahedron* **2002**, *58*, 1631–1646; (b) Duke, S. O. *Rev. Weed Sci.* **1986**, *2*, 15–44; (c) Macías, F. A. In *Allelopathy: Organisms, Processes, and Applications*; Inderjit; Dakshini, K. M. M.; Einhellig, F. A., Eds.; ACS Symposium Series, 582: Washington, DC, USA, 1995; Chapter 23, pp. 310–329; (d) Duke, S. O. In *The Science of Allelopathy*; Putnam, A. R.; Tang, C. S., Eds.; John Wiley & Sons: New York, USA, 1986; Chapter 17, pp. 287–304; (e) Duke, S. O.; Dayan, F. E.; Hernandez, A. In *Proceedings of Weeds. The 1997 Brighton Crop Protection Conference*; Pallett, K. E., Ed.; British Crop Protection Council: Farnham, UK, 1997; Vol. 2, pp. 579–586; (f) Rice, E. L. *Biological Control of Weeds and Plant Diseases*; University of Oklahoma Press: Norman, USA, 1995; (g) Waller, G. R.; Yamasaki, K. *Advances in Experimental Medicine and Biology*; Saponins Used in Food and Agriculture. Plenum Press: New York, 1996; Vol. 405.
5. (a) Ono, M.; Ogura, Y.; Hatogai, K.; Akita, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1829–1832; (b) Fuganti, C.; Serra, S. *Synlett* **1998**, 1252–1254; (c) Sugahara, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2215–2217.
6. Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon: Oxford; Vol. 2, 745–747, 1991.
7. Analytical data for (±)-6-[2,5-dihydroxy-4-methylphenil]-2,2,6-trimethyltetrahydropyran-3-ol (**8**): ^{1}H NMR (C_3D_6O, 400 MHz) δ (ppm): 6.58 (1H, s, H-3), 6.72, (1H, s, H-6), 2.46 (1H, ddd, H-8a), 2.13 (1H, m, H-8b), 2.03 (1H, dddd, H-9a), 1.86, (1H, dddd, H-9b), 3.87 (1H, dd, H-10), 1.23* (3H, s, H-12), 1.29* (3H, s, H-13), 1.56 (3H, s, H-14), 2.18 (3H, s, H-15); J (Hz): 8a,8b = 8b,8a = 12.3; 10,9a = 9a,10 = 7.7; 10,9b = 9b,10 = 7.1; 9a,9b = 9b,9a = 12.3; ^{13}C NMR (C_3D_6O, 100 MHz) δ (ppm): 129.51 (C-1), 148.53 (C-2), 112.86 (C-3), 124.26 (C-4), 148.15 (C-5), 119.23 (C-6), 86.92 (C-7), 38.70 (C-8), 25.74 (C-9), 86.82 (C-10), 70.69 (C-11), 25.74* (C-12), 28.94* (C-13), 28.45 (C-14), 15.63 (C-15) (* interchangeable values); HREIMS, m/z calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1524; λ_{max} (MeOH) = 201.6 nm; FTIR 3386 cm^{-1} (intense), 1020 cm^{-1}.
8. Analytical data for (±)-helibisabonol A (**10**): ^{1}H NMR (C_3D_6O, 400 MHz) δ (ppm): 6.51 (1H, s, H-3), 6.59, (1H, s, H-6), 3.06 (1H, ddq, H-7), 1.74 (1H, dddd, H-8a), 1.55 (1H, m, H-8b), 1.45 (1H, dddd, H-9a), 1.23 (1H, m, H-9b), 3.66 (1H, dd, H-10), 1.03* (3H, s, H-12), 1.04* (3H, s,

H-13), 1.09 (3H, s, H-14), 2.04 (3H, s, H-15); *J* (Hz): 7,8a = 8a,7 = 7.1; 7,8b = 8b,7 = 7.5; 7,14 = 14,7 = 5.1; 8a,8b = 8b,8a = 12.4; 8a,9a = 9a,8a = 5.5; 8a,9b = 9b,8a = 9.8; 8b,9a = 9a,8b = 8.7; 8b,9b = 9b,8b = 5.8; 9a,9b = 9b,9a = 13.1; 10,9a = 9a,10 = 1.38; 10,9b = 9b,10 = 4.9; ^{13}C NMR (C_3D_6O, 100 MHz) δ (ppm): 132.0 (C-1), 148.8* (C-2), 117.9 (C-3), 121.9 (C-4), 147.5* (C-5), 113.3 (C-6), 29.7 (C-7), 35.4 (C-8), 24.4 (C-9), 79.2 (C-10), 72.4 (C-11), 25.4* (C-12), 28.9* (C-13), 21.5 (C-14), 15.4 (C-15) (* interchangeable values); HREIMS, *m*/*z* calcd for $C_{15}H_{24}O_4$ 268.1674, found 268.1678; λ_{max} (MeOH) = 201.6 nm; FTIR 3364 cm^{-1} (very intense). These data are in good agreement with the previous reported for the natural product.[3]

9. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. Molecular orbital calculations were carried out using PM3 Hamiltonian as implemented in MOPAC 6.0. Geometries were fully optimized using the PRECISE keyword.