Pergamon

Tetrahedron 58 (2002) 2163–2166

TETRAHEDRON

Synthesis of 6-methoxy-4*H*-1-benzopyran-7-ol, a character donating component of the fragrance of *Wisteria sinensis*

Jan Demyttenaere,[a] Kris Van Syngel,[a] A. Peter Markusse,[a] Stijn Vervisch,[a] Silvia Debenedetti[b] and Norbert De Kimpe[a,*]

[a]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

[b]*Instituto de Quimica y Metabolismo del Farmaco, Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Junin 956, 1113 Buenos Aires, Argentina*

This paper is dedicated to Professor Al Padwa on the occasion of his 65th birthday

Received 21 September 2001; revised 20 December 2001; accepted 22 January 2002

Abstract—6-Methoxy-4*H*-1-benzopyran-7-ol **7**, a major impact flavor compound of *Wisteria sinensis* has been synthesized from 2,4,5-trimethoxybenzaldehyde **1** via scopoletin **3**. The synthetic sequence comprised (i) bisdemethylation of 2,4,5-trimethoxybenzaldehyde **1**, (ii) Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane, (iii) hydrogenation on palladium/carbon in glacial acetic acid, (iv) DIBAL-H reduction of the intermediate lactone and (v) dehydration of the lactol with anhydrous oxalic acid.

1. Introduction

Recently, a number of volatile compounds has been isolated from the flowers of *Wisteria sinensis*, a popular garden plant (Leguminosae), which blooms in May with large clusters of violet flowers.[1] 6-Methoxy-4*H*-1-benzopyran-7-ol **7** was isolated from the hexane extract of the flowers as a key flavor compound, imparting the characteristic smoked odour to this flower, along with 6,7-dimethoxy-4*H*-1-benzopyran.[1] This result was confirmed by our group by GC/MS analysis of the dichloromethane extract, obtained by steam distillation solvent extraction of blossoms of *W. sinensis*.

In this communication, a convenient synthesis of this peculiar flavor compound **7** is presented.

2. Results and discussion

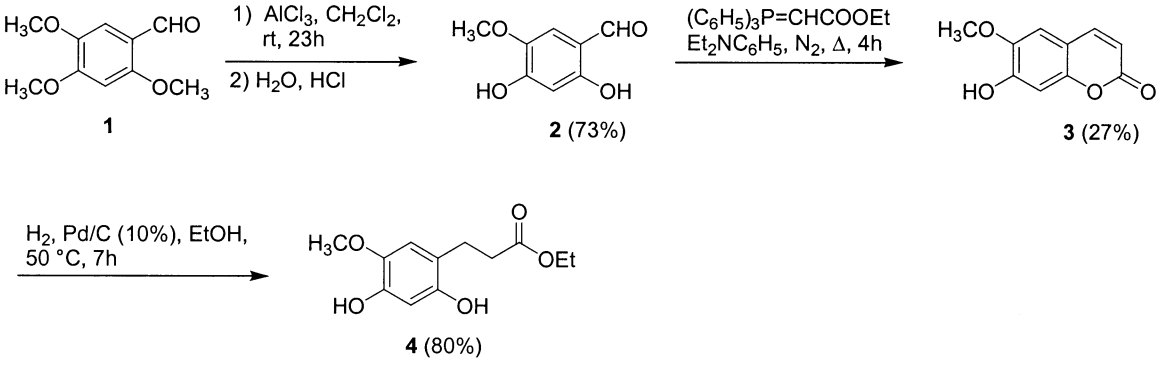
As a suitable precursor for the synthesis of 6-methoxy-4*H*-1-benzopyran-7-ol **7** the coumarin derivative scopoletin **3**, i.e. 7-hydroxy-6-methoxycoumarin, was chosen because it has the right substitution pattern at the 6- and 7-position. It can be prepared in two steps from 2,4,5-trimethoxybenzaldehyde **1** by double ether cleavage with aluminum(III) chloride in dichloromethane via an improved procedure (see Section 3) to give pure 2,4-dihydroxy-5-methoxybenzaldehyde **2** in 73% yield. Subsequent Wittig olefination of the resulting 2,4-dihydroxy-5-methoxybenzaldehyde **2**[2] with ethoxycarbonylmethylenetriphenylphosphorane in *N*,*N*-diethylamine at 188°C afforded scopoletin **3**.[3] The Wittig reagent was freshly prepared from ethyl bromoacetate and triphenylphosphine through the intermediate (ethoxycarbonylmethyl)triphenylphosphonium bromide. Scopoletin was obtained pure in a straightforward way but the yield was rather low (27%). However, the present synthesis offers the advantage of being simple, fast and reliable in affording substantial amounts of the pure natural coumarin scopoletin. It is known that major problems occur in the synthesis of scopoletin reported in the literature. Scopoletin has been prepared previously from several sources, including 2,4-dihydroxy-5-methoxybenzaldehyde,[4,5] 2,4-dihydroxyanisole,[5] esculin[6] and isovanillin.[7] Several of these syntheses suffer from harsh reaction conditions, multiple protection–deprotection reactions and the use of expensive coumarin derivatives itself. In our hands, the reported scopoletin synthesis from isovanillin[7] could not be reproduced in the reported yields at various stages. Our synthesis of scopoletin is based on an improved double demethylation of 2,4,5-trimethoxybenzaldehyde **1** and the utilization of a recent protocol for coumarin synthesis from *ortho*-hydroxybenzaldehydes and a Wittig reagent.[3]

Two subsequent reductions of scopoletin and a final

Keywords: 6-methoxy-4*H*-1-benzopyran-7-ol; scopoletin; fragrance; *Wisteria sinensis*.

* Corresponding author. Tel.: +32-9-264-59-51; fax: +32-9-264-62-43; e-mail: norbert.dekimpe@rug.ac.be

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00081-9



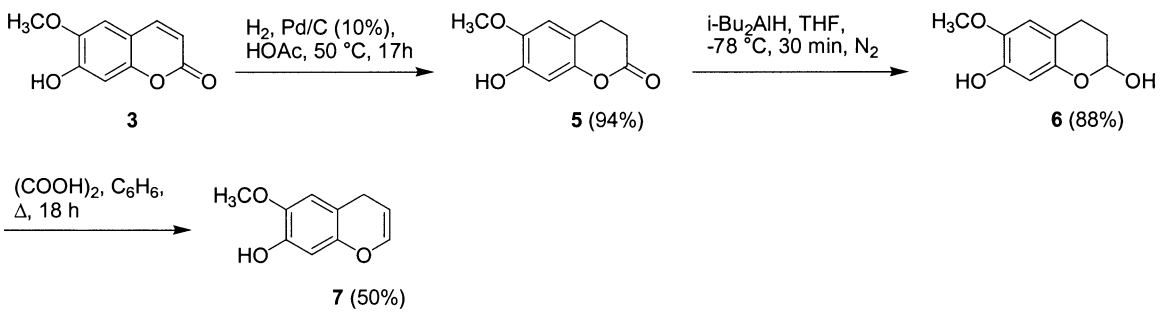
Scheme 1.

dehydration should lead to the title compound **7**. The reaction of scopoletin **3** with hydrogen and 10% palladium on charcoal in ethanol led to reduction of the olefinic double bond and ring opening of the lactone, affording ethyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate **4** in 80% yield (Scheme 1). Other less reactive solvents were investigated. 1,2-Dimethoxyethane is a suitable solvent for the reduction of coumarin itself, but in the case of scopoletin no reduction upon treatment under hydrogenation conditions was achieved, which is probably due to the low solubility of scopoletin in this solvent. Finally, a quantitative reduction of scopoletin **3** was accomplished using hydrogen and palladium on carbon in glacial acetic acid at 50°C, affording 7-hydroxy-6-methoxychroman-2-one **5** in 94% yield. This chromanone has been obtained previously by distillation of 3-(2,4-dihydroxy-5-methoxyphenyl)propionic acid under reduced pressure.[8]

The chromanone **5** was easily reduced with diisobutylaluminum hydride in tetrahydrofuran at −78°C affording 6-methoxychroman-2,7-diol **6** as a faintly pink crystalline substance in 88% yield. The reaction mixture was best worked up using sodium fluoride and a small amount of water.[9]

The final step in the synthesis of 6-methoxy-4*H*-1-benzopyran-7-ol **7** proved to be difficult due to problems encountered using the normal dehydration methods. Reflux of lactol **6** with *p*-toluenesulfonic acid in benzene in a Dean–Stark apparatus gave only tars. Treatment of the hemiacetal **6** with trimethylsilyl triflate only afforded *O*-silylated products. The reaction of **6** with thionyl chloride and trimethylamine in a dichloromethane/chloroform mixture left the starting material unchanged, while stirring in concentrated sulfuric acid at 0°C proved to be too aggressive. Attempts to dehydrate **6** with anhydrous sodium sulfate or anhydrous copper(II) sulfate in diethyl ether[5] were unsuccessful. The combined dehydrating effect of *p*-toluenesulfonic acid and anhydrous calcium chloride in dichloromethane at room temperature were not strong enough, whereas *p*-toluenesulfonic acid and anhydrous calcium chloride at 40°C in acetic acid led to decomposition products.

Dehydration of 4-chromanol[10] and 2-chromanol[11] by means of heating at 150°C with anhydrous copper(II) sulfate has been reported. Applying this method to **6** resulted in a mixture of unchanged starting material and tar. The action of titanium(IV) chloride in diethyl ether at room temperature on **6** led to no reaction, but the reaction with titanium(IV) chloride in dichloromethane at room temperature left only decomposition products. The dehydration with anhydrous oxalic acid in boiling benzene[12] proved to be suitable for the dehydration of 6-methoxychroman-2,7-diol **6** (see Scheme 2). The reaction mixture contained 40% of 6-methoxy-4*H*-1-benzopyran-7-ol **7**, the remainder being starting material. Attempts to improve the formation of the flavor compound **7** by increasing the reaction time or the added amount of oxalic acid were unsuccessful. The desired flavor compound **7** was isolated from the reaction mixture by preparative gas chromatography, as other separation techniques (distillation, flash chromatography) precluded its isolation due to its instability. This method of isolation of the natural flavor substance proved to be very useful for the obtention of pure material, suitable for the study of the flavor characteristics.



Scheme 2.

Unsubstituted 4*H*-1-benzopyran has been synthesized previously.[13] Dihydrocoumarin was reduced using lithium tri-*tert*-butoxyaluminum hydride, which gave 2-chromanol, which was acetylated with acetic anhydride. The pyrolysis product of the latter ester afforded 4*H*-1-benzopyran.[13]

3. Experimental

3.1. General experimental procedures

The ^{1}H, ^{13}C, DEPT, COSY and HETCOR NMR spectra were obtained from $CDCl_3$ at 270 MHz (^{1}H) and at 68 MHz (^{13}C) using a JEOL JNM-EX270 FT NMR spectrometer. Chemical shifts are reported relative to TMS. Mass spectra were obtained with a Varian MAT-112S EI (70 eV) mass spectrometer. IR spectra were recorded on a Thermo Optec Nicolet Impact 410 FT-IR spectrometer. Melting points were determined on a Büchi 535 apparatus.

3.2. General data and product analysis

3.2.1. 2,4-Dihydroxy-5-methoxybenzaldehyde 2 (improved procedure of a literature method).[2] To a stirred suspension of aluminum(III) chloride (67 g, 0.50 mol) in dry dichloromethane (350 ml), a solution of 2,4,5-trimethoxybenzaldehyde **1** (24.53 g, 0.125 mol) in dry dichloromethane (125 ml) was added dropwise. After stirring for 4 h at room temperature, another portion of aluminum(III) chloride (67 g, 0.50 mol), suspended in dry dichloromethane (150 ml), was added. The suspension was further stirred for 19 h and the reaction mixture was poured onto 1 kg of ice to which 45 ml of concentrated hydrochloric acid was added. The organic layer was separated and the aqueous phase was extracted twice with dichloromethane (200 ml). The combined organic layers were filtered over silica gel, dried over magnesium sulfate, evaporated and recrystallized from ethyl acetate to give 2,4-dihydroxy-5-methoxybenzaldehyde **2** (14.98 g, 73%, mp 150°C (lit.[2] mp 152°C)).

3.2.2. Scopoletin 3. A mixture of 2,4-dihydroxy-5-methoxybenzaldehyde **2** (12.58 g, 74.8 mmol) and (ethoxycarbonylmethylene)triphenylphosphorane (31.57 g, 90.6 mmol)[14] were dissolved in *N*,*N*-diethylaniline (500 ml). Under a nitrogen atmosphere, the mixture was heated at 190°C for 4 h, after which it was cooled and kept at room temperature under nitrogen for 4 days. The formed crystals were filtered off and washed with dry diethyl ether. The crude product contained some *N*,*N*-diethylaniline and triphenylphosphinoxide. Therefore, the precipitate was recrystallized from methanol/hexane, giving pure scopoletin **3** (3.89 g, 27%), mp 205–206°C (lit.[5] mp 204°C; lit.[7] 198–200°C). The ^{1}H NMR[15] and ^{13}C NMR data[16] completely match the data reported in the literature.

3.2.3. Ethyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate 4. A solution of scopoletin (0.10 g, 0.52 mmol) in ethanol (5 ml), to which was added 10% palladium on charcoal (50 mg), was stirred at 50°C under a hydrogen atmosphere (50 psi, 3.4 bar) for 7 h, after which the catalyst was filtered off and washed with ethanol. The filtrate was evaporated to give ethyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate **4** (0.10 g, 80%; purity>96% based on NMR). ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.2 (3H, t, J=8 Hz, Me), 2.6–2.9 (4H, m, Ar-CH_2–CH_2–CO), 3.8 (3H, s, OMe), 4.2 (2H, q, J=8 Hz, OCH_2), 6.6 and 6.7 (each 1H, each s, H-5 and H-8).

3.2.4. 7-Hydroxy-6-methoxychroman-2-one 5. To a solution of scopoletin **3** (0.96 g, 5.0 mmol) in warm acetic acid (25 ml), 10% palladium on charcoal (0.15 g) was added and the mixture was stirred for 17 h at 50°C under hydrogen (3.4 bar). The catalyst was filtered off and washed with acetic acid, and the filtrate was evaporated and dried in vacuo, giving pure (>96%) 7-hydroxy-6-methoxychroman-2-one **5** (0.92 g, 94%), mp 151.5–153°C (recrystallized from ether/hexane, lit.[8] mp 155°C). IR (KBr) ν_{max} 3500–3200 (OH), 1740 (C=O), 1515, 1438, 1147, 1119 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.72–2.77 and 2.89–2.94 (each 2H, m, Ar-CH_2–CH_2–CO), 3.88 (3H, s, OMe), 6.64 (1H, s, H-5), 6.66 (1H, s, H-8); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 23.52 and 29.45 (C-3 and C-4), 56.42 (OMe), 104.04 (C-8), 109.76 (C-5), 113.10 (C-4a), 143.32, 143.35 and 146.04 (C-6, C-7 and C-8a), 168.80 (C=O). EIMS (70 eV) *m*/*z* (rel. int.): 194 (M^+, 100), 179 (19), 152 (50), 151 (44), 137 (17), 81 (14), 69 (27), 53 (14).

3.2.5. 6-Methoxychroman-2,7-diol 6. A solution of 7-hydroxy-6-methoxychroman-2-one **5** (0.88 g, 4.5 mmol) in THF (20 ml) was cooled to −78°C under a nitrogen atmosphere. To this solution, a solution of 1N diisobutylaluminum hydride in hexane (10 ml; 0.01 mmol) was added dropwise and the mixture was stirred for 30 min at −78°C. The cooling bath was removed for 10 min, and dichloromethane (125 ml), sodium fluoride (3.78 g, 90 mmol) and water (1.26 g, 70 mmol) were added. The mixture was stirred vigorously for 30 min, then filtered, and dried over magnesium sulfate. After evaporation of the solvents, pure 6-methoxychroman-2,7-diol **6** (0.78 g, 88%) was obtained, mp 135–136°C (recrystallized from ethyl acetate). IR (KBr) ν_{max} 3450–3280 (OH), 2950, 2550, 2460, 1512, 1350, 1190, 1123, 1045, 1024, 898 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.94–2.02 (2H, m, 4-H), 2.61 (1H, dt, J_d=16.2 Hz, J_t=5.3 Hz, H-3a), 2.90 (1H, ddd, J_1=16.2 Hz, J_2=10.2 Hz, J_3=6.6 Hz, H-3b), 3.01 (1H, broad, 2-OH), 3.83 (3H, s, OMe), 5.53 (1H, broad, H-2), 5.56 (1H, broad, 7-OH), 6.44 (1H, s, H-8), 6.54 (1H, s, H-5); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 19.93 (C-3), 27.12 (C-4), 56.50 (OMe), 91.84 (C-2), 103.54 and 112.31 (C-4a and C-8a), 103.61 (C-8), 111.23 (C-5), 144.92 and 145.96 (C-6 and C-7). EIMS (70 eV) *m*/*z* (rel. int.): 196 (M^+, 75), 179 (12), 177 (13), 163 (11), 153 (100), 140 (40), 137 (12), 125 (15), 93 (13), 77 (12), 69 (38), 67 (15), 55 (17). Elem. Anal. ($C_{10}H_{12}O_4$): Calcd 61.22% C, 6.16% H; found 61.44% C, 6.02% H.

3.2.6. 6-Methoxy-4*H*-1-benzopyran-7-ol 7. Anhydrous oxalic acid was prepared by keeping powdered oxalic acid dehydrate at 120°C for 1 day. To a solution of 6-methoxychroman-2,7-diol **6** (0.10 g, 0.51 mmol) in benzene (20 ml), anhydrous oxalic acid (0.23 g, 2.5 mmol) was added and the mixture was refluxed for 18 h. The reaction mixture was filtered and the residue was washed with benzene (five times with 2 ml). The solvent was evaporated to afford a reaction mixture (0.10 g) containing starting material **6** and

6-methoxy-4*H*-1-benzopyran-7-ol **7** in a 55:45 ratio. The nature identical flavor compound **7** was isolated by preparative gas chromatography (Delsi Intersmat IGC 120 ml glass column, 3 m, 5% SE 30, chromosorb W-AW 60–80, TCD, H_2 carrier gas; collection in glass U-shaped vessel, used in flavor analysis laboratories) as a yellow oil.[1] Amounts of about 15 mg per injection could be collected. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.28–3.33 (2H, m, H-4), 3.84 (3H, s, OMe), 4.88 (1H, dt, J_d=6.5 Hz, J_t=3.3 Hz, H-3), 5.50 (1H, s, OH), 6.41–6.47 (3H, m, H-2, H-5 and H-8); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 22.93 (C-4), 56.35 (OMe), 99.73 (C-3), 103.22 and 110.73 (C-5 and C-8), 140.57 (C-2). The quaternary aromatic carbon atoms were not detected at the low concentration used. EIMS (70 eV) *m/z* (rel. int.): 178 (M^+, 96), 177 (M^+-1, 100), 163 (31), 162 (35), 147 (6), 135 (13), 134 (12), 107 (11), 93 (10), 89 (8), 79 (7), 78 (8), 77 (12), 69 (17), 65 (11), 53 (8), 51 (9).

3.3. Preparation and analysis of the essential oil of *W. sinensis*

3.3.1. Steam distillation solvent extraction. 41 g freshly picked blossoms of *W. sinensis*, collected at the National Plant Garden (Ghent University, K.L. Ledeganckstraat 35, B-9000 Ghent, Belgium) in May 1999, were steam distilled in a 500-ml round bottomed flask to which 200 ml distilled water was added. Steam distillation solvent extraction was performed with 14 ml CH_2Cl_2 (ACS 99.5%, Acros, Belgium) with a Likens–Nickerson extraction device[17] during 1.5 h. The extract was dried over $MgSO_4$ and concentrated to 0.5 ml. The extract was analyzed by GC/MS and contained 2.6% of 6-methoxy-4*H*-1-benzopyran-7-ol **7** and 11.0% of 6,7-dimethoxy-4*H*-1-benzopyran.

3.3.2. GC/MS analysis. For the analysis of the extract, a HP 6890 GC Plus coupled with a HP 5973 MSD (Mass Selective Detector—Quadrupole type), equipped with a CIS-4 PTV (programmed temperature vaporization) Injector (Gerstel), and a HP5-MS capillary column (30 m×0.25 mm i.d.; coating thickness 0.25 μm) was used. Working conditions were: injector 250°C, transfer line to MSD 250°C, oven temp: start 50°C, hold 2 min; programmed from 50 to 180°C at 5°C min^{-1} and from 180 to 220°C at 10°C min^{-1}, hold 5 min; carrier gas (He) 1.2 ml min^{-1}; split 1/20; ionization: EI 70 eV; acquisition parameters: scanned *m/z*: 40–200 (5–15 min), 40–300 (15–20 min), 40–400 (>20 min). Co-injection with a *n*-alkane series (C15–C17) was performed to calculate the Kováts retention indexes of the compounds.

3.3.3. 6-Methoxy-4*H*-1-benzopyran-7-ol 7. Kováts retention index 1597.

3.3.4. 6,7-Dimethoxy-4*H*-1-benzopyran. MS (70 eV) *m/z* (rel. int.) 192 (M^+, 90), 191 (M^+-1, 100), 177 (23), 175 (7), 161 (5), 147 (16), 134 (6), 118 (5), 106 (5), 77 (8). Kováts retention index 1629.

Acknowledgements

The authors are grateful to Professor Paul Goetghebeur (Department of Biology, Faculty of Sciences, Ghent University, Ghent, Belgium) for providing the blossoms of *Wisteria sinensis*.

References

1. Joulain, D.; Tabacchi, R. *Phytochemistry* **1994**, *37*, 1769–1770.
2. Mali, R. S.; Manekar, A. R.; Tilve, S. G. *Org. Prep. Proced. Int.* **1992**, *24*, 52–54.
3. Ishi, H.; Ishikawa, T.; Wada, H.; Miyazaki, H.; Kaneko, Y.; Harayama, T. *Chem. Pharm. Bull.* **1992**, *40*, 2614–2619.
4. Seka, R.; Kallir, P. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 909–917.
5. Head, F. S. H.; Robertson, A. *J. Chem. Soc.* **1931**, 1241–1245.
6. Ahluwalia, V. K.; Sachdev, G. P.; Seshadri, T. R. *Indian J. Chem.* **1969**, *7*, 59–60.
7. Crosby, D. G. *J. Org. Chem.* **1961**, *26*, 1215–1217.
8. Moore, C. W. *J. Chem. Soc.* **1911**, *99*, 1043–1048.
9. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsurama, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2840–2844.
10. Baranton, F.; Fontaine, G.; Maitte, P. *Bull. Soc. Chim. Fr.* **1968**, 4203–4208.
11. Clark-Lewis, J. W.; McGarry, E. J. *Aust. J. Chim.* **1973**, *26*, 819–826.
12. Webster, W.; Young, D. P. *J. Chem. Soc.* **1956**, 4785–4795.
13. Parham, W. E.; Huestis, L. D. *J. Am. Chem. Soc.* **1962**, *84*, 813–816.
14. Villa, M.-J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1569–1572.
15. Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1979**, *18*, 1367–1370.
16. Sankar, S.; Gilbert, R.; Fornes, R. *Org. Magn. Reson.* **1982**, *19*, 222–226.
17. Nickerson, G. B.; Likens, S. T. *J. Chromatogr.* **1966**, *21*, 1–5.