Tetrahedron Letters 53 (2012) 2993–2995

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New scalable and eco-friendly synthesis of gingerols

N. Vijendra Kumar, P. Srinivas, B.K. Bettadaiah *

Plantation Products, Spices and Flavour Technology Department, Central Food Technological Research Institute, Council of Scientific and Industrial Research, Mysore 570 020, India

ARTICLE INFO

Article history:
Received 3 February 2012
Revised 21 March 2012
Accepted 22 March 2012
Available online 29 March 2012

Keywords:
6-Gingerol
Eugenol
Hydroboration
Eugenyl iodide
Isoxazolines
Olefins
Reduction

ABSTRACT

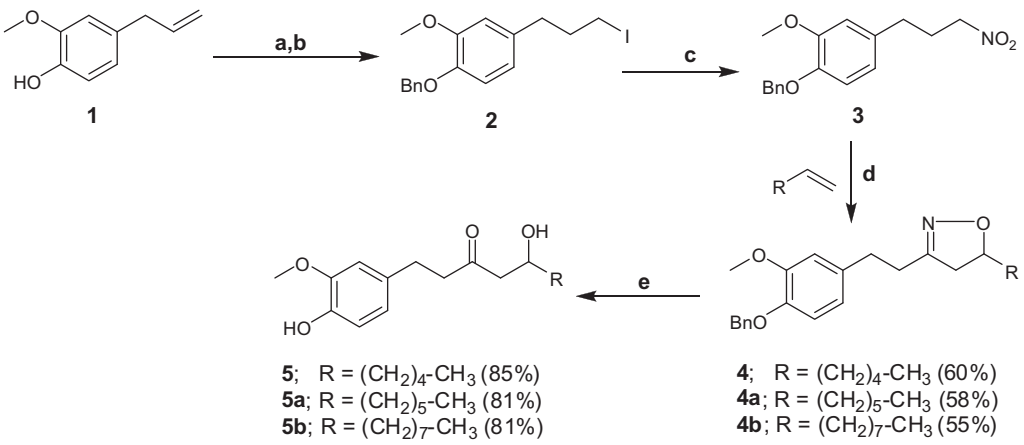
Synthesis of 6-gingerol and its congeners 7- and 9-gingerols has been achieved from eugenol by a new scalable and eco-friendly protocol. The key steps are functionalization of eugenol to the nitro compound and its reaction under optimized condition with terminal alkenes to afford intermediate isoxazolines. The latter on catalytic hydrogenation in presence of Raney nickel afford corresponding gingerols in good yields.

Ginger (*Zingiber officinale* Roscoe) is used in food as a spice and has been an important ingredient in Ayurvedic, Tibb-Unani and Chinese herbal medicines for the treatment of various ailments like catarrh, rheumatism, gingivitis, toothache, asthma, stroke, constipation, and diabetes.[1] 6-Gingerol is the key phenolic compound of rhizomes of ginger and responsible for the flavor, pungency, and bio-active attributes like antioxidant,[2] anti-inflammatory,[3] anti-tumor-promoting,[4] anti-platelet aggregation,[5] and anti-bacterial effects.[6] As it is present in the rhizomes in a complex mixture of homologues along with other components, its isolation and purification is difficult. Hence, commercial availability of 6-gingerol is low and it is highly expensive. In spite of broad and interesting bioactivities associated with gingerol and its structural simplicity, only a few synthetic methods have been reported.[7,8] Due to its attractive medicinal properties, synthetic methods with experimental simplicity would be valuable additions when compared to the existing methods, which are either not easily amenable or involving severe experimental conditions, for example, a protocol involving the condensation of lithium-enolate with 1-alkanals at −78 °C affords good yield but not easily reproducible.[9] Hence, a simple eco-friendly and scalable protocol with the use of inexpensive starting materials is envisioned in this work. Eugenol (**1**), a major phenolic constituent of clove bud essential oil, is used as starting compound to synthesize 6-gingerol and its higher homologues.[10] Eugenol is widely available, inexpensive and has 4-homoallyl, *o*-methoxy-substituted phenolic moiety. Structurally, eugenol is an ideal substrate for the synthesis of gingerols. To our knowledge this is the first report of synthesis of gingerols starting from eugenol.

In the synthesis (Scheme 1), phenolic group in eugenol was first protected as benzyl ether and then converted into eugenyl iodide (**2**) by hydroboration followed by iodination.[11] This was performed by addition of iodine to double bond of eugenol *via* hydroboration reaction using sodium borohydride and sodium methoxide, which resulted in anti-Markovnikov's addition of iodine across the double bond. Compound **2** was then converted into nitro compound (**3**) in water using sodium nitrite and silver nitrate. In the presence of sodium nitrite alone, **3** was obtained in low yield as the corresponding nitrite was competing.[12] This was overcome when the reaction was performed under optimized reaction conditions, wherein silver nitrate and sodium nitrite were used in three and four equivalents respectively to afford good yield of product.[13] The compound **3** was then converted into isoxazoline (**4**) by reaction with 1-heptene in presence of base triethylamine and acetic anhydride in 40% yield.[14] A few exploratory experiments at this stage were conducted to improve the yield of isoxazoline. Under the optimized conditions that employed acetic anhydride (3 equiv) and 4-(dimethylamino)pyridine (1.5 equiv), isoxazoline could be obtained in 60% yield.[15] The experiment on higher scale (1.5 g) also afforded the nitro compound **4** in 60% yield. The isoxazoline, thus prepared was subjected to reduction using hydrogen at 30 psi in the presence of Raney nickel in moist ethanol to afford β-hydroxy carbonyl compound. Further, it was filtered and taken directly for benzyl de-protection of phenolic group by hydrogenolysis at 30 psi pressure in

* Corresponding author.
E-mail address: bettadaiah@cftri.res.in (B.K. Bettadaiah).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.03.092



Scheme 1. Reagents and conditions: (a) benzyl bromide, K_2CO_3, AcCN, rt, 4 h, 98%; (b) $NaBH_4$, I_2, THF, 0 °C, 2.5 h then benzyl protected eugenol, rt, 3 h; NaOMe, I_2, 0 °C, 3 h, 75%; (c) $AgNO_3$, $NaNO_2$, H_2O, rt, 10 h, 75%; (d) Ac_2O, DMAP, DCM, N_2, rt, 5–6 h; (e) (i) Ra-Ni, H_2, EtOH, ~6 h, (ii) Pd/C, H_2, EtOH, ~3 h.

presence of Pd/C (10%) to afford excellent yield of 6-gingerol (**5**).[16] On a small scale run (100 mg) the yield of 6-gingerol was 85%. On higher scale (1 g), the isolated yield of **5** was 80% from steps **e (i)** and **e (ii)**. The isolated yield of **5** over two steps **d** and **e** was found to be in the range of 48–51%.[17]

Further, synthesis of isoxazolines containing 6 and 8 carbons [R = $(CH_2)_5CH_3$ and $(CH_2)_7CH_3$] was undertaken. Starting from **3**, as a scaffold, isoxazolines **4a** and **4b** were synthesized by replacing 1-heptene with 1-octene and 1-decene respectively. The isolated yields of **4a** and **4b** run on 0.6 g scale of compound **3** were 58% and 55%, respectively. On continuing the sequence, 7- and 9-gingerols (**5a** and **5b**) were prepared from **4a** and **4b** in 81% yield.[17]

The products from various stages were isolated by normal work-up followed by silica gel chromatography to afford compounds, which gave satisfactory ^1H and ^{13}C NMR data. The TLC (2% EA in hexane) visualization under UV at 254 and 366 nm, and charring of spots with phosphomolybdic acid indicated single spot products. They were further confirmed from HRMS data. The synthesized 6-gingerol was also compared with HPLC of natural sample isolated from ginger.

In conclusion, we have developed a simple, new synthesis of 6-gingerol and its homologues from eugenol the main compound present in clove bud essential oil, which is easily available and inexpensive. The experimental conditions are easily scalable and involve an eco-friendly step for conversion into nitro compound (**3**). Since 6-gingerol is an important bioactive principle, the present protocol is advantageous in preparing this food/pharmaceutical grade compound in good quantity.

Acknowledgments

Author N.V.K. is thankful to UGC, New Delhi for the award of Junior Research Fellowship. We are grateful to Mr. J. R. Manjunatha, Senior Research Fellow, Plantation Products, Spices and Flavour Technology Department, CFTRI, Mysore for NMR analyses.

References and notes

1. (a) Awang, D. *Can. Pharm. J.* **1992**, *125*, 309–311; (b) Tapsell, L. C.; Hemphill, I.; Cobiac, L.; Patch, C. S.; Sullivan, D. R.; Fenech, M.; Roodenrys, S.; Keogh, J. B.; Clifton, P. M.; Williams, P. G.; Fazio, V. A.; Inge, K. E. *Med. J. Aust.* **2006**, *185*, S4–S24.
2. (a) Murad, N. A.; Ngah, W. Z. W.; Yusof, Y. A. M.; Abdul Aziz, J. M.; Semarak, J. *Asian J. Biochem.* **2007**, *2*, 4214–4226; (b) Kim, J. K.; Kim, Y.; Na, K. M.; Surh, Y.-J.; Kim, T. Y. *Free Radical Res.* **2007**, *41*, 603–614.
3. Ahui, M. L. B.; Champy, P.; Ramadan, A.; Pham Van, L.; Araujo, L.; Brou Andre, K.; Diem, S.; Damotte, D.; Kati-Coulibaly, S.; Offoumou, M. A.; Dy, M.; Thieblemont, N.; Herbelin, A. *Int. Immunopharmacol.* **2008**, *8*, 1626–1632.
4. (a) Lee, H. S.; Seo, E. Y.; Kang, N. E.; Kim, W. K. *J. Nutr. Biochem.* **2008**, *19*, 313–319; (b) Lee, S. H.; Cekanova, M.; Baek, S. *J. Mol. Carcino.* **2008**, *47*, 197–208.
5. Hibino, T.; Yuzurihara, M.; Terawaki, K.; Kanno, H.; Kase, Y.; Takeda, A. *J. Pharmacol. Sci.* **2008**, *108*, 89–94.
6. Nagoshi, C.; Shiota, S.; Kuroda, T.; Hatano, T.; Yoshida, T.; Kariyama, R.; Tsuchiya, T. *Biol. Pharm. Bull.* **2006**, *29*, 443–447.
7. (a) Kato, N.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 1679–1682; (b) Barco, A.; Benetti, S.; Baraldi, P. G.; Guarneri, M.; Pollini, G. P.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1981**, 599–600; (c) Denniff, P.; Macleod, I.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 82–87; (d) Banno, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1453–1454; (e) Hirao, N.; Toyama, T.; Takahata, A.; Yasui, B. *Chem. Pharm. Bull.* **1972**, *20*, 2287–2289.
8. (a) Fukuda, H.; Tetsu, M.; Kitazume, T. *Tetrahedron* **1996**, *52*, 157–164; (b) Solladie, G.; Ziani-Cherif, C. *J. Org. Chem.* **1993**, *58*, 2181–2185; (c) Martin, M.; Guibet, P. *Chirality* **1991**, *3*, 151–155; (d) Annunziata, R.; Cardani, S.; Gennari, C.; Poli, G. *Synthesis* **1984**, 702–703; (e) Cinquini, M.; Cozzi, F.; Gilardi, A. *J. Chem. Soc., Chem. Commun.* **1984**, 551–552; (f) Gall, T. L.; Lellouche, J. P.; Beaucourt, J. P. *Tetrahedron Lett.* **1989**, *30*, 6521–6524; (g) Baraldi, P. G.; Fabio, M.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2983–2987; (h) Enders, D.; Eichenauer, H.; Pieter, R. *Chem. Ber.* **1979**, *112*, 3703–3714; (i) Hirao, N.; Kawachi, J.; Yasui, B. *Chem. Pharm. Bull.* **1973**, *21*, 2569–2571.
9. Fleming, S. A.; Dyer, C. W.; Eggington, J. *Synth. Commun.* **1999**, *29*, 1933–1939.
10. Santos, A. L.; Chierice, G. O.; Alexander, K. S.; Riga, A.; Matthews, E. *J. Therm. Anal. Calorim.* **2009**, *96*, 821–825.
11. Brown, H. C.; Rathke, M. W.; Rogic, M. M.; De Lue, N. R. *Tetrahedron* **1988**, *44*, 2751–2762.
12. Kornblum, N. *Org. React.* **1962**, *12*, 101–156.
13. *Compound* ***3***: To a mixture of **2** (1.5 g, 3.94 mmol) in H_2O (50 mL), $AgNO_3$ (2 g, 11.82 mmol) and $NaNO_2$ (1.1 g, 15.76 mmol) were added and the mixture was stirred in dark at ambient temperature for 10 h. The reaction mixture was filtered and the filtrate was extracted with DCM (3 × 50 mL). The combined organic layer was concentrated to afford the crude product which was purified by column chromatography on silica gel (200–400 mesh) using mixtures of EA and petroleum ether (60–80 °C) to afford the pure compound (0.88 g, 75%). Yellow solid; mp 48–50 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45(d, 2H, *J* = 7.6 Hz), 7.38(t, 2H, *J* = 7.5 Hz), 7.32(t, 1H, *J* = 7.4 Hz), 6.84(d, 1H, *J* = 8.12 Hz), 6.73(s, 1H), 6.66(d, 1H, *J* = 8.04 Hz), 5.15(s, 2H), 4.38(t, 2 H, *J* = 6.9 Hz), 3.91(s, 3H), 2.67(t, 2H, *J* = 7.4 Hz), 2.31(p, 2H, *J* = 7.1 Hz); Mass (ESI): $[M^+$+Na] for $C_{17}H_{19}NO_4Na$, Calculated: 324.1211; Found: 324.2504.
14. Maugein, N.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 1547–1550.
15. *General procedure for synthesis of isoxazolines (****4****,* ***4a*** *and* ***4b****)*: To a solution of **3** (0.6 g, 1.99 mmol), under inert atmosphere, in DCM (10 mL), an appropriate olefin (9.95 mmol) was added at ambient temperature followed by the addition of acetic anhydride (0.55 g, 5.97 mmol) and DMAP (0.36 g, 2.98 mmol). The reaction mixture was stirred until the disappearance of nitro compound by TLC (~5–6 h). Aqueous work-up followed by concentration and silica gel column chromatography afforded pure compound. Compound **4**; Light yellow solid; mp 63–65 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45(d, 1H, *J* = 7.13 Hz), 7.38(t, 2H, *J* = 7.4 Hz), 7.31(t, 1H, *J* = 7.4 Hz), 6.82(d, 1H, *J* = 8.32 Hz), 6.78(s, 1H), 6.69(d, 1H, *J* = 8.03 Hz), 5.14(s, 2H), 4.50–4.55(m, 1H), 3.90(s, 3H), 2.92(dd, 1H, J_1 = 16.72 Hz, J_2 = 10.15 Hz), 2.85(t, 2H, *J* = 7.8 Hz), 2.64(t, 2H, *J* = 7.8 Hz), 2.50(dd, 1H, J_1 = 16.82 Hz, J_2 = 8.13 Hz), 1.28–1.50(m, 8H), 0.9(t, 3H, *J* = 6.6 Hz); Mass (ESI): $[M^+$+Na] for $C_{24}H_{31}NO_3Na$, Calculated: 404.2201; Found: 404.4111. Compound **4a**; Light yellow solid; mp 58–61 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45(d, 2H, *J* = 7.6 Hz), 7.38(t, 2H, *J* = 7.4 Hz), 7.31(t, 1H, *J* = 7.5 Hz), 6.82(d, 1H, *J* = 8.2 Hz), 6.78(s, 1H), 6.69(d, 1H, *J* = 8.03 Hz), 5.14(s, 2H), 4.50–4.54(m, 1H), 3.90(s, 3H), 2.92(dd, 1H, J_1 = 16.68 Hz, J_2 = 10.25 Hz), 2.85(t, 2H, *J* = 7.8 Hz), 2.64(t, 2H, *J* = 7.7 Hz), 2.50(dd, 1H, J_1 = 16.82 Hz, J_2 = 8.13 Hz), 1.27–1.50(m, 10H), 0.90(t, 3H,

J = 6.8 Hz); Mass (ESI): [M^++1] for $C_{25}H_{33}NO_3$, Calculated: 396.5344; Found: 396.4690. Compound **4b**; Light yellow solid; mp 57–59 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45(d, 1H, J = 7.2 Hz), 7.38(t, 2H, J = 7.4 Hz), 7.31(t, 1H, J = 7.3 Hz), 6.82(d, 1H, J = 8.1 Hz), 6.78(s, 1H), 6.69(d, 1H, J = 8.0 Hz), 5.14(s, 2H), 4.51–4.53(m, 1H), 3.90(s, 3H), 2.92(dd, 1H, J_1 = 16.48 Hz, J_2 = 10.34 Hz), 2.85(t, 2H, J = 7.8 Hz), 2.64(t, 2H, J = 7.6 Hz), 2.50(dd, 1H, J_1 = 16.76 Hz, J_2 = 8.14 Hz), 1.27–1.49(m, 14H), 0.90(t, 3H, J = 6.5 Hz); Mass (ESI): [M^++1] for $C_{25}H_{33}NO_3$, Calculated: 424.5875; Found: 424.5268.

16. Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123–3126.
17. *General procedure for synthesis of gingerols (**5**, **5a** and **5b**)*: To a solution of isoxazolines (**4**, **4a** and **4b**, 0.1 g) in ethanol and water (3:1, 4 mL) Raney nickel (10 mg) was added and hydrogenated at 30 psi pressure for ~6 h. After completion of the reaction by TLC analyses, the mixture was filtered. To the filtrate Pd/C (10%, 10 mg) was added and set for hydrogenolysis at 30 psi hydrogen pressure for ~3 h. After completion of the reaction, the reaction mixture was filtered and filtrate was taken into DCM (5 mL) and washed with brine (10 mL). The organic layer was concentrated to get the crude product which was purified by column chromatography on silica gel (200–400 mesh) using EA in petroleum ether (60–80 °C) to afford the pure compounds. Compound **5**; Yellow oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.84(d, 1H, J = 7.80 Hz), 6.67–6.70(m, 2H), 5.53(s, 1H), 4.02–4.07(m, 1H), 3.89(s, 3H), 2.98(s, 1H), 2.85(t, 2H, J = 7.4 Hz), 2.75(t, 2H, J = 7.3 Hz), 2.51–2.57(m, 2H), 1.27–1.46(m, 8H), 0.90(t, 3H, J = 6.9 Hz); ^{13}C NMR (125 MHz $CDCl_3$): 211.04, 146.12, 143.69, 132.32, 120.43, 114.06, 110.69, 67.37, 55.56, 49.04, 45.10, 36.12, 31.31, 28.97, 24.78, 22.23, 13.64; Mass (ESI): [M^+] for $C_{17}H_{24}O_4$, Calculated: 294.1831; Found: 294.4097. Compound **5a**; Yellow oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.84(d, 1H, J = 7.86 Hz), 6.67–6.70(m, 2H), 5.50(s, 1H), 4.03–4.05(m, 1H), 3.89(s, 3H), 2.85(t, 2H, J = 7.2 Hz), 2.75(t, 2H, J = 7.2 Hz), 2.48–2.61(m, 2H), 1.29–1.45(m, 10H), 0.89(t, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 211.05, 146.12, 143.69, 132.34, 120.44, 114.07, 110.69, 67.36, 55.57, 49.06, 45.12, 36.18, 31.45, 28.98, 28.87, 25.09, 22.26, 13.72. Mass (ESI): [M^++Na] for $C_{18}H_{28}O_4Na$, Calculated: 331.4125; Found: 331.4143. Compound **5b**; Yellow oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.84(d, 1H, J = 7.89 Hz), 6.66–6.73(m, 2H), 5.53(s, 1H), 4.03–4.05(m, 1H), 3.89(s, 3H), 2.85(t, 2H, J = 7.3 Hz), 2.75(t, 2H, J = 7.3 Hz), 2.48–2.60(m, 2H), 1.27–1.46(m, 14H), 0.89(t, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 199.44, 147.51, 143.65, 132.34, 120.50, 113.99, 110.82, 67.37, 55.57, 49.06, 45.12, 36.18, 31.50, 29.37, 29.21, 28.84, 28.78, 25.13, 22.32, 13.74; Mass (ESI): [M^++Na] for $C_{20}H_{32}O_4Na$, Calculated: 359.2198; Found: 359.3834.