Synthesis of the naturally occurring prenylated coumarins balsamiferone and cedrelopsin by domino reactions

Rupesh E. Patre,[a] Perunninakulath S. Parameswaran,[b] and Santosh G. Tilve[a]*

[a]Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 206, India
[b]National Institute of Oceanography, Dona Paula, Goa 403 004, India
E-mail: stilve@unigoa.ac.in

Dedicated to Professor S. Chandrasekaran on the occasion of his 65th birthday

Abstract
Regioselective one step synthesis of naturally occurring prenyl coumarin balsamiferone is described using domino Wittig reaction, 3,3-sigmatropic rearrangements and deprenylation, while regioselective synthesis of cedrelopsin is described *via* domino Wittig reaction, prenylation and deprenylation..

Keywords: Domino reaction, Wittig reaction, Claisen rearrangement, Cope rearrangement, balsamiferone, cedrelopsin

Introduction

Coumarin is a oxygen heterocycle widely distributed throughout the plant kingdom.[1] Coumarins have received considerable attention, since they exhibit diverse biological activities such as anti HIV, antimalarial, antibacterial, anticancer, cytotoxic, antitumor, antihypertension, antiarrhythmia, anti osteoporosis, pain relief, preventing asthma and antisepsis.[2] Several of these compounds have isoprenoid units (mostly prenyl/isoprenyl) attached at different positions in the benzopyran ring system.[3] For example gravelliferone **1** [3-(1,1-dimethylallyl)-6-(3,3-dimethylallyl)-7-hydroxycoumarin] isolated[4] from *Ruta graveolens*, balsamiferone **2** [3,6-di-(3,3-dimethylallyl)-7-hydroxycoumarin] isolated[5] from *Amyris balsamifera*, and 6,8-diprenylumbelliferone **3** isolated[6] from Citrus species are three typical diprenylated coumarins, while cedrelopsin **4** isolated from the bark of *Cedrelopsis grevei*[7] has one prenyl group (Figure 1).

Domino reactions[8] play crucial role in the biosynthesis of natural products. Chemists are interested in emulating these reactions in laboratory due to the tremendous savings they offer in terms of time, energy and cost as compared to conventional sequential synthesis. It also provides

opportunity to construct complex target compounds by the introduction of several diversity elements in a single chemical event. It can also be exploited to make libraries of structurally diverse compounds. Typically, purification of products resulting from domino reactions is also simple since all the organic reagents employed are consumed and are incorporated into the target compounds. Several methods/reviews are reported for the construction of complex molecular framework using domino reactions.[8,9]

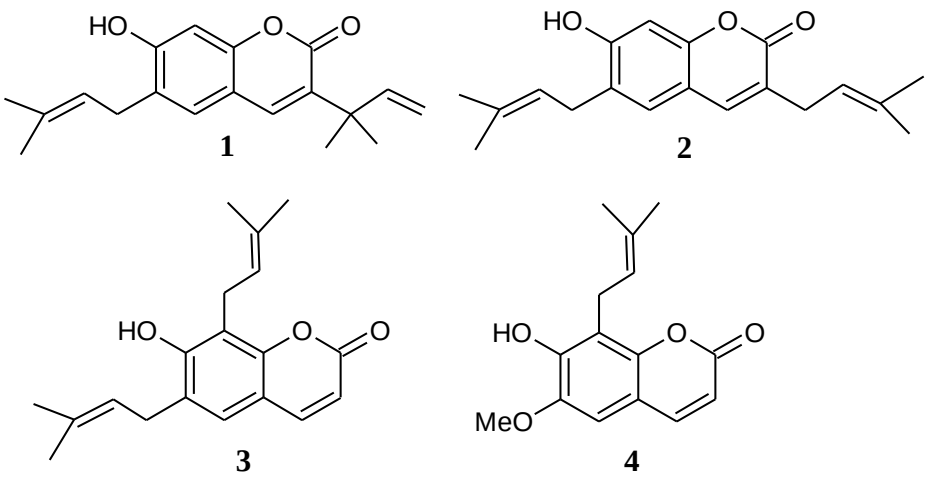
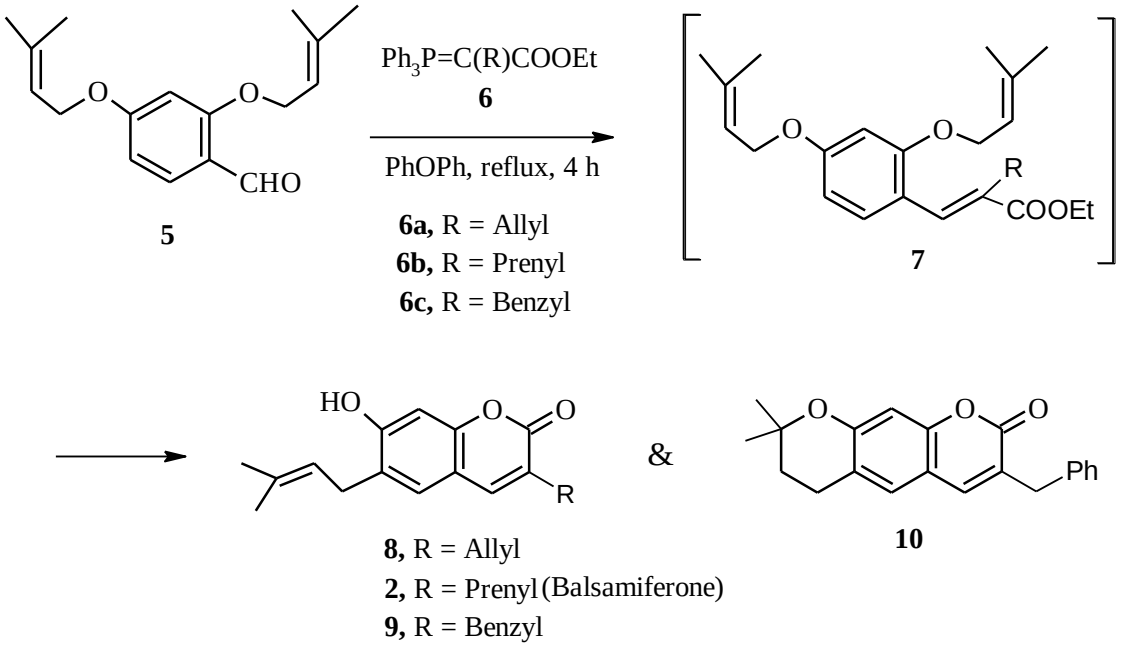


Figure 1

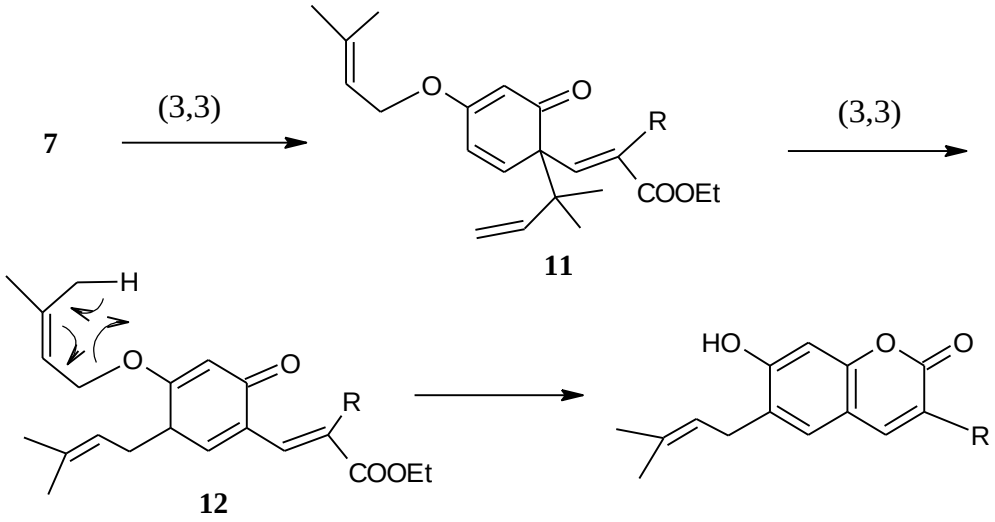
Results and Discussion

In our earlier communication[10] we had used domino Wittig reaction, double Claisen-Cope rearrangements for the one pot synthesis of gravelliferone **1.** This is one of the shortest syntheses of this natural coumarin. During this experiment, we also obtained 6,8-diprenylumbelliferone **3**, another natural coumarin. Incidentally this constituted its first synthesis. The formation of **3** was postulated to take place by domino Wittig reaction, Claisen rearrangement and two consecutive Cope rearrangements of the 2-prenyloxy group and intramolecular prenylation of the 4-prenyloxy group. At this stage, we conjectured that if steric crowding in the molecule is increased the second Claisen rearrangement observed for the formation of **1** or the intramolecular prenylation observed in the formation of **3** may be precluded. If this happens we can synthesize balsamiferone **2**, another natural coumarin from the same starting using appropriately substituted phosphorane. Towards this goal initially we condensed **5** with phosphorane **6a** in refluxing diphenyl ether (Scheme 1). As speculated 3-allyl-7-hydroxy-6-prenyl coumarin **8** was obtained in 65% yield. Encouraged by this result we undertook synthesis of balsamiferone **2**. Thus, 2,4-diprenyloxybenzaldehyde **5** was heated with prenyl phosphorane **6b** in a similar manner. We found that balsamiferone **2** was the only pure product obtained in 42% yield from the complex mixture. The spectral data of it were in accordance with literature data.[11] The formation of **2** was

rationalized by simultaneous Claisen-Cope rearrangements of the 2′-prenyloxy group of the intermediate ester (Scheme 2) to deliver the prenyl group at the 6-position of the coumarin nucleus and deprenylation of the 4′-prenyloxy group.



Scheme 1



Scheme 2

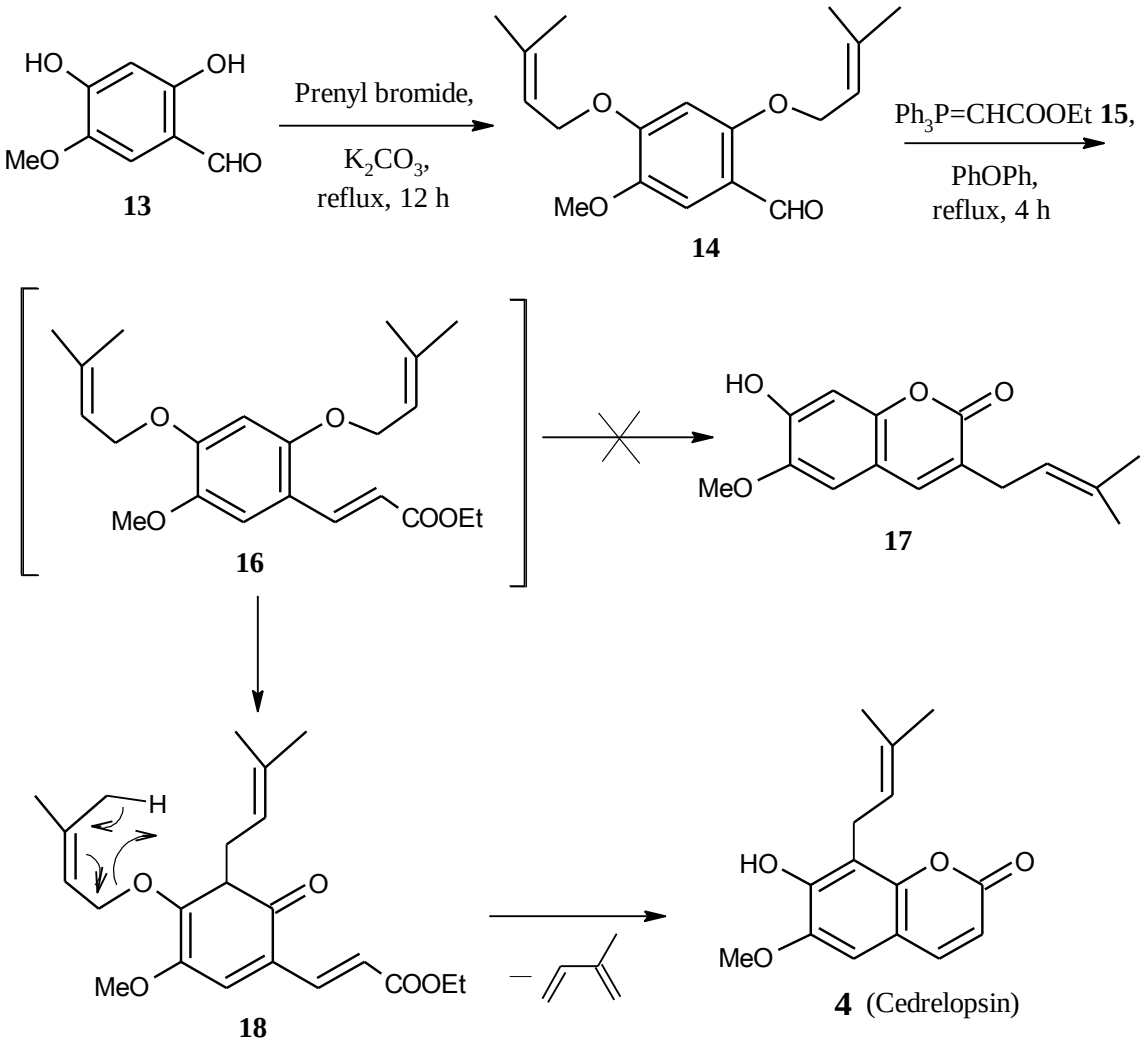
Kapil *et al.*[12] have synthesized balsamiferone **2** beginning from umbelliferone-3-carboxylic acid in 13 steps. Cairns *et al.*[8c] synthesized the target molecule **2** in six steps, *via* a cascade

Claisen-Cope rearrangement, from 7-hydroxyumbelliferone *via* demethylsuberosin. Both the above examples use preformed coumarin as the starting material. Mali *et al.*[13] have reported one step synthesis of methyl ether of **2** using tandem Wittig and Claisen-Cope rearrangement from 2-prenyloxy-4-methoxybenzaldehyde. However, these authors could not demethylate the methyl ether to **2** due to the problem of concurrent cyclisation to corresponding pyranocoumarin. The present synthesis of balsamiferone **2** described herein is the shortest route for this heterocycle. Similarly, further, when **5** was condensed with phosphorane **6c** the corresponding 3-benzyl-7-hydroxy-6-prenylcoumarin **9** was obtained in 20% yield while pyranocoumarin **10** was obtained in 40% yield.

Having tested the success in one pot deprenylation for the synthesis of **2** and direct intramolecular C-prenylation[10] for the synthesis of **3** we decided to study this protocol on 2,4-di-*o*-(3,3-dimethylallyl)-5-methoxybenzaldehyde **14**. If the 2′-prenyloxy group of the intermediate ester undergoes Claisen-Cope rearrangement, cyclisation and deprenylation then it would provide coumarin **17**, since C-5 position is blocked (Scheme 3). Coumarin **17** is recently isolated[14] from *Coriaria nephalensis.* However, presence of the methoxy group at 5-position in **16** makes the benzene ring electron rich which should facilitate the intramolecular C-prenylation of one of the prenyloxy group rather than its sigmatropic rearrangement, leading to formation of cedrelopsin **4**, a coumarin isolated from the bark of *Cedrelopsis grevei*.[7] Thus, 2,4-di-(3,3-dimethylallyl)-5-methoxybenzaldehyde **14** prepared from 2,4-dihydroxy-5-methoxy benzaldehyde[15] was heated with phosphorane **15** in diphenyl ether. The ^{1}H NMR data of the product obtained indicated that prenyl group is attached to the benzene ring rather than to the pyrone ring. The spectral data were in a close agreement with that of the natural product **4**. The yield of this was found to be 45%. Cedrelopsin has been synthesized before by Anet *et al.* to confirm the structure of naturally occurring coumarin baryllin.[16] The formation of **4** could be rationalized by deprenylation of one of the prenyloxy group and intramolecular C-prenylation of the other (Scheme 3).

Conclusions

In summary, a one step synthesis of naturally occurring coumarin balsamiferone **2** is achieved by domino Wittig reaction, Claisen-Cope rearrangement, deprenylation and lactonisation. The corresponding 3-allyl and 3-benzyl analogues were synthesized using the same protocol. Also a novel one pot synthesis of cedrelopsin **4**, a natural prenylated coumarin, is accomplished using domino Wittig reaction, deprenylation, intramolecular prenylation and cyclisation.



Scheme 3

Experimental Section

General. All reactions were carried out under an inert atmosphere. Solvents were purified & dried by standard procedure before use. Column chromatography was performed on silica gel (60-120mesh) and flash chromatography was performed on combi flash. Infrared Spectra (IR) were recorded in a Shimadzu FTIR instrument. NMR spectra were recorded on a Brucker 300MHz and 400MHz instruments using $CDCl_3$ as solvent and TMS as internal standard. The multiplicities of carbon signal were obtained from DEPT experiments. HRMS were recorded on a micromass ES-QTOF.

General procedure for the synthesis of 2,4-diprenyloxybenzaldehyde (5) and 2,4-diprenyloxy-5-methoxybenzaldehyde (14)

To a refluxing mixture of resorcylaldehyde (1 mmol) and potassium carbonate (2.5 mmol) in acetone (40 mL), prenyl bromide (2.5 mmol) was added slowly in portions over a period of 12h. The reaction mixture was then cooled, filtered and washed with acetone (10mL). The filtrate was concentrated under vacuum. To the residue, water (20 mL) was added and extracted with diethyl ether (3 X 20 mL). The combined organic layer was washed with 2N sodium hydroxide (2 X 15 mL) and then with water (2 X 15 mL). The organic layer was dried over anhydrous sodium sulphate. Evaporation of solvent under reduced pressure gave viscous liquid, which was purified over silica gel column chromatography (EtOAc:hexanes = 1:99)

2,4-Diprenyloxybenzaldehyde (5). Yield: 0.228 g (82%); viscous oil; IR (KBr) 1675 (C=O) cm^{-1}; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.19, 18.23, 25.70, 25.75, 65.14, 65.43, 99.65, 106.43, 118.81, 118.90, 119.23, 130.18, 138.59, 139.01, 163.04, 165.33, 188.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (3H, s, C*H*$_3$), 1.77 (3H, s, C*H*$_3$), 1.82 (6H, s, 2 X C*H*$_3$), 4.59 (4H, m, CH_2), 5.50 (2H, m, C*H*), 6.48 (1H, s, *H*-3), 6.54 (1H, d, *J* = 8.7 Hz, *H*-5), 7.80 (1H, d, *J* = 8.7 Hz, *H*-6), 10.32 (1H, s, CHO); HRMS *m/z* $[M+Na]^+$ 297.1460 (calcd for $C_{17}H_{22}O_3$, 297.1467).

2,4-Diprenyloxy-5-methoxybenzaldehyde (14). Yield: 0.187 g (61%); viscous oil; IR (KBr); 1680 (C=O) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.27, 18.30, 25.76, 25.83, 56.18, 66.03, 66.48, 99.09, 108.82, 117.93, 118.97, 119.14, 138.64, 138.73, 144.04, 154.98, 157.89, 188.25; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (3H, s, C*H*$_3$), 1.79 (3H, s, C*H*$_3$), 1.81 (6H, s, 2 X C*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 4.62 (4H, m, 2 X C*H*$_2$), 5.50 (2H, m, 2 X C*H*), 6.53 (1H, s, *H*-3), 7.32 (1H, s, *H*-6), 10.32 (1H, s, C*H*O).

General procedure for the reaction of phosphoranes 6a-c with 2,4-diprenyloxybenzaldehyde (5) and phosphoranes 15 with 2,4-diprenyloxy-5-methoxybenzaldehyde (14)

A solution of 2,4-diprenyloxybenzaldehyde **5/14** (1 mmol) and phosphorane **7**/**15** (1.5 mmol) in diphenyl ether was refluxed for 4 h. The reaction mixture was loaded over silica gel column. Using hexanes, diphenyl ether was removed. The column was washed with ethyl acetate and the washings were concentrated. The concentrated washings were further separated by combi flash chromatography using 10% ethyl acetate and hexanes as an eluent.

Preparation of 3-allyl demethylsuberosin (8) using phosphorane 6a. Yield: 0.178 g (65%); gummy mass; IR (KBr): 1725(C=O), 3200 (OH) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$); δ 17.85, 25.81, 28.32, 34.30, 102.73, 112.74, 117.74, 121.23, 123.38, 125.69, 127.65, 134.27, 134.64, 140.11, 153.01, 157.63, 163.00; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.75 (3H, s, CH_3), 1.80 (3H, s, C*H*$_3$), 3.29 (2H, d, *J* = 6.9 Hz, C*H*$_2$), 3.38 (2H, d, *J* = 6.9 Hz, C*H*$_2$), 5.24 (1H, m, C*H*), 5.32 (1H, m, *J* = 6.9 Hz, C*H*), 5.96 (2H, m, CH_2), 7.01 (1H, s, *H*-8), 7.17 (1H, s, *H*-5), 7.48 (2H, s, *H*-4 & O*H*); HRMS: m/z $[M+K]^+$ cal for $C_{17}H_{18}O_3$: 309.0893; found: 309.0904

Preparation of balsamiferone (2) using phosphorane 6b. Yield: 0.127 g (42%); white solid; mp 135-136ºC: Lit[11] 134-136ºC; IR (KBr) 3420 (OH) and 1725 (C=O) cm^{-1}; ^{13}C NMR (75 MHz,

$CDCl_3$); δ 17.82, 17.86, 25.82(2 X *C*), 28.46, 28.58, 102.75, 112.97, 119.53, 121.00, 124.55, 125.39, 127.63, 134.70, 135.33, 139.00, 152.82, 157.28, 163.22; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (3H, s, *CH*$_3$), 1.76 (3H, s, C*H*$_3$), δ 1.80 (3H, s, C*H*$_3$), 1.81 (3H, s, C*H*$_3$), 3.23 (2H, d, *J* = 6.9 Hz, C*H*$_2$), 3.39 (2H, d, *J* = 6.9 Hz, C*H*$_2$), 5.33 (2H, m, 2 X C*H*), 6.99 (1H, s *H*-8), 7.17 (1H, s, *H*-5), 7.42 (1H, s, *H*-4); HRMS *m/z* $[M+Na]^+$ 321.1459 (calcd for $C_{19}H_{22}O_3$, 321.1467).

Preparation of 3-benzyldemethylsuberosin (9) and 3-benzyldihydroxanthyletin (10) using phosphorane 6c

3-Benzyldemethylsuberosin (9). Yield: 0.065 g (20%) ; viscous oil; IR (KBr): 1725(C=O) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$); δ 17.83, 25.79, 29.67, 36.29, 102.78, 112.78, 121.11, 125.02, 125.40, 126.66, 127.79, 128.68 (2 X *C*), 129.34 (2 X *C*), 134.11, 138.12, 140.17, 152.82, 157.49, 163.30; ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.74 (3H, s, C*H*$_3$), δ 1.77 (3H, s, C*H*$_3$), 3.33 (2H, d, *J* = 7.2 Hz, C*H*$_2$), 3.85 (2H, s, C*H*$_2$-Ar), 5.27 (1H, m, C*H*), 6.35 (1H, s, O*H*), 6.87 (1H, s, *H*-8), 7.09 (1H, s, *H*-5), 7.24-7.36 (6H, m, *H*-4 & Ar-*H*); HRMS: m/z $[M+Na]^+$ cal for $C_{21}H_{20}O_3$: 343.1310; found: 343.1308.

3-Benzyldihydroxanthyletin (10). Yield: 0.130 g (40%); viscous oil; IR (KBr): 1725(C=O) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$); 26.86 (2 X *C*), 21.90, 32.45, 36.37, 75.57, 104.16, 112.72, 118.27, 125.35, 126.64, 127.72, 128.67 (2 X *C*), 129.05 (2 X *C*), 138.28, 139.45, 153.00, 156.88, 162.30; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.37 (6H, s, 2 X CH_3), 1.84 (2H, t, *J* = 6.6 Hz, C*H*$_2$), 2.79 (2H, t, *J* = 6.6 Hz, C*H*$_2$), 3.86 (2H, s, C*H*$_2$-Ar), 6.73 (1H, s, *H*-10), 7.05 (1H, s, *H*-5), 7.17 (1H, s, *H*-6), 7.28-7.31 (5H, m, Ar-*H*); HRMS: m/z $[M+Na]^+$ cal for $C_{21}H_{20}O_3$: 343.1310; found: 343.1318.

Preparation of 8-(3-methyl-2-butenyl)-7-hydroxy-6-methoxycoumarin (cedrelopsin 4) using phosphorane 15. Yield: 0.118 g (45%); white solid; mp: 171-172ºC (lit[7,16] mp: 170-172ºC); IR (KBr): 1730 (C=O) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.15 (2 X *C*), 25.74, 56.30, 105.05, 111.18, 113.09, 120.67, 133.15, 134.12, 143.60, 145.46, 147.37, 157.00, 162.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (3H, s, C*H*$_3$), 1.87 (3H, s, C*H*$_3$), 3.59 (2H, d, *J* = 7.2 Hz, C*H*$_2$), 3.96 (3H, s, OC*H*$_3$), 5.31 (1H, m, C*H*), 6.21 (1H, s, O*H*), 6.27 (1H, d, *J* = 9.2 Hz, *H*-3), 6.74 (1H, s, *H*-5), 7.59 (1H, d, *J* = 9.2 Hz, *H*-4); HRMS: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{16}O_4$: 283.0946; found: 283.0933.

Acknowledgements

We thank IISc Bangalore for HRMS, and the UGC New Delhi for the financial support.

References

1. (a) Murray, R. D. H. *Nat. Prod. Rep*. **1995**, *12*, 477. (b) Estvez-Braun, A.; Gonzalez, A. G. *Nat. Prod. Rep*. **1997**, *14*, 465. (c) Malikov, V. M.; Saidkhodzhaev, A. I. *Khim. Prir. Soedin*, **1998**, *234*, 250.
2. (a) Garazd, M. M.; Garazd, Y. L.; Khilya, V. P.; *Khim. Prir. Soedin*, **2003**, *39*, 47. (b) Patil, A.D.; Freyer, A. J.; Eggleston, D. S.; Haltiwanger, R. C.; Bean, M. F.; Taylor, P. B.; Carranfer, M. J.; Breen, A. L.; Bartus, H. R.; Johnson, R. K.; Hertzberg, R. P.; Westley, J. W. *J. Med. Chem*. **1993**, *36*, 4131. (c) Argotle-Ramos, R.; Ramirez-Avila, G.; Rodriquez-Gutierrez, M. D. C.; Qvilla-Munoz, M.; Lanz-Mendoz, H.; Rodriguez, M. H.; Gonzalez-Cartazar, M.; Alvarez, L. *J. Nat. Prod*. **2006**, *69*, 1442. (d) Verotta, L.; Lovaglio, E.; Vidari, G.; Finzi, P. V.; Neri, M. G.; Raimondi, A.; Parapini, S.; Taramelli, D.; Riva, A.; Bombardelli, E. *Phytochemistry* **2004**, *65*, 2867. (e) Guilet, D.; Helesbeux, J. –J.; Seraphin, D.; Serenet, T.; Richomme, P.; Bruneton, J. *J. Nat. Prod*. **2001**, *64*, 563. (f) O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*, Wiley & Sons, Chichester, **1997**.
3. Murray, R. D. *Natural Coumarin: Occurrence, Chemistry and Biochemistry* Wiley: New York, 1982.
4. Reisch, J.; Szendrei, K.; Minker, K. E.; Novak, I. *Experientia* **1968**, *24*, 992.
5. Burke, B. A.; Parkins, H. *Phytochemistry* **1979**, *18*, 1073.
6. (a) Prakash, D.; Lakshmi, V.; Raj, K.. Kapil, R. S. *Fitoterapia* **1989**, *60*, 347. (b) Ito, C. Itoigawa, M.; Ju-ichi, M.; Sakamoto, N.; Tokuda, H.; Nishino, H.; Furukawa, H. *Plant Medica* **2005**, *71*, 84.
7. Eshiett, T; Taylor, D. A. H. *J. Chem. Soc.* **1968**, 481.
8. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
9. (a) Posner, G. H. *Chem. Rev.* **1986**, I, 831. (b) Jasperse, C. P.; Curran, D. P; Fevig ,T. L. *Chem. Rev*. **1991**, *91*, 1237. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P.G. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134. (d) Pelliser, H. *Tetrahedron* **2006**, *4*, 2076. (e) Kirsch, S.F. *Synthesis* **2008**, *20*, 3183. (f) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed*. **1993**, *32*, 131. (g) Tietze, L. F.; Lieb, M. *Curr. Opin. Chem. Biol*. **1998**, *2*, 363. (h) Tietze L. F.; Modi, A. *Med. Res. Rev*. **2000**, *20*, 304. (i) Tietze, L. F.; Brasche, G.; Gericke, G. *Domino Reactions in Organic Synthesis*, Wiley-VCH:Weinheim, **2006**. (j) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev*. **1996**, *96*, 195. (k) Ho, T. L. *Tandem Reactions in Organic Synthesis*, Wiely Interscience, New York, **1997**. (l) Taylor, R. J. K.; Reid, M.; Foot, M. J.; Raw, S. S. *Acc Chem Res*, **2005**, *38*, 851.
10. Patre, R. E.; Gawas, S.; Parameswaran, P. S.; Tilve, S. G. *Tetrahedron Lett*. **2009**, *50*, 6488.
11. Cairns, N.; Harwood, L. M.; Astle, D. P. *J. Chem. Soc., Perkin Trans 1* **1994**, 3101.
12. (a) Sharma, R. B.; Swarrop, D.; Kapil, R. S. *Indian J. Chem.* **1983**, *22B*, 408. (b) Sharma, R. B.; Swarrop, D.; Kapil, R. S. *Indian J. Chem.* **1982**, *22B*, 105.

13. Mali, R. S.; Joshi, P. P.; Sandhu, P. K.; Manekar-Tilve, A. *J. Chem. Soc. Perkin. Trans. 1* **2002**, 371.
14. Shen, Y. H.; Li, S. H; Han, Q. B.; Sun, H. D. *J. Asian. Nat. Prod. Res.* **2006**, *8*, 345.
15. Mali, R. S.; Manekar, A. R.; Tilve, S. G. *Org. Prep. Proced. Int.* **1992**, *24*, 52.
16. Anet, F. A.; Hughes, G. K.; Ritchie, E. *Austral. J. Sci. Res.* **1949**, *A2*, 608.

