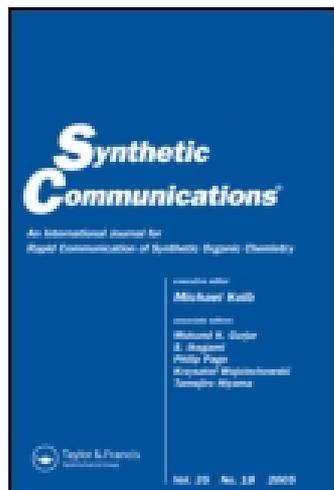


This article was downloaded by: [Universiteit Twente]

On: 30 November 2014, At: 12:17

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
<http://www.tandfonline.com/loi/lcyc20>

USEFUL SYNTHESSES OF PRENYLATED- AND PYRANO-3-ARYLCOUMARINS

Raghao S. Mali^a & Priya P. Joshi^a

^a Department of Chemistry, Garware Research Center, University of Pune, Pune, 411 007, India

Published online: 15 Aug 2006.

To cite this article: Raghao S. Mali & Priya P. Joshi (2001) USEFUL SYNTHESSES OF PRENYLATED- AND PYRANO-3-ARYLCOUMARINS, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 31:18, 2753-2760, DOI: [10.1081/SCC-100105321](https://doi.org/10.1081/SCC-100105321)

To link to this article: <http://dx.doi.org/10.1081/SCC-100105321>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

USEFUL SYNTHESSES OF PRENYLATED- AND PYRANO-3-ARYLCOUMARINS

Raghao S. Mali* and Priya P. Joshi

Garware Research Center, Department of Chemistry,
University of Pune, Pune 411 007, India

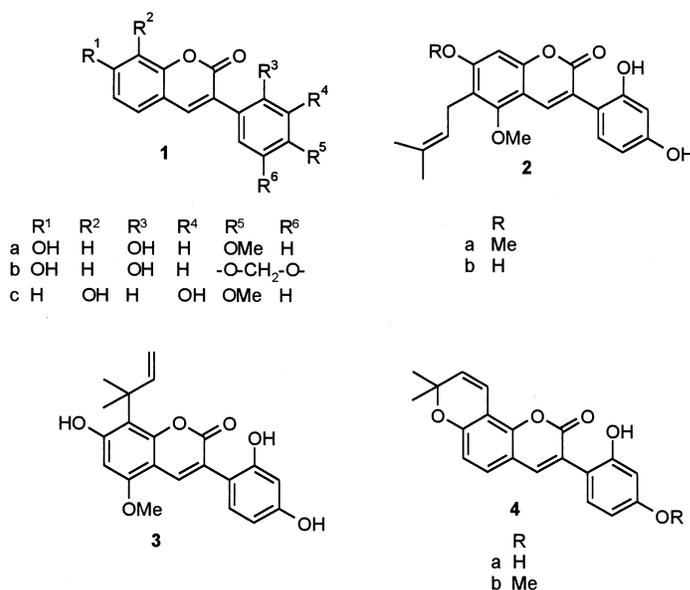
ABSTRACT

Convenient syntheses of 6-prenyl- and 8-isoprenyl-3-aryl-coumarins (**7a–d** and **8c–d**) from 2-prenyloxy-4-methoxy-benzaldehydes (**5a** and **5b**) and of pyrano-3-arylcoumarins (**10a–b**) from 2-hydroxy-4-(1,1-dimethylpropynyloxy) benzaldehyde (**9**) using Wittig reaction are described.

Coumarins constitute an important class of naturally occurring oxygen ring compounds.¹ Various simple and 3-substituted coumarins have been isolated¹ from natural sources. A few simple 3-arylcoumarins (**1a–c**), 6-prenyl-3-arylcoumarins (glycyrin **2a** and glycy-coumarin **2b**) and 8-isoprenyl-3-arylcoumarin (licoaryl-coumarin, **3**) have also been reported² from various plant sources. A large number of natural coumarins¹ possess prenyl- or functionalised prenyl-units at C-6 position. The number of natural 3-arylcoumarins having prenyl unit at C-6 position is small. Some natural 3-arylcoumarins¹ have a pyran ring instead of the prenyl or isoprenyl group.

*Corresponding author. Fax: +(91) 020 5651728; E-mail: rsmali@chem.unipune.ernet.in

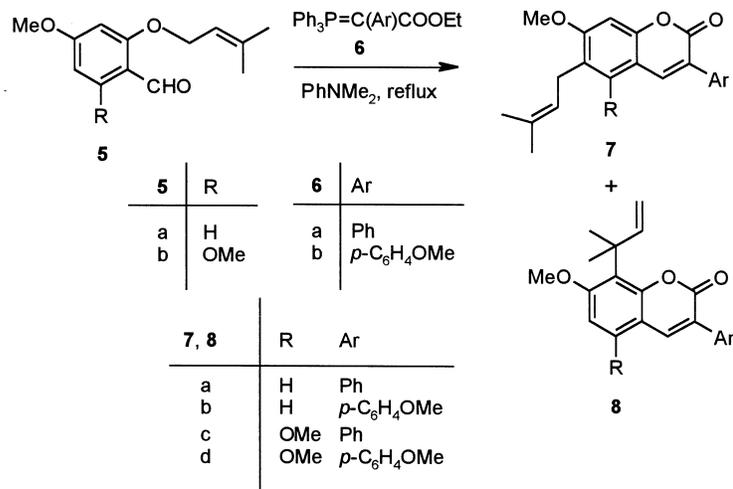
Thus, the pyrano-3-arylcoumarins viz. kanzonol W (**4a**) and its mono methyl ether (**4b**) have been isolated³ from *Glycyrrhiza glabra*. Apart from their importance as natural products, 3-arylcoumarins are reported to possess interesting biological activities. Thus, glycycomarin (**2b**) is known to possess anti-HIV⁴ and antitumor activities⁵ besides being anti-oxidant.⁶ It also inhibit xanthine oxidase activity^{2d} (an enzyme responsible for formation of gout). Licoarylcoumarin (**3**) exhibits strong inhibition of cAMP phosphodiesterase.⁷ Recently,⁸ glycyrin (**2a**), glycycomarin (**2b**) and kanzonol W (**4a**) have been found to be potent antibacterials.



In view of the natural occurrence associated with various biological activities, a few methods, making use of the classical Perkin⁹ and Knoevenagel¹⁰ reactions, have been reported for the synthesis of simple 3-arylcoumarins of type **1**. The synthesis of 6-prenylcoumarins from naturally occurring 7-hydroxy/alkoxy coumarins have been reported in the literature,¹¹ however, the synthesis of 6- and 8-prenylated-3-arylcoumarins of type **2** and **3** remain almost untouched. Pyrano-3-arylcoumarins **4a** and **4b**, however, have been synthesized recently^{3b} by making use of the classical Perkin reaction. The overall yields of the final products (**1** and **4**) in these reactions are invariably low and/or involve a multistep sequence of reactions.^{3b} The syntheses of prenylated 3-arylcoumarins have not been



reported in the literature. Hence, it was decided to develop convenient methods for the syntheses of prenylated-3-arylcoumarins of type **2** and **3** and pyrano-3-arylcoumarins of type **4**.



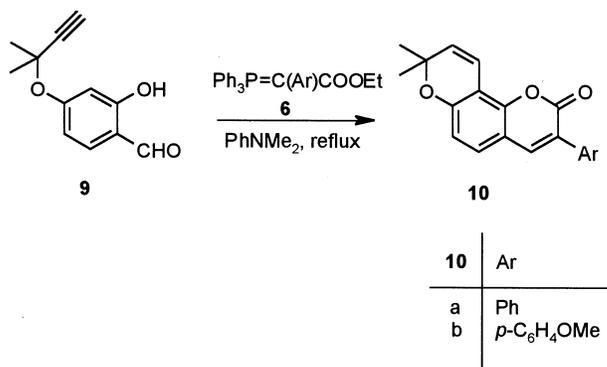
Scheme 1.

In continuation of our work^{12,13} on the synthesis of naturally occurring coumarins, we report herein a simple and convenient method (Scheme 1) for the synthesis of 6-prenyl-3-arylcoumarins (**7a–d**) and 8-isoprenyl-3-arylcoumarins (**8c–d**) from the corresponding 2-prenyloxy-4-methoxybenzaldehydes (**5a** and **5b**).

The synthesis of angular pyrano-3-arylcoumarins (**10a–b**) has been achieved (Scheme 2) starting from 2-hydroxy-4-(1,1-dimethylpropynyloxy) benzaldehyde¹³ (**9**). The literature method for the synthesis of pyrano-3-arylcoumarin requires several steps and provide the final product in low overall yield.^{3b}

In our approach 2-prenyloxy-4-methoxybenzaldehyde¹⁴ (**5a**) was refluxed with phosphoranes (**6a** and **6b**) in *N,N*-dimethylaniline, to give 7-methoxy-6-prenyl-3-phenylcoumarin (**7a**) and 2',5-dideoxy-4'-*O*-methylglycyrin (**7b**) respectively. 4,6-Dimethoxy-2-prenyloxybenzaldehyde¹² (**5b**) when reacted similarly with phosphoranes **6a** and **6b**, provided 5,7-dimethoxy-6-prenyl-3-phenylcoumarin (**7c**) and 2'-deoxy-4'-*O*-methylglycyrin (**7d**) along with minor amounts of 5,7-dimethoxy-8-isoprenyl-3-phenylcoumarin (**8c**) and 2'-deoxy-7,4'-di-*O*-methyl licoarylcoumarin (**8d**)





Scheme 2.

respectively. 2-Hydroxy-4-(1,1-dimethylpropynyloxy) benzaldehyde¹³ (**9**) on similar reaction with phosphoranes **6a** and **6b** gave the desired pyrano-3-phenylcoumarin (**10a**) and 2'-deoxy-4'-O-methyl kanzonol W (**10b**) respectively. The synthesis of pyrano-3-phenylcoumarin (**10a**) has been reported¹⁵ in the literature starting from 7-hydroxy-3-phenylcoumarin.

The syntheses of 6- and 8-prenylated-3-aryl coumarins (**7a-d** and **8c-d**) have been reported here for the first time. The approaches (Schemes 1 and 2) described here for the syntheses of prenylated-3-aryl coumarins (**7a-d** and **8c-d**) and pyrano-3-aryl coumarins (**10a** and **10b**) do not require preformed coumarins. In both the approaches the Claisen rearrangement, Wittig reaction and cyclization occur in one-pot.

EXPERIMENTAL

All mps are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 337 IR spectrophotometer. ¹H NMR (300 MHz) spectra were recorded on Varian VXR 300S instrument in CDCl₃ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) downfield from TMS and coupling constants are in Hertz. Analyses were obtained on a Hosli's rapid carbon-hydrogen analyzer.

The preparation of phosphorane **6a** is reported¹⁶ in the literature. Phosphorane **6b** was prepared from ethyl-α-bromo-4-methoxyphenylacetate¹⁷ following the procedure reported for **6a**.

General procedure for the syntheses of 6-prenyl- and 8-isoprenyl-3-aryl coumarins (7a-d and 8c-d). A mixture of 2-prenyloxy-4-methoxy benzaldehyde (**5a**,¹⁴ **5b**,¹² 1.2 mmol) and phosphorane¹⁶ (**6a** and **6b**, 1.8 mmol)



in *N,N*-dimethylaniline (15 ml) was refluxed, under nitrogen atmosphere, for 4–12 h (monitored by TLC). Excess of *N,N*-dimethylaniline was removed under reduced pressure. The residue was extracted with ethyl acetate (3 × 15 ml), washed first with dilute hydrochloric acid and finally with water. The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated. The residue was chromatographed over silica gel using pet. ether–ethyl acetate (98:2) as an eluent to provide 6-prenyl-3-arylcoumarins (**7a–d**) in initial fractions. In the reaction of 4,6-dimethoxy-2-prenyloxybenzaldehyde (**5b**) with phosphoranes **6a** and **6b**, the 6-prenyl-3-arylcoumarins **7c** and **7d** were obtained in the initial fractions and the 8-isoprenyl-3-arylcoumarins **8c** and **8d** in later fractions. All these solid products were recrystallized from pet. ether–ethyl acetate.

7-Methoxy-6-prenyl-3-phenylcoumarin (7a). A mixture of **5a** and **6a** was refluxed for 12 h to give **7a** in 37% yield, mp 77–78°C, $\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1716 (C=O); δ_{H} 1.71 (3H, s, CH₃), 1.78 (3H, s, CH₃), 3.33 (2H, d, *J* 7.3 Hz, ArCH₂CH=), 3.91 (3H, s, OCH₃), 5.3 (1H, m, ArCH₂CH=), 6.81 (1H, s, 8-H), 7.24 (1H, s, 5-H), 7.4–7.46 (3H, m, Ar-H), 7.67–7.7 (2H, m, Ar-H), 7.76 (1H, s, 4-H) (Found: C, 78.58; H, 6.42. C₂₁H₂₀O₃ requires C, 78.72; H 6.29%).

2',5-Dideoxy-4'-O-methylglycyrin (7b). A mixture of **5a** and **6b** was refluxed for 11 h to give **7b** in 38% yield, mp 97–99°C, $\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1717 (C=O); δ_{H} 1.71 (3H, s, CH₃), 1.77 (3H, s, CH₃), 3.32 (2H, d, *J* 7.3 Hz, ArCH₂CH=), 3.85 (3H, s, OCH₃), 3.9 (3H, s, OCH₃), 5.3 (1H, m, ArCH₂CH=), 6.8 (1H, s, 8-H), 6.96 (2H, d, *J* 8.8 Hz, Ar-H), 7.23 (1H, s, 5-H), 7.65 (2H, d, *J* 8.8 Hz, Ar-H), 7.7 (1H, s, 4-H) (Found: C, 75.64; H, 6.22. C₂₂H₂₂O₄ requires C, 75.41; H, 6.33%).

5,7-Dimethoxy-6-prenyl-3-phenylcoumarin (7c). A mixture of **5b** and **6a** was refluxed for 4 h to give **7c** (20% yield) in the initial fractions, mp 133–135°C, $\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1720 (C=O); δ_{H} 1.69 (3H, s, CH₃), 1.79 (3H, s, CH₃), 3.37 (2H, d, *J* 6.8 Hz, ArCH₂CH=), 3.85 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 5.16 (1H, m, ArCH₂CH=), 6.66 (1H, s, 8-H), 7.38–7.48 (3H, m, Ar-H), 7.68–7.76 (2H, m, Ar-H), 7.98 (1H, s, 4-H) (Found: C, 75.21; H, 6.55. C₂₂H₂₂O₄ requires C, 75.41; H 6.33%).

Further elution with the same solvent gave **8c** in 10% yield.

5,7-Dimethoxy-8-(isoprenyl)-3-phenylcoumarin (8c). Mp 158–160°C, $\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1708 (C=O); δ_{H} 1.67 (6H, s, 2 × CH₃), 3.85 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 4.87 (1H, dd, *J* 1.1 and 10.4 Hz, CH₂=), 4.89 (1H, dd, *J* 1.1 and 17.4 Hz, CH₂=), 6.3 (1H, dd, *J* 17.4 and 10.4 Hz, CH=), 6.33 (1H, s, 6-H), 7.34–7.46 (3H, m, Ar-H), 7.72–7.76 (2H, m, Ar-H), 8.15 (1H, s, 4-H) (Found: C, 75.38; H, 6.47. C₂₂H₂₂O₄ requires C, 75.41; H, 6.33%).

2'-Deoxy-4'-O-methylglycyrin (7d). A mixture of **5b** and **6b** was refluxed for 10 h to give **7d** in (27% yield) in the initial fractions, mp 102–104°C,



$\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1716 (C=O); δ_{H} 1.68 (3H, s, CH₃), 1.79 (3H, s, CH₃), 3.37 (2H, d, *J* 6.6 Hz, ArCH₂CH=), 3.85 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 5.16 (1H, m, ArCH₂CH=), 6.65 (1H, s, 8-H), 6.97 (2H, d, *J* 8.8 Hz, Ar-H), 7.67 (2H, d, *J* 8.8 Hz, Ar-H), 7.92 (1H, s, 4-H) (Found: C, 72.53; H, 6.6. C₂₃H₂₄O₅ requires C, 72.61; H, 6.36%).

Further elution with the same solvent furnished **8d** in 10% yield.

2'-Deoxy-7,4'-di-O-methylcoarylcoumarin (8d). Mp 147–151°C, $\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1702 (C=O); δ_{H} 1.67 (6H, s, 2 × CH₃), 3.84 (6H, s, 2 × OCH₃), 3.93 (3H, s, OCH₃), 4.86 (1H, dd, *J* 1.5 and 10.4 Hz, CH₂=), 4.88 (1H, dd, *J* 1.5 and 17.4 Hz, CH₂=), 6.3 (1H, dd, *J* 17.4 and 10.4 Hz, CH=), 6.33 (1H, s, 6-H), 6.95 (2H, d, *J* 8.8 Hz, Ar-H), 7.7 (2H, d, *J* 8.8 Hz, Ar-H), 8.09 (1H, s, 4-H) (Found: C, 72.46; H, 6.48. C₂₃H₂₄O₅ requires C, 72.61; H, 6.36%).

General procedure for the synthesis of pyrano-3-arylcoumarins (10a and 10b). A mixture of 2-hydroxy-4-(1,1-dimethylpropynyloxy)benzaldehyde¹³ (**9**, 1.5 mmol) and appropriate phosphorane¹⁶ (**6a** and **6b**, 2.2 mmol) in *N,N*-dimethylaniline was refluxed, under nitrogen atmosphere, for 4–9 h (monitored by TLC). The residue obtained on usual work up, was chromatographed over silica gel using pet. ether–ethyl acetate (98:2) as an eluent to give a solid product which was recrystallized from pet. ether–ethyl acetate to provide pyrano-3-arylcoumarin **10a** and **10b** respectively.

Pyrano-3-phenylcoumarin (10a). A mixture of **9** and **6a** was refluxed for 4 h to give **10a** in 45% yield, mp 139–141°C (lit.,¹⁵ 143–144°C), $\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1717 (C=O); 1.48 (6H, s, 2 × CH₃), 5.74 (1H, d, *J* 10 Hz, 9-H), 6.74 (1H, d, *J* 8.8 Hz, 6-H), 6.94 (1H, d, *J* 10 Hz, 10-H), 7.27 (1H, d, *J* 8.8 Hz, 5-H), 7.39–7.49 (3H, m, Ar-H), 7.66–7.69 (2H, m, Ar-H), 7.71 (1H, s, 4-H) (Found: C, 79.02; H, 5.4. C₂₀H₁₆O₃ requires C, 78.93; H, 5.3%).

2'-Deoxy-4'-O-methylkansonol W (10b). A mixture of **9** and **6b** was refluxed for 9 h to give **10b** in 57% yield, mp 152–153°C, $\nu_{\max}/\text{cm}^{-1}$ (Nujol) 1712 (C=O); δ_{H} 1.48 (6H, s, 2 × CH₃), 3.85 (3H, s, OCH₃), 5.73 (1H, d, *J* 10 Hz, 9-H), 6.73 (1H, d, *J* 8.4 Hz, 6-H), 6.94 (1H, d, *J* 10 Hz, 10-H), 6.96 (2H, d, *J* 8.7 Hz, Ar-H), 7.25 (1H, d, *J* 8.4 Hz, 5-H), 7.64 (2H, d, *J* 8.7 Hz, Ar-H), 7.66 (1H, s, 4-H) (Found: C, 75.54; H, 5.58. C₂₁H₁₈O₄ requires C, 75.43; H, 5.43%).

ACKNOWLEDGMENTS

We thank Mr. A. P. Gadgil for IR and analytical data and IIT Mumbai for use of High Resolution NMR facility. One of us PPJ thanks UGC-New Delhi for the award of a senior research fellowship.



REFERENCES

1. (a) Murray, R.D.H.; Mendez, J.; Brown, S.A. *The Natural Coumarins, Occurrence, Chemistry and Biochemistry*, Wiley Interscience: New York, 1982. (b) Murray, R.D.H. *Progress in the Chemistry of Organic Natural Products, Naturally Occurring Plant Coumarins*, Springer Wien: New York, 1991, 58, 83. (c) Murray, R.D.H. *Progress in the Chemistry of Organic Natural Products, Naturally Occurring Plant Coumarins*, Springer Wien: New York, 1997, 72, 1.
2. (a) Donnelly, D.M.X.; Kavanagh, P.J. *Phytochemistry* **1974**, *13*, 2587. (b) Kinoshita, T.; Saitoh, T.; Shibata, S. *Chem. Pharm. Bull.* **1978**, *26*, 135. (c) Hattori, M.; Miyachi, Y.-Z.; Kakiuchi, N.; Namba, T. *Shoyakugaku zasshi* **1986**, *40*, 406; *Chem. Abstr.* **1987**, *107*, 46132. (d) Hatano, T.; Yasuhara, Y.; Fukuda, T.; Nora, T.; Okuda, T. *Chem. Pharm. Bull.* **1989**, *37*, 3005.
3. (a) Fuaki, T.; Cai, B.-S.; Horikoshia, T.; Nomura, T. *Phytochemistry* **1996**, *43*, 1119. (b) Kinoshita, T.; Yukiyoishi, T.; Kenji, M. *Nat. Prod. Lett.* **1997**, *9*, 289. (c) Baba, M.; Asano, R.; Okada, Y.; Singab, A.-N.; Fushiya, S.; Shibano, M.; Kusano, G.; Okuyama, T. *Heterocycles* **1999**, *51*, 387.
4. Hatano, T.; Yasuhara, T.; Miyamoto, K.; Okuda, T. *Chem. Pharm. Bull.* **1988**, *36*, 2286.
5. Okuda, T.; Yoshida, T.; Hatano, T.; Mori, T.; Fukuda, T. *J. Liq. Chromatogr.* **1990**, *13*, 3637.
6. Demizu, S.; Kajiyama, K.; Takahashi, K.; Hiraga, Y.; Yamamoto, S.; Tamura, Y.; Okada, K.; Kinoshita, T. *Chem. Pharm. Bull.* **1988**, *36*, 3474.
7. Kusano, A.; Nikaïdo, T.; Kuge, T.; Ohmoto, T.; Delle Monache, G.; Botta, B.; Botta, M.; Saitoh, T. *Chem. Pharm. Bull.* **1991**, *39*, 930.
8. Fukai, T.; Cai, B.-S.; Maruno, K.; Miyakawa, Y.; Konishi, M.; Nomura, T. *Phytochemistry* **1998**, *49*, 2005.
9. (a) Langmuir, M.E.; Yang, J.R.; Moussa, A.M.; Laura, R.; Lecompte, K.A. *Tetrahedron Lett.* **1995**, *36*, 3990. (b) Ahluwalia, V.K.; Sheshadri, T.R.; Venkateswarlu, P. *Ind. J. Chem.* **1971**, *9*, 1052. (c) Lawrence, A.S.; Noland, P.K. *J. Am. Chem. Soc.* **1966**, *88*, 5213. (d) Baker, W.; Eastwood, F.M. *J. Chem. Soc.* **1929**, 2906.
10. (a) Khiri, C.; Ladhar, F.; El Gharbi, R.; Le Bigot, Y. *Synth. Commun.* **1999**, *29*, 1451. (b) Akio, S.; Hiroshi, M. *J. Org. Chem.* **1969**, *34*, 3616.
11. Cairns, N.; Harwood, L.M.; Astles, D.P. *J. Chem. Soc. Perkin Trans. 1* **1994**, *21*, 3101.
12. Mali, R.S.; Sandhu, P.K.; Manekar-Tilve, A. *J. Chem. Soc. Chem. Commun.* **1994**, 251.





2760

MALI AND JOSHI

13. Mali, R.S.; Pandhare, N.A.; Sindkhedkar, M.D. *Tetrahedron Lett.* **1995**, *36*, 7109.
14. Murayama, M.; Seto, E.; Okuda, T.; Morita, I. *Chem. Pharm. Bull.* **1972**, *20*, 741.
15. Ahluwalia, V.K.; Bhat, K.; Prakash, C.; Khanna, M. *Montasch. Chem.* **1981**, *112*, 119.
16. Filtsch, W.; Hermann, U. *Chem. Ber.* **1971**, *104*, 2170.
17. Wasserman, H.H.; Hlasta, D.J.; Tremper, A.W.; Wu, J.S. *J. Org. Chem.* **1981**, *41*, 2997.

Received in Japan August 17, 2000



Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

[Order now!](#)

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081SCC100105321>