JOC*Note*

pubs.acs.org/joc

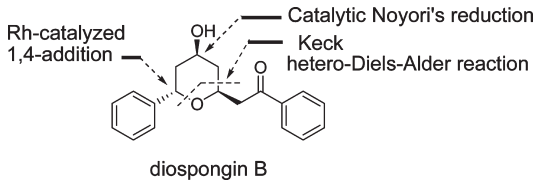
A Flexible Enantioselective Total Synthesis of Diospongins A and B and Their Enantiomers Using Catalytic Hetero-Diels−Alder/Rh-Catalyzed 1,4-Addition and Asymmetric Transfer Hydrogenation Reactions as Key Steps

Gullapalli Kumaraswamy,*[,†] Gajula Ramakrishna,[†] Police Naresh,[‡] Bharatam Jagadeesh,[‡] and Balasubramanian Sridhar[§]

[†]*Organic Division-III, Indian Institute of Chemical Technology, Hyderabad, 500 007, India,* [‡]*NMR Division, Indian Institute of Chemical Technology, Hyderabad, 500 007, India, and* [§]*Laboratory of X-ray crystallography, Indian Institute of Chemical Technology, Hyderabad, 500 007, India*

gkswamy_iict@yahoo.co.in

Received August 12, 2009



A unified enantioselective route to total synthesis of diospongins A and B and their enantiomers has been developed employing achiral starting materials. All three stereocenters were introduced by means of catalytic reactions.

Oxacycles possessing pharmacophoric active sites are common structural motifs in several biologically active natural products.[1] In general, the aryl-substituted tetrahydropyran core is prevalent in many of these biologically significant small natural product molecules.[2] Owing to their privileged tetrahydropyran scaffold, these natural product molecules exhibit potent inhibitory activity. Among them, the intriguing *C*-aryl glycoside natural products diospongins A (**2**) and B (**1**) which were isolated from the rhizomes of *Diocorea spongiosa* through a bioassay-guided fractionation show promising antiosteoporotic activity (^{45}Ca release at 200 μM (30.5%) and 20 μM (18.2%),[3] hence, can be considered to be a lead for the discovery of potent and novel antiosteoporotic agents (Figure 1)).

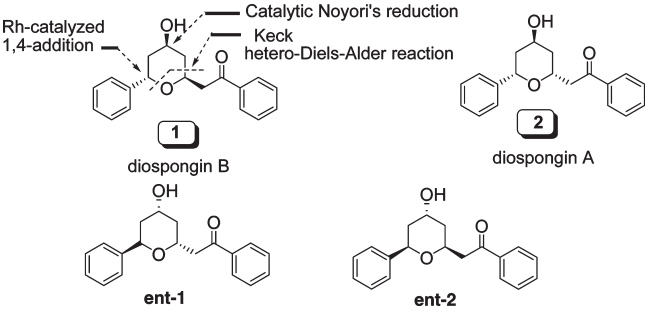


FIGURE 1. Diospongins A and B and their enantiomers.

Diospongins A (**2**) and B (**1**) contain a six-membered cyclic ether structural unit with 2-aryl and 6-phenacyl substitution. Despite their structural similarity, they exhibit remarkable differences in their biological profile. Diospongin B displays potent inhibitory activity on bone resorption induced by parathyroid hormone, which is comparable to that of elcitionin, a drug used clinically for osteoporosis while diospongin A did not show any activity.

Initially, Jennings et al.[4] not only achieved unambiguous total syntheses of both (−)-diospongins A (**2**) and B (**1**) but also validated the structures proposed by Kadota.[3] Subsequently, a flurry of synthetic methods has appeared in the literature for this class of compounds.[4,5] Prevalent approaches used for the introduction of 2-aryl and 6-phenacyl substitution of the diospongins are Keck allylation and stereoselctive nucleophilic additions to the appropriate oxocarbenium cations, respectively. With our continued interest in developing catalytic routes to bioactive small molecules,[6] herein, we report a flexible route for the synthesis of the diospongins based on three catalytic steps: (a) catalytic asymmetric hetero-Diels−Alder reaction, (b) diastereoselective rhodium(I)-catalyzed 1,4-addition, and (c) catalytic asymmetric transfer hydrogenation (CATHy) reaction (Figure 1).

The catalytic asymmetric hetero-Diels−Alder reaction between Danishefsky's diene **5** and furfuraldehyde **6** using

*To whom correspondence should be addressed. Phone: + 91-40-27193154. Fax: + 91-40-27193275.

(1) (a) Claeson. P.; Claeson. U. P.; Tuchinda. P.; Rentrakul. V. *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 2002; Vol. 26, p 881. (b) Kadota, S.; Tezuka, Y.; Prasaim, J. K.; Ali, M. S.; Banskota, A. H. *Curr. Top. Med. Chem.* **2003**, *3*, 203.

(2) (a) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176. (b) Ko, M. H.; Lee, D. G.; Kim, M. A.; Park, J. H.; Lee, M. S.; Lee, E. *Org. Lett.* **2007**, *9*, 141. (c) Paterson, I.; Miller, N. A. *Chem. Commun.* **2008**, 4708.

(3) Yin, J.; Kouda, K.; Tezuka, Y.; Le Tran, Q.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med.* **2004**, *70*, 54.

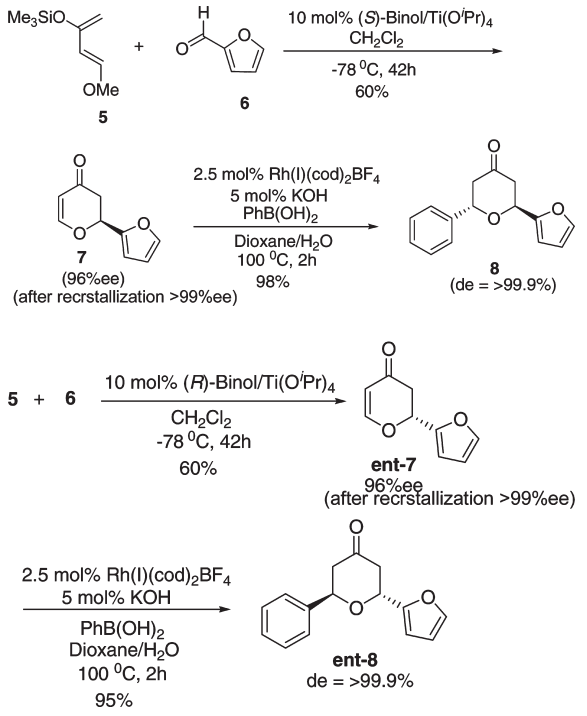
(4) Jennings, M. P.; Sawant, K. B. *J. Org. Chem.* **2006**, *71*, 7911.

(5) (a) Bressy, C.; Allais, F.; Cossy, J. *Synlett* **2006**, 3455. (b) Bates, R. W.; Song, P. *Tetrahedron* **2007**, *63*, 4497. (c) Hiebel, M.-A.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874. (d) Kawai, N.; Hande, S.-M.; Uenishi, J. *Tetrahedron*. **2007**, *63*, 9049. (e) Yadav, J. S.; Padmavani, B.; Reddy, B. V. S.; Venugopal, C.; Rao, A. B. *Synlett* **2007**, 2045. (f) Sabitha, G.; Padmaja, P. *Helv. Chim. Acta* **2008**, *91*, 2235. (g) Wang, H.; Shuhler, B. J.; Xian, M. *Synlett* **2008**, 2651. (h) Chandrasekhar, S.; Shyamsunder, T.; Jaya Prakash, S.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 47.

(6) (a) Kumaraswamy, G.; Sadaiah, K.; Ramakrishna, D. S.; Naresh, P.; Sridhar, B.; Jagadeesh, B. *Chem. Commun.* **2008**, 5324. (b) Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Udaya Kiran, M. *J. Org. Chem.* **2006**, *71*, 337. (c) Kumaraswamy, G.; Padmaja, M. *J. Org. Chem.* **2008**, *73*, 5198. (d) Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett.* **2007**, *48*, 1707. (e) Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett.* **2008**, *49*, 327.

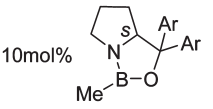
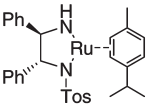
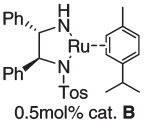
Published on Web 10/09/2009 DOI: 10.1021/jo901739y

SCHEME 1. Synthesis of 8 and *ent*-8

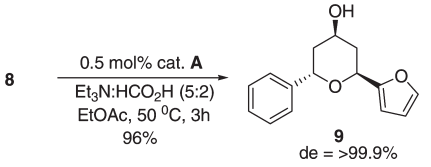


10 mol % of the (*S*)-BINOL/Ti(OiPr)$_4$ derived catalyst generated dihydropyranone **7** with 96% enantiomeric excess.[7] Further, single recrystallization of **7** from hexane:ether (2:1) solvent mixture resulted in 99.9% enantiomeric excess with 60% yield. With enantioenriched **7** in hand, we sought a flexible and appropriate means for introducing a *C*-aryl group into the pyranose ring. To this end, we have examined the rhodium(I)-catalyzed stereoselective 1,4-addition of an arylboronic acid to a cyclic enone, a protocol developed by Miyaura,[8a] Hayashi,[8b] and Maddaford.[9] Primarily, we have explored Maddaford conditions. Accordingly, the reaction of **7** with phenylboronic acid in the presence of 5 mol % of Rh(cod)$_2$BF$_4$ in dioxane/water was heated to 100 °C for 2 h. Surprisingly, after workup, only a trace amount of the expected 1,4-addition product **8** was isolated. However, the addition of 5 mol % of KOH to the reaction, under otherwise identical conditions, furnished the product **8** in 70% yield. In another set of reactions, when the molar ratio of the Rh catalyst was reduced to 2.5 mol % and the KOH loading was increased 2-fold (1:2 catalyst:KOH), the reaction proceeded smoothly to yield the required product in 98%. The de was determined to be >99.9% by chiral HPLC (ODH column, 2% isopropanol in hexane, flow rate 0.5 mL/min). As proposed,[9] the organometallic species ArRh(cod)$_2$ addition proceeded from the less hindered α-face of the enone double bond and subsequent hydrolysis of Rh−O bond led to high diastereoselectivity. The stereochemistry of **8** was assigned α configuration at the anomeric center based on ^{1}H NMR data reported in the literature.[9] The 10 mol % of (*R*)-BINOL/Ti(O^{i}Pr)$_4$ derived catalyst generated *ent*-**7**. Then, *ent*-**7** was converted to *ent*-**8** following the same sequence of reagents (Scheme 1).

TABLE 1. Reduction of Ketone 8 with Various Reducing Agents

entry	Reducing agent	dr ratio	%yield
1	$NaBH_4$	55:45	90
2	DIBAL-H	60:40	92
3	10mol%  ; BH_3.DMS	55:45	93
4	 0.5mol% cat. **A**	>99.9	96
5	 0.5mol% cat. **B**	60:40	94

SCHEME 2. Catalytic Asymmetric Transfer Hydrogenation Reaction



Next, we focused on the reduction of the keto group of **8**. An array of achiral and chiral reducing agents were screened for this transformation and the results are shown in Table 1. The experimental results reveal that the reduction proceeded with Noyori's catalyst, i.e., *R*,*R*-diamine-Ru catalyst **A** (0.5 mol %) with the Et$_3$N·HCO$_2$H azeotropic mixture and heating at 50 °C for 3 h afforded the alcohol **9** in 96% isolated yield with >99.9% diastereoselectivity (Chiral HPLC, ODH column, 10% isopropanol in hexane at a flow rate of 0.5 mL/min) (Scheme 2). The absolute configuration of the hydroxyl group was assigned as *R* based on single X-ray crystallography of **9** (Figure 2). Our efforts to synthesize the C$_4$ epimer of **9**, by using substrate **8** employing *S*,*S*-diamine-Ru catalyst **B** (0.5 mol %), under otherwise identical conditions resulted in a lower level of diastereoselectivity (entry 5, Table 1). The *R*,*R*-diamine-Ru catalyst/substrate **8** appears to be a matched combination, which has overcome the inherent substrate bias, thus resulting in high diastereoselectivity. On the other hand, *S*,*S*-diamine-Ru catalyst/substrate **8** is a mismatched combination as evidenced by the modest level of diastereoselctivity.

However, the reduction of the keto group of *ent*-**8** with *R*,*R*-diamine-Ru catalyst **A** (0.5 mol %), using a Et$_3$N·HCO$_2$H azeotropic mixture, smoothly furnished the alcohol *ent*-**9** in 98% yield. Further, the optical rotation of *ent*-**9** was found to be approximately equal in magnitude to that

(7) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

(8) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(9) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2571.

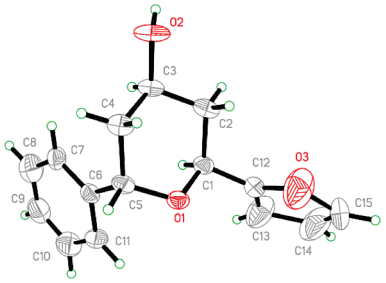
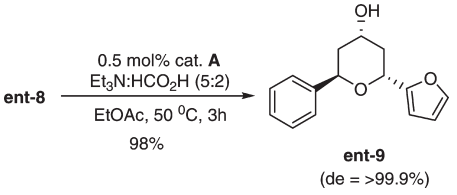


FIGURE 2. ORTEP representation of **9** with 50% probability. (CCDC reference no. 735811. The crystal obtained from 5% EtOAc in hexane and crystal is weakly diffracting. For the crystal structure of **7**, please see the Supporting Information.)

of **9** but opposite in sign, indicating an enantiomeric relationship. Consequently, the newly formed chirogenic center absolute configuration was assigned as *S* (Scheme 3). In principle, the *ent*-**9** should be achieved by employing the catalyst **B**. To our surprise, two enantiomeric ketones **8** and *ent*-**8** are reduced with the same enantiomer of catalyst **A** leading to a pair of enantiomers, i.e., **9** and *ent*-**9**. These findings suggest that the enantiomeric Ru-template catalyst **A** is efficiently differentiating diastereofaces of pro chiral ketone **8** and *ent*-**8**. However, these findings warrant a detailed investigation to establish the plausible mechanism.

SCHEME 3. Catalytic Asymmetric Transfer Hydrogenation Reaction



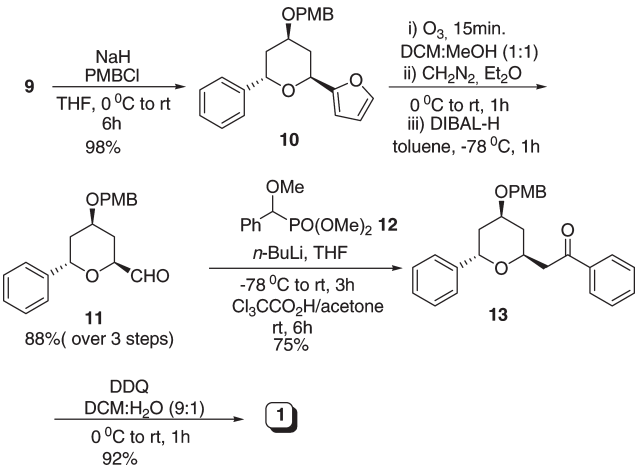
Proceeding further, the hydroxy group **9** was converted to a PMB ether **10** (NaH/PMBCl, THF, 0 °C to rt, 6 h) in 98% yield. The furyl group of **10** was oxidatively cleaved to acid (O_3, 15 min, DCM/MeOH, [1:1]), and the resulting acid on esterification with diazomethane (CH_2N_2, ether, 0 °C to rt) gave methyl ester. Then, the methyl ester was subjected to reduction (DIBAL-H, −78 °C) leading to **11** in 88% yield (after 3 steps). The aldehyde **11** was then treated with the anion derived from Horner−Emmons reagent **12** and subsequent hydrolysis of intermediate enol ether resulted in **13** (75%).[10]

Finally, **13** was exposed to DDQ in DCM/H_2O (9:1) for 1 h to furnish the target compound **1** in 92% isolated yield. The chirooptical data of **1** were in full agreement with those reported in the literature[4] ($[\alpha]^{23}_D$ −22.5 (*c* 0.2, $CHCl_3$) {lit.[4] $[\alpha]^{23}_D$ −22.6 (*c* 0.0114, $CHCl_3$)}) (Scheme 4).

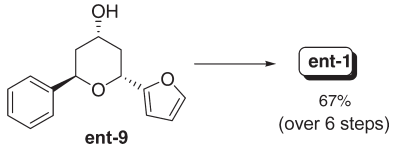
The 2,6-*trans* enantiomer *ent*-**1** was synthesized in 67% yield (over 6 steps) from *ent*-**9** following the above-mentioned conditions (Scheme 5).

The C-5 hydroxyl group of diospongin B (**1**) was protected as TBDPS ether to give **14** (^{t}Bu(Ph)$_2$SiCl, Et_3N, DCM, 0 °C to rt, 6 h). Unexpectedly,[11] deprotection of the TBDPS group of compound **14** with excess TBAF[12] in THF at ambient temperature furnished product **2** in 86% yield.

SCHEME 4. Synthesis of Diospongin B



SCHEME 5. Synthesis of *ent*-1



Moreover, the optical data of **2** were in full agreement with that of diospongin A reported in the literature[4] ($[\alpha]^{23}_D$ −19.2 (*c* 1.2, $CHCl_3$) {lit.[4] $[\alpha]^{23}_D$ −19.6 (*c* 0.0084, $CHCl_3$)}). Also the ^{1}H NMR and ^{13}C NMR data were in full accord with those reported for the natural product. Under identical conditions *ent*-**14** also resulted in *ent*-**2**. The structure of *ent*-**2** was confirmed by ^{1}H and ^{13}C NMR data.[13] Furthermore, the optical rotation of *ent*-**2** was found to be equal in magnitude to **2**, but opposite in sign, and hence was considered as enantiomer to **2** (Scheme 6).

The reaction could be rationalized on the basis of retro-Michael opening of the pyran ring and the subsequent intramolecular Michael reaction of the hydroxy nucleophile to the enone leads to the thermodynamically more stable cis-conformer (Scheme 7).

In conclusion, we have accomplished the total synthesis of diospongins A (**2**) and B (**1**) and their enantiomers employing achiral starting materials. To the best of our knowledge, the syntheses of 2,6-trans isomer *ent*-**1** and 2,6-cis isomer *ent*-**2** are described here for the first time. All three

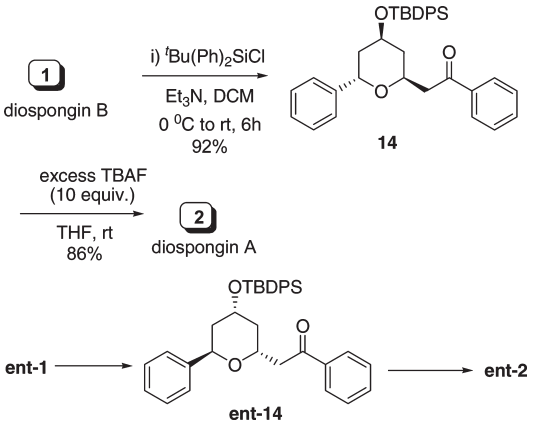
(10) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tamber, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745.

(11) Initially, the hydroxyl group of **9** was protected with TBDPS and carried out a complete sequence. To our surprise, the final product ^{1}H NMR and ^{13}C data did not match to reported data of **1**. Consequently, changing the protecting group TBDPS to PMB followed by the same set of reactions resulted in the expected product **1**. The TBDPS protected **9** also exposed to TBAF (10 equiv) but only deprotected **9** was recovered.

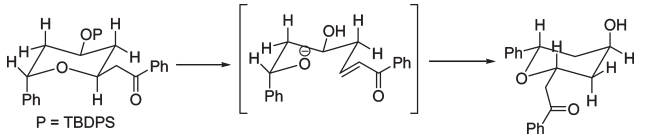
(12) Reaction did not proceed with less than 10 equiv of TBAF. Using Aldrich supplied TBAF, reaction did not initiate whereas addition of 5 mol equiv of H_2O (based on TBAF mole equivalent) to the reaction under otherwise identical conditions yielded the expected product **2**. However, TBAF supplied by Spectochem.Pvt.Ltd., India without addition of H_2O resulted in **2**.

(13) For complete details of ^{1}H and ^{13}C NMR data, please see the Supporting Information.

SCHEME 6. Diospongin A and Enantiomer



SCHEME 7



stereocenters are introduced by means of catalytic reactions and this strategy in turn could be used to generate a library of small molecules with varying substitutions in the aromatic nucleus.

Experimental Section

Diospongin B (1). To a stirred solution of **13** (1.40 g, 3.37 mmol) in CH_2Cl_2:H_2O (9:1) (70 mL) was added DDQ (0.919 g, 4.05 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O followed by brine solution and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The crude residue was purified by flash column chromatography (30% EtOAc in hexane) to afford the product **1** (0.91 g, 92%) as an amorphous solid. $[\alpha]^{23}_D$ −22.5 (*c* 0.2, $CHCl_3$); IR (KBr) 3624, 2925, 2857, 2312, 1740, 1682, 1515, 1452, 1174, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.9 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 8.2 Hz, 2H), 7.34 (m, 5H), 5.19 (t, J = 4.4 Hz, 1H), 4.23 (m, 1H), 4.02 (m, 1H), 3.45 (dd, J = 7.0, 15.7 Hz, 1H), 3.17 (dd, J = 5.9, 15.7 Hz, 1H), 2.51 (ddd, J = 3.8, 5.1, 13.4 Hz, 1H), 2.05 (ddd, J = 4.4, 8.9, 14.6 Hz, 1H), 1.92 (ddd, J = 5.0, 9.7, 13.5 Hz, 1H), 1.50 (dt, J = 9.3, 12.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 140.2, 137.2, 133.2, 128.6, 128.5, 128.3, 127.1, 126.3, 72.3, 66.9 64.2, 44.6, 40.1, 36.7; MS (ES) m/z 319 $(M + Na)^+$; HRMS (ESI) m/z 319.1301 (calcd for $C_{19}H_{20}O_3Na$ 319.1310).

Diospongin A (2). To a stirred solution of **14** (0.853 g, 1.59 mmol) in THF (15 mL) was added TBAF (Specrochem Pvt.Ltd., India) (15.7 mL, 15.9 mmol, 1 M solution in THF) at 0 °C and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel (26% EtOAc in hexane) to afford product **2** (0.238 g, 86%) as an amorphous solid. $[\alpha]^{23}_D$ −19.2 (*c* 1.2, $CHCl_3$); IR (KBr) 3624, 2925, 2857, 2312, 1740, 1682, 1515, 1452, 1174, 753 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.97 (d, J = 6.8 Hz, 2H), 7.53 (t, J = 6.8 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.22 (m, 2H), 4.90 (dd, J = 1.5, 11.3 Hz, 1H), 4.60 (m, 1H), 4.34 (t, J = 2.3 Hz, 1H), 3.39 (dd, J = 5.3, 15.9 Hz, 1H), 3.04 (dd, J = 7.5, 16.6 Hz, 1H), 1.95 (m, 2H), 1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 142.8, 137.5, 133.0, 128.5, 128.3, 128.2, 127.2, 125.8, 73.8, 69.1, 64.7, 45.2, 40.4, 38.8; MS (ESI) m/z 319 $(M + Na)^+$ HRMS (ESI) m/z 319.1319 (calcd for $C_{19}H_{20}O_3Na$ 319.1310).

Acknowledgment. We are grateful to Dr. J. S. Yadav, Director, IICT, for his constant encouragement. Financial support was provided by the DST, New Delhi, India (Grant No. SR/SI/OC-12/2007), and CSIR (New Delhi) is also gratefully acknowledged for awarding a fellowship to G.R.K. Thanks are also due to Dr. G. V. M. Sharma for his support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds along with copies of ^1H, ^{13}C NMR spectra, crystallographic data, and NOE. This material is available free of charge via the Internet at http://pubs.acs.org.