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New insight into the mechanism of hypervalent iodine oxidation of flavanones

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This paper is dedicated with respect and admiration to Professor András Messmer on the occasion of his 80th birthday

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Abstract—Flavanone (**1**) on oxidation with iodobenzene diacetate (PIDA) in the presence of sulfuric acid in trimethyl orthoformate (TMOF) undergoes a stereospecific ring contraction by an aryl shift to result in *trans* methyl 2-aryl-2,3-dihydrobenzo[*b*]furan-3-carboxylate (**4a**) as a major product. The mechanism of this transformation has been discussed on the basis of NMR, CD and chiral HPLC evidence.

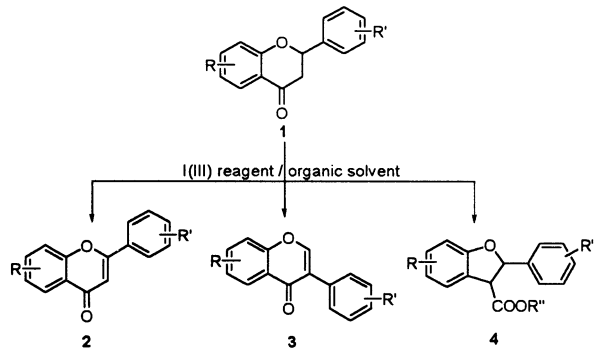
1. Introduction

Recently, hypervalent iodine reagents such as iodobenzene diacetate (PIDA), iodobenzene bis(trifluoroacetate) (PIFA), and [hydroxy(tosyloxy)iodo]benzene (HTIB) are extensively used in organic synthesis.[1–5]

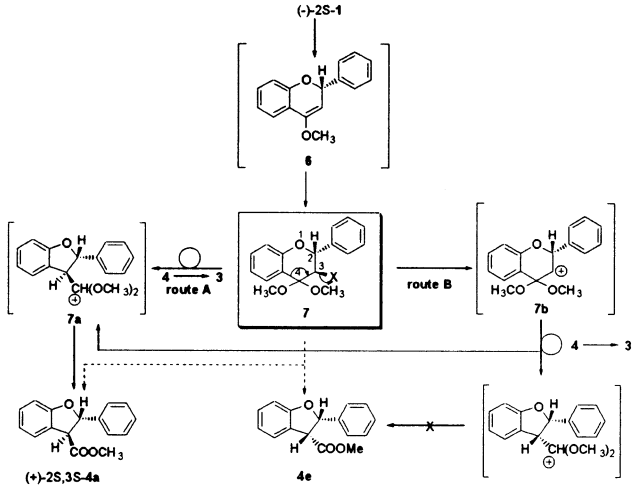
Among the various transformations, a reaction involving rearrangement[6–10] is of broad interest since similar oxidative rearrangements with Tl(III) salts have been reported.[11–14] One of the important advantages of these transformations is the oxidation of flavanones (**1**) resulting in flavones (**2**), isoflavones (**3**), or alkyl 2-aryl-2,3-dihydrobenzo[*b*]furan-3-carboxylates (**4**) depending on the reaction conditions[15–19] (Scheme 1).

When trimethyl orthoformate (TMOF) is employed as the solvent, oxidation of flavanones (**1**) with PIDA in the presence of a catalytic amount of sulfuric acid proceeds with ring contraction by an aryl shift to give **4** (R″=Me) as the major product.[19]

A plausible mechanism was proposed by Prakash and Tanwar,[19] (Scheme 2) which involves (i) the formation of a hypervalent iodine intermediate (**7**) by the electrophilic attack of PIDA on the enol ether (**6**) generated in situ from flavanone as depicted in Scheme 2, (ii) aryl migration to result in **4** (broken line). Although a similar mechanism for the transformation of **1** to **4** was postulated by Kapoor et al.[20] using thallium(III)nitrate as the oxidizing agent in



Scheme 1.



Scheme 2.

Keywords: 2,3-dihydrobenzo[*b*]furans; flavanones; hypervalent iodine; stereospecific ring contraction.
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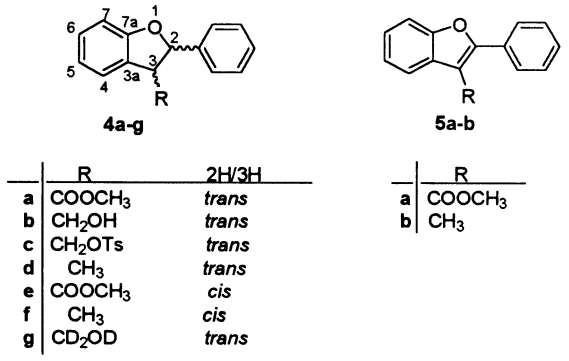
the presence of perchloric acid in TMOF, they also did not take sides regarding either the stereochemistry of the aryl migration or the relative configuration of the chirality centres of **4** (*cis* or *trans*).

In order to establish these important details of the transformation, we decided to investigate the oxidation of racemic and laevorotatory flavanone [(*rac*-**1**, (−)-2*S*-**1**, R=R′=H)] with PIDA–H_2SO_4 in TMOF.

2. Result and discussion

Oxidation of racemic flavanone (**1**, R=R′=H) with PIDA–H_2SO_4 in TMOF at room temperature resulted in *rac*-methyl 2-phenyl-2,3-dihydrobenzo[*b*]furan-3-carboxylate (**4a**) as the major product as described by Prakash and Tanwar.[19] The stereochemistry of **4a** was proven to be *trans* on the basis of NMR evidence, and by chemical correlation with the *cis*-2,3-dihydrobenzo[*b*]furan derivatives **4e** and **4f** synthesized in stereocontrolled reaction (Scheme 3).



Scheme 3.

The synthesis of *rac-cis*-methyl 2-phenyl-2,3-dihydrobenzo[*b*]furan-3-carboxylate (**4e**) was achieved from **4a** in two steps. First, **4a** was transformed into **5a** using 2,6-dichloro-3,5-dicianoquinone (DDQ) as the oxidizing agent according to the literature,[21] whose catalytic hydrogenation over Pd–C in methanol resulted in racemic *cis*-**4f** in low yield (12%).

Racemic *cis*-2-phenyl-3-methyl-2,3-dihydrobenzo[*b*]furan (**4f**) was also prepared by catalytic hydrogenation from **5a**, which was synthesized from 2-benzoyloxyacetophenone under McMurry conditions.[22]

Finally, the product of the ring contraction of **1** (**4a**) could be very simply transformed into **4d** in three steps (**4a→4b→4c→4d**) and the reduction of **4a** with $LiAlD_4$ furnishing **4g** clearly showed that the relative configuration of C-2 and C-3 has not changed in this step.

Comparison of NMR data of **4a** and **4d** [^1H and ^{13}C chemical shifts and coupling constants ($J_{2,3}$)] (see Section 3) with those of the corresponding *cis* compounds (**4e**, **4f**) clearly indicated that the coupling constant between the hydrogen at C-2 and C-3 can not be used for the determination of their relative stereochemistry, although it is widely applied in the literature.[23–25]

Table 1. Chemical shift differences for diastereomers of **4**

	^1H				^{13}C			
	$\Delta\delta_{2H}$	$\Delta\delta_{3\text{-}H}$	$\Delta\delta_{OMe}$	$\Delta\delta_{Me}$	$\Delta\delta_{C\text{-}2}$	$\Delta\delta_{C\text{-}3}$	$\Delta\delta_{OMe}$	$\Delta\delta_{Me}$
a vs. **e**	0.19	−0.27	0.68	–	−0.2	1.0	2.1	–
d vs. **f**	−0.62	−0.24	–	0.61	4.8	4.8	–	1.9

From the data given in Table 1 it can be concluded that only the ^1H-chemical shift differences of substituents at C-3 are suitable for this purpose. Thus, the values of the corresponding chemical shifts of the *cis* compounds (**4e**, **4f**) have been found to be significantly different ($\Delta\delta_{3H}$=−0.27 and −0.24 ppm; $\Delta\delta_{OMe}$=0.68 ppm; $\Delta\delta_{Me}$=0.61 ppm) from those of the *trans* ones (**4a**, **4d**) due to the anisotropic effect of the phenyl ring at C-2. Our findings are in good accordance with the observations on chemical shift differences of methyl groups at C-3 of the isomeric 2-phenyl-3-methyl-2,3-dihydrobenzo[*b*]furan derivatives published by Ollis[26] and Pappas et al.[27] In addition to this result, NOE experiments also proved the *trans* (0.8% effect between H-2 and H-3 of **4a**, **4b** and **4d**)/*cis* (6% effect between H-2 and H-3 of **4f**) relative configuration of these compounds.

The stereoselectivity of the addition of the electrophilic iodine(III) reagent at C-3 of the enol ether **6** followed by its rearrangement into **4a** could be proven by the transformation of (−)-2*S*-flavanone [(−)-2*S*-**1**] prepared as described by Bognár et al.[28] Since the enantiomeric excess of (−)-2*S*-**1** (50%) determined by HPLC using Chiralcel OJ column as stationary phase has been found to be practically the same with that of (+)-**4b** and (−)-**4d** prepared from the ring contraction product (+)-**4a**, the base line separation of which could not be achieved under various conditions. Therefore both the addition of PIDA to the enol ether (**6→7**) and the aryl migration (**7→7a**) occurred in a stereoselective manner controlled by the configuration of C-2 to result in (+)-2*S*,3*S*-**4a**. This absolute configuration could also be deduced from the negative ^1L_b-band of (+)-**4b** and (−)-**4d**.

Since the measured Cotton effects at 280 nm (Fig. 1) correspond well to the predicted ^1L_b transition of

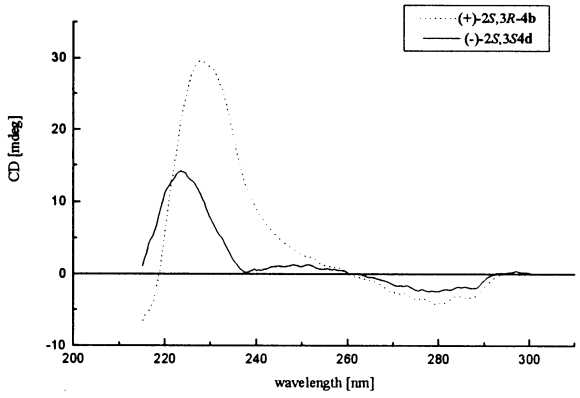


Figure 1.

dihydrobenzo[*b*]furan chromophore, the hetero-ring of both compounds should adopt the P-helicity[29] according to our helicity rule.[30] Taking into account that the substituents attached to the hetero-ring at C-2 and C-3 are equatorially oriented, their absolute configurations are therefore 2*S*,3*R* (**4b**) and 2*S*,3*S* (**4d**), which is in full agreement with the 2*S*,3*S* absolute configuration of (+)-**4a** mentioned above. This total diastereo- and enantioselectivity is in full accordance with reaction proceeding via **7a** (dihydrobenzo[*b*]furan-type ion, Scheme 2, route A) and casts doubt on route B.

In conclusion, it is to be noted that the present stereoselective oxidative approach followed by reduction of the ester group to hydroxymethyl allows a simple synthesis starting from the appropriate optically active flavanone derivatives to yield naturally occurring *O*-heterocycles carrying 2-aryl-3-hydroxymethyl moieties.

3. Experimental

3.1. General

Analytical and preparative TLC were done on plates Kieselgel 60 F_{254} (Fa. Merck). The reagents were purchased from Sigma-Aldrich. For workup the solutions were dried ($MgSO_4$) and concentrated *in vacuo*. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker WP-200 spectrometer with TMS as internal standard in $CDCl_3$. The chemical shifts are given in δ (ppm). Optical rotations were measured on a Perkin–Elmer 341 polarimeter (l=10 cm) at room temperature. CD spectra were recorded on a Jasco J-715 spectropolarimeter at room temperature in online mode with LCCD-311 HPLC flow cell unit. Experimental details of the HPLC analysis are reported for all compounds in the form: column (mobile phase), enantiomeric ratio, retention time (R_t) in min. HRMS were recorded in FAB mode (glycerol) on a VG 70HS MS spectrometer.

3.1.1. (2*S,3*S**)-3-Carboxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]furan (*rac*-4a).** To a stirred solution of flavanone (**1**) (2.24 g, 10 mmol) in trimethyl orthoformate (250 mL) H_2SO_4 (0.5 mL) was added a solution of PIDA (3.5 g, 10.8 mmol) in trimethyl orthoformate (100 mL) dropwise at room temperature over 20 min and stirring was continued for 12 h. Subsequently, the solvent was removed and water (150 mL) was added to the residue and stirring was continued for 2 h. Then the mixture was extracted with dichloromethane (3×50 mL), washed with an aqueous solution of $NaHCO_3$ and dried. Evaporation of the solvent gave an oil (3.2 g) which was purified by column chromatography on silica gel (hexane–ethyl acetate=9:1) to furnish **4a** (620 mg, 25%) as a yellow oil. ^{1}H NMR: 3.80 (s, 3H, COOMe), 4.27 (1H, d, $J_{2,3}$=7.7 Hz, H_3), 6.10 (1H, d, $J_{2,3}$=7.7 Hz, H_2), 6.85–7.45 (9H, m, aromatic protons) ^{13}C NMR: δ: 52.6 (C-3), 55.7 (OMe), 85.4 (C-2), 109.8 (C-7), 120.9 (C-5), 123.7 (C-3a), 125.1 (C-4), 125.6 (C-4′), 128.3 (C-2′, C-6′), 128.7 (C-3′, C-5′), 129.6 (C-6), 140.6 (C-1′), 159.2 (C-7a), 171.3 (C=O); HRMS *m*/*z* 254.0947 (calcd for $C_{16}H_{14}O_3$, 254.0943).

3.1.2. (2*S*,3*S*)-3-Carboxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]furan [(+)-4a]. Starting from 700 mg (3.12 mmol) (−)-2*S*-**1** gave 312 mg (39%) (+)-**4a** as a colourless oil. $[\alpha]_D$=32.0 (c=0.3, $CHCl_3$). Chiraspher NT (heptane), 5.8 min.

3.1.3. (2*S,3*R**)-3-Hydroxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]furan (*rac*-4b).** (A) A solution of **4a** (500 mg, 1.97 mmol) in dry ether (20 mL) was added dropwise to a suspension of $LiAlH_4$ (100 mg) in dry ether (10 mL) at 0°C and the reaction mixture was stirred for 20 min. Then ethyl acetate (2 mL) and water (10 mL) were added, the organic layer was separated, washed with water and dried. Evaporation of the solvent gave an oil which was purified by column chromatography (toluene–ethyl acetate=4:1) to furnish **4b** (390 mg, 87.6%) as a colourless oil.

(B) To a stirred solution of **4a** (87.7 mg, 0.34 mmol) in dry ether (10 mL), 1.1 equiv. of DIBAL-H in THF was added at 0°C under argon atmosphere and stirring was continued for 50 min. Then the reaction mixture was acidified (1 mL 10% HCl), and the organic layer was washed with water and dried. Evaporation of the solvent gave an oil which was purified by preparative TLC (toluene–ethyl acetate=4:1) to obtain **4b** (32 mg, 41%) as a colourless oil. ^{1}H NMR: 1.89 (1H, brs, OH), 3.53 (1H, m, H_3), 3.88 (2H, d, J=5.48 Hz, CH_2), 5.59 (1H, d, $J_{2,3}$=6.21 Hz, H_2), 6.84–7.40 (9H, m, aromatic protons). ^{13}C NMR: 53.5 (C-3), 64.5 (CH_2), 86.7 (C-2), 109.6 (C-7), 120.7 (C-5), 124.5 (C-4), 125.6 (C-3′, C-5′), 126.3 (C-3a), 127.9 (C-4′), 128.6 (C-2′, C-6′), 129.1 (C-6), 141.7 (C-1′), 160.1 (C-7a). HRMS *m*/*z* 226.0999 (calcd for $C_{15}H_{14}O_2$, 226.0994).

3.1.4. (2*S*,3*R*)-3-Hydroxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]furan [(+)-4b]. Starting from (+)-2*S*,3*S*-**4a** (250 mg) using method B to furnish (+)-**4b** (150 mg, 67%) as a colourless oil. $[\alpha]_D$=+5.3 (c=0.24, $CHCl_3$); enantiomeric excess=52%; Chiral AGP; (0.01 M phosphate buffer: *i*PrOH=9:1); 6.58 and 9.82 min.

3.1.5. (2*S,3*R**)-2-Phenyl-3-*p*-tosyloxymethyl-2,3-dihydrobenzo[*b*]furan (*rac*-4c).** To a stirred solution of **4b** (300 mg, 1.37 mmol) and *p*-TsCl (310 mg, 1.63 mmol) in dry CH_2Cl_2 (20 mL) 20 drops of dry pyridine were added and stirring was continued for 24 h. Subsequently, the reaction mixture was washed with 10% HCl (10 mL), water and dried. Evaporation of the solvent gave an oil which was purified by column chromatography on silica gel (hexane–ethyl acetate=3:1) to obtain **4c** as a colourless oil (300 mg, 60%). ^{1}H NMR: 2.48 (3H, s, CH_3), 3.72 (1H, m, H_3), 4.27 (2H, m, CH_2), 5.49 (1H, d, $J_{2,3}$=5.48 Hz, H_2), 6.91 and 7.82 (2H, d, J=7.68 Hz, aromatic protons) 7.05–7.45 (9H, m, aromatic protons). HRMS *m*/*z* 380.1078 (calcd for $C_{22}H_{20}O_4S$, 380.1082).

3.1.6. (2*S,3*S**)-3-Methyl-2-phenyl-2,3-dihydrobenzo[*b*]-furan (*rac*-4d).** A solution of **4c** (300 mg, 0.79 mmol) in dry THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (300 mg, 8.1 mmol) in dry THF (20 mL) and the reaction mixture was refluxed for 40 min. Then ethyl acetate (2 mL) and water (10 mL) were added and the organic layer was separated, washed with water and dried. Evaporation of

the solvent gave an oil which was purified by column chromatography (hexane–ethyl acetate=3:1) to furnish **4d** (116 mg, 70%) as a colourless oil. ^{1}H NMR: δ: 1.38 (3H, d, J=6.94 Hz, CH_3), 3.38 (1H, m, H_3), 5.11 (1H, d, $J_{2,3}$=8.77 Hz, H_2), 6.78–7.45 (9H, m, aromatic protons). ^{13}C NMR: δ: 18.1 (CH_3); 45.6 (C-3); 92.4 (C-2); 109.4 (C-7); 120.8 (C-5); 123.6 (C-6); 126.0 (C-2′, C-3′); 128.2 (C-4); 128.2 (C-4′); 128.6 (C-3′, C-5′); 131.8 (C-4a); 140.9 (C-1′). HRMS *m/z* 210.1051 (calcd for $C_{15}H_{14}O$, 210.1045).

3.1.7. (2*S*,3*S*)-3-Methyl-2-phenyl-2,3-dihydrobenzo[*b*]furan [(−)-4d]. Starting from (+)-2*S*,3*R*-**4c** gave 16 mg (−)-**4d** as a colourless oil (25%). $[\alpha]_D$=−4.8 (c=0.3, $CHCl_3$); enantiomeric excess=46%; Whelk01 (heptane); 9.2 and 11.2 min.

3.1.8. 2-Phenyl-3-carboxymethylbenzo[*b*]furan (5a). To a stirred solution of **4a** (406 mg, 1.6 mmol) in dry dioxane (50 mL) 1.5 g of DDQ (6.6 mmol) was added. The reaction mixture was refluxed for 96 h, then it was filtered and evaporation of the solvent gave an oil which was purified by column chromatography (hexane–ethyl acetate=9:1) to obtain (**5b**) as a yellow oil (300 mg, 74%). ^{1}H NMR: δ: 3.85 (3H, s, OCH_3), 7.10–7.54 (6H, m, aromatic protons), 7.88–8.1 (3H, m, aromatic protons). HRMS *m/z* 252.0775 (calcd for $C_{16}H_{12}O_3$, 252.0786).

3.1.9. (2*S,3*R**)-2-Phenyl-3-carboxymethyl-2,3-dihydrobenzo[*b*]furan (*rac*-4e).** 100 mg (0.39 mmol) of **5a** in dry methanol (5 mL) was added to a stirred suspension of Pd(C) (100 mg, 10%) in dry methanol (10 mL) under a H_2 atmosphere and stirring was continued for 24 h. Subsequently, the mixture was filtered and the solvent was removed by evaporation. Purification by preparative TLC (toluene–hexane=4:1) gave **4f** as a colourless oil (12 mg, 11%). ^{1}H NMR: δ: 3.12 (3H, s, OCH_3), 4.54 (1H, d, $J_{2,3}$=10 Hz, H_3), 5.91 (1H, d, $J_{2,3}$=10 Hz, H_2), 6.81–7.40 (9H, m, aromatic protons). ^{13}C NMR: δ: 51.6 (C-3), 53.9 (OMe), 85.6 (C-2), 109.9 (C-7), 121.2 (C-5), 124.6 (C-3a), 125.8 (C-4), 126.2 (C-4′), 126.2 (C-2′, C-6′), 128.1 (C-3′, C-5′), 128.3 (C-6), 137.0 (C-1′), 160.4 (C-7a), 170.4 (C=O). HRMS *m/z* 254.0939 (calcd for $C_{16}H_{14}O_3$, 254.0943).

3.1.10. 3-Methyl-2-phenylbenzo[*b*]furan (5b). To a stirred solution of 2-benzoyloxyacetophenone (2.4 g, 10 mmol) in dry dioxane (100 mL), $TiCl_4$ (3.3 mL), and 30 min later Zn (3.93 g) was added under argon atmosphere at 5°C. The reaction mixture was refluxed for 6 h and then a saturated solution of NH_4Cl was added (20 mL) and the product was extracted with dichloromethane (3×20 mL) and the organic layer was washed and dried. Evaporation of the solvent gave an oil, which was purified by column chromatography (hexane–ethyl acetate=6:1) to furnish **5a** as a colourless oil (438 mg, 22%). ^{1}H NMR: δ: 2.48 (3H, s, CH_3); 7.15–8.45 (9H, m, aromatic protons). ^{13}C NMR: δ: 9.2 (CH_3); 150.7 (C-3); 153.9 (C-2). HRMS *m/z* 208.0885 (calcd for $C_{15}H_{12}O$, 208.0888).

3.1.11. (2*S,3*R**)-2-Phenyl-3-methyl-2,3-dihydrobenzo-[*b*]furan (*rac*-4f).** 400 mg (1.78 mmol) of **5b** in dry methanol (10 mL) was added to a stirred suspension of Pd(C) (250 mg, 10%) in dry methanol (10 mL) under a H_2 atmosphere and the stirring was continued for 8 h. Subsequently, the mixture was filtered and the solvent was removed upon evaporation. Purification by column chromatography (hexane) gave **4f** as a colourless oil (195 mg, 48%). ^{1}H NMR: δ: 0.77 (3H, d, J=7.31 Hz, CH_3), 3.62 (1H, m, H_3), 5.73 (1H, d, $J_{2,3}$=8.8 Hz, H_2), 6.75–7.82 (9H, m, aromatic protons). ^{13}C NMR: δ: 16.9 (CH_3); 40.8 (C-3); 87.6 (C-2);109.4 (C-7); 120.7 (C-5); 124.3 (C-6); 126.3 (C-2′, C-6′); 127.6 (C-4); 128.1 (C-3′, C-5′); 129.7 (C-4′); 139.0 (C-4a); 159.1 (C-1′); 165.4 (C-7a). HRMS *m/z* 210.1048 (calcd for $C_{15}H_{14}O$, 210.1045).

3.1.12. (2*S,3*R**)-2-Phenyl-3-(trideuterohydroxymethyl)-2,3-dihydrobenzo[*b*]furan (*rac*-4g).** To a stirred suspension of 50 mg $LiAlD_4$ in dry ether (5 mL), 100 mg of **4a** (0.43 mmol) was added dropwise in dry ether (5 mL) at 0°C and stirring was continued for 1 h. Subsequently, the reaction mixture was acidified with the mixture of D_2SO_4 (10 drops) and D_2O (2 mL) and the organic layer was separated, washed and dried. Evaporation of the solvent furnished **4g** (89 mg, 94%) as a colourless oil. ^{1}H NMR: δ: 3.51 (2H, d, $J_{2,3}$=6.2 Hz, H_3); 5.58 (2H, d, $J_{2,3}$=6.2 Hz, H_2); 6.83–7.42 (9H, m, aromatic protons). HRMS *m/z* 229.1184 (calcd for $C_{15}H_{11}D_3O_2$, 229.1182).

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References

1. Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179–1255.
2. Kitamura, T.; Fuliwara, Y. *Org. Prep. Proced. Int.* **1977**, *29*, 409–458.
3. Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244–250.
4. Wirth, T.; Hirt, U. H. *Synthesis* **1999**, *8*, 1271–1287.
5. Prakash, O. *Aldrichim. Acta* **1995**, *28*, 63–71.
6. Tamura, Y.; Shirouchi, Y.; Haruta, J. *Synthesis* **1984**, 231–232.
7. Tamura, Y.; Yukura, T.; Shirouchi, Y.; Harota, J. *Chem. Pharm. Bull.* **1985**, *33*, 1097–1103.
8. Moriarty, R. M.; Khosrowshahi, J. S.; Prakash, O. *Tetrahedron Lett.* **1985**, *26*, 2961–2964.
9. Singhi, O. V.; Prakash, O.; Grag, C. P.; Kapoor, R. P. *Ind. J. Chem.* **1989**, *28B*, 814–817.
10. Prakash, O.; Goyal, S.; Moriarty, R. M.; Khosrowshahi, J. S. *Ind. J. Chem.* **1990**, *29B*, 304–309.
11. McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 4919–4920.
12. Farkas, L.; Gottsegen, A.; Nógrádi, M.; Antus, S. *J. Chem. Soc., Chem. Commun.* **1972**, 825–826.
13. Farkas, L.; Gottsegen, A.; Nógrádi, M.; Antus, S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 305–312.
14. Taylor, E. C.; Robey, R. L.; Liu, K. T.; Favre, B.; Bozimo, H. T.; Conley, R. A.; Chiang, C. S.; McKillop, A.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 3037–3038.
15. Prakash, O.; Pahuja, S.; Goyal, S.; Moriarty, P. M. *Synlett* **1990**, 337–338.

16. Prakash, O.; Pahuja, S.; Moriarty, P. M. *Synth. Commun.* **1990**, *20*, 1417–1422.
17. Prakash, O.; Saini, N.; Sharma, P. K. *Synlett* **1994**, 221–222.
18. Prakash, O.; Saini, N.; Sharma, P. K. *Heterocycles* **1994**, *38*, 409–431.
19. Prakash, O.; Tanwar, M. P. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1168–1171.
20. Khanna, M. N.; Singh, O. V.; Garg, C. P.; Kapoor, R. P. *Synth. Commun.* **1993**, *23*, 585–590.
21. Banerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1990**, 150–151.
22. Pieters, L.; Van Dyck, A.; Gao, M.; Bai, R.; Hamel, E.; Vlientinck, A.; Lamiere, G. *J. Med. Chem.* **1999**, *42*, 5475–5481.
23. Valcic, S.; Montenegro, G.; Timmermenn, B. N. *J. Nat. Prod.* **1998**, *61*, 771–775.
24. Achenbach, H.; Groß, J.; Domínguez, X. A.; Cano, G.; Verde, S. J.; Brussolo, L. D. C.; Munoz, G.; Salgado, F.; López, L. *Phytochemistry* **1987**, *26*, 1159–1166.
25. Gottlieb, O. R.; Mourao, J. C.; Yoshida, M.; Mascarenhas, Y. P.; Rodrigues, M.; Rosenstein, R. D.; Tomita, K. *Phytochemistry* **1977**, 1003–1006.
26. Gregson, M. G.; Ollis, W. B.; Redman, B. T.; Sutherland, I. O. *Chem. Commun.* **1968**, 1394–1395.
27. Pappas, S. P.; Zehr, R. D.; Alexander, J. E. *J. Heterocycl. Chem.* **1970**, *7*, 1215–1217.
28. Rákosi, M.; Tőkés, A. L.; Bognár, R. *Act. Chim. Acad. Sci. Hung.* **1975**, *87*, 161–164.
29. Descriptor P or M is defined by the torsion angle (ω) along the C-7a, O, C-2, C-3 atoms. Since $\omega>0$, therefore chirality of the five membered ring is chracterized by P-helicity.
30. Kurtán, T.; Baitz-Gács, E.; Majer, Zs.; Antus, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 453–461.