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Bioorganic & Medicinal Chemistry 14 (2006) 7910–7916
Bioorganic & Medicinal Chemistry

5-Substituted-2,3-diphenyltetrahydrofurans: A new class of moderately selective COX-2 inhibitors

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Received 13 June 2006; revised 25 July 2006; accepted 26 July 2006
Available online 10 August 2006

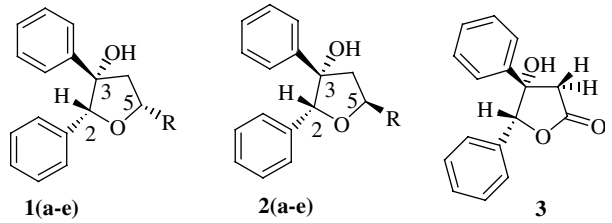
Abstract—The nature of *C*-5 substituent and the configuration at *C*-5 carbon of 2,3-diphenyltetrahydrofurans, with chiral centres at *C*-2, *C*-3 and *C*-5, show a remarkable influence on their COX-2 inhibition and selectivity. Out of the eight compounds investigated here, **1b** with COOH group and R^* configuration at *C*-5, and **2d** with $CH_2SCH_2CH_3$ group and S^* configuration at *C*-5 have been identified as lead molecules for further studies on COX-2 inhibition.

1. Introduction

The successful treatment of inflammation, arising due to the production of prostaglandins from arachidonic acid metabolism mediated by cyclooxygenase,[1] is mainly facing two problems. First, the close similarity between the two isoforms of cyclooxygenase,[2] that is, COX-1 and COX-2, performing different metabolic functions,[2] makes the selective inhibition of COX-2 (responsible for inflammation) difficult. Second, the too much inhibition of COX-2 (which under normal conditions produces prostaglandins acting as vasodilators) leads to cardiac problems.[3] In the framework of these two aspects, the present status of anti-inflammatory agents is the use of either COX-1, COX-2 non-selective drugs like ibuprofen, diclofenac, nimesulide, etc. (causing side effects due to COX-1 blockage)[4] or the selective COX-2 drugs, the coxibs[5] (rofecoxib, celecoxib, etc.), where too much inhibition of COX-2 leads to their cardiac toxicity and ultimately their withdrawal from the market.[6] In view of these problems, to treat inflammation at the cyclooxygenase stage, the anti-inflammatory agent should be neutral towards COX-1 and moderate inhibitor of COX-2 without interfering with its normal metabolic functions. A number of new compounds have been developed and screened for their COX inhibitory activities[4,7–12] but in spite of the fact that COX-2 active site is chiral and difference in activity of two enantiomers of ibuprofen[13] is known, most of the COX-2 selective inhibitors are achiral in nature.

Bearing in mind the reasonable flexibility and chirality of COX-2 active site, we have recently investigated the dockings of different stereoisomers of tetrahydrofurans[14] in the active sites of COX-1 and COX-2. These molecules show appreciable selectivity for COX-2 (less than rofecoxib, celecoxib and more than ibuprofen, diclofenac). Also the nature of substituent at C-5 remarkably affects their binding with R120 (the residue active during the metabolic phase of arachidonic acid) of COX-2.

In the present contribution, the compounds **1** and **2** (Fig. 1) with R^* and S^* configuration at *C*-2 and *C*-3



1-2: a, R =CH_2OH ; b, R = COOH ; c, R = CH_2I; d, R = $CH_2SCH_2CH_3$; e, R = CH_2NH_2;

Figure 1.

Keywords: Inflammation; Cyclooxygenase; Chiral COX-2 inhibitors; 2,3-Diphenyltetrahydrofurans; In-vitro COX-2 inhibition.
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doi:10.1016/j.bmc.2006.07.044

carbons, respectively, either R^* or S^* configuration at *C*-5, possessing varied substituents at *C*-5 (CH_2I, CH_2NH_2, COOH, CH_2OH and $CH_2SCH_2CH_3$) and compound **3** (Fig. 1) with R^* and S^* configurations at *C*-2 and *C*-3, respectively, have been synthesized and evaluated for their COX-1, COX-2 inhibitory activities.

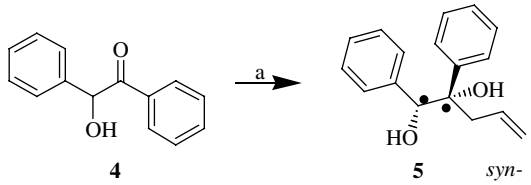
2. Results

2.1. Chemistry

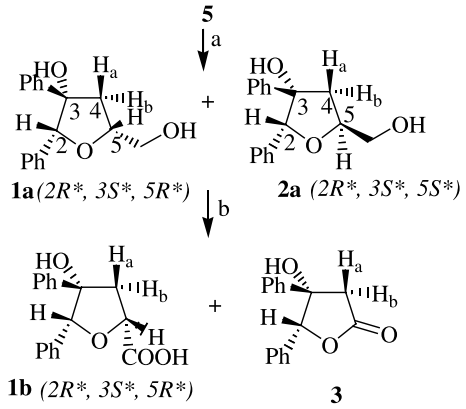
The previously established[15] synthetic strategy has been used for procuring the target compounds in which the allylation of benzoin has been followed by iodocyclisation or epoxidation.

The indium mediated allylation of benzoin **4** in THF + H_2O provided the diastereoselective allylated product **5** in quantitative yield (Scheme 1).

Treatment of **5** with 4 equivalents of *m*-CPBA in dry $CHCl_3$ at 0 °C, after usual work up, gave a mixture of two diastereomers **1a** and **2a** in the ratio 63:37[15a] which on recrystallisation gave pure **1a**, while **2a** was still left with some impurities of **1a** and due to their very close R_f values they were even not separated by column chromatography. Stirring a mixture of **1a** and **2a** with pyridinium chloro chromate (PCC) in dichloromethane at room temperature after usual work up and column chromatography provided two white compounds, the higher R_f component [15%, FAB mass (M^++1) 249, mp 131 °C] and lower R_f component [31%, FAB mass (M^++1) 277, mp 126 °C]. The higher R_f component with mp 131 °C, in its ^{1}H NMR spectrum, does not show a 1H multiplet in the region 5–6 ppm due to H-5 and in ^{13}C NMR spectrum, the C-5 carbon appears as a quaternary signal at δ 174 instead of the secondary carbon normally observed in the region 75–80 ppm. These spectral data corroborate structure **3** for this compound. The lower R_f component with mp 126 °C from its spectral data has been assigned the structure **1b** (Scheme 2). It seems as if out of the two diastereomers **1a** and **2a**, **1a** undergoes mild oxidation to the corresponding diastereomer **1b** with COOH group at *C*-5. In contrast to the earlier reports where hydroxymethyl tetrahydrofurans undergo extensive oxidation to furanones only, here, PCC mediated oxidation of mixture of **1a** + **2a** gave mixture of **1b** (31%) and **3** (15%). However, in this reaction, the second diastereomer of **1b**, that is, compound **2b**, could not be isolated.



Scheme 1. Reagents and conditions: (a) 1 equiv In, 1.5 equiv allyl bromide, THF/H_2O (2:1), 30 °C, 6–8 h, 92%.



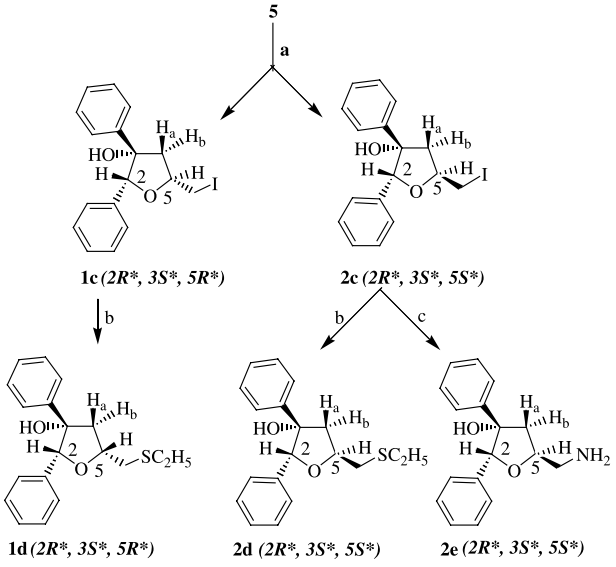
Scheme 2. Reagents and conditions: (a) 4 equiv MCPBA, dry $CHCl_3$, 0 °C, 24 h, 83%; (b) 4 equiv PCC, DCM, rt, 48 h, 15%, 31%.

The stirring of a solution of **5**, iodine and $NaHCO_3$ in CH_3CN at 0 °C gave a mixture of two diastereomers **1c** and **2c** in the ratio 14:86[15a] (Scheme 3) which were separated by column chromatography. Compounds **1c** and **2c** on treatment with ethanethiol provided the corresponding *C*-5 substituted products **1d** (72%) and **2d** (72%).

Treatment of **2c** with ammonia in ethanol provided **2e** (60%) while the similar reaction of **1c** did not provide **1e**; instead a polymeric product was formed (Scheme 3).

The structures of all the compounds have been established by various spectroscopic techniques and the relative stereochemistry at the chiral centres has been determined by NOE experiments or one in analogy with X-ray structure of the compound.[15a]

Therefore, easily available benzoin, through multi-step synthetic strategy involving indium mediated allylation



Scheme 3. Reagents and conditions: (a) 3 equiv $NaHCO_3$, 3 equiv I_2, CH_3CN, 0 °C, 76 h, 90%; (b) 1.1 equiv C_2H_5SH, 1.1 equiv NaH, DMF, 0 °C, 5 min, 72%; (c) excess aq NH_3, C_2H_5OH, THF, rt, 48 h, 60%.

with subsequent oxidative cyclisation/iodocyclisation and nucleophilic/oxidative transformation, provides the target compounds.

2.2. Biology

In vitro COX-2 inhibiting activities of these compounds have been evaluated using 'COX (ovine) inhibitor screening assay' kit with 96-well plates. Both ovine COX-1 and COX-2 enzymes were included. This screening assay directly measures $PGF_{2\alpha}$ produced by $SnCl_2$ reduction of COX-derived PGH_2. COX-1, COX-2 initial activity tubes were prepared taking 950 μl of reaction buffer, 10 μl of heme and 10 μl of COX-1 and COX-2 enzymes in respective tubes. Similarly, COX-1, COX-2 inhibitor tubes were prepared by adding 20 μl of inhibitor (compound under test) in each tube in addition to the above ingredients. The background tubes correspond to inactivated COX-1 and COX-2 enzymes obtained after keeping the tubes containing enzymes in boiling water for 3 min. Reactions were initiated by adding 10 μl of arachidonic acid in each tube and quenched with 50 μl of 1 M HCl. PGH_2 thus formed was reduced to $PGF_{2\alpha}$ by adding 100 μl $SnCl_2$. The prostaglandin produced in each well was quantified using broadly specific prostaglandin antiserum that binds with major prostaglandins and reading the 96-well plate at 405 nm. The wells of the 96-well plate showing low absorption at 405 nm indicate the low level of prostaglandins in these wells and hence the less activity of the enzyme. Therefore, the COX inhibitory activities of the compounds could be quantified from the absorption values of different wells of the 96-well plate. The results of these studies have been represented in terms of the percentage inhibition of COX-1 and COX-2 enzymes as well as the respective IC_{50} values of each inhibitor for the two enzymes.

3. Discussion

The percentage inhibition of COX-1 and COX-2 by each compound and the corresponding IC_{50} values are given in Table 1.

All the compounds have been evaluated in duplicate and Table 1 shows the average results. For COX-2, two concentrations of the compounds viz. 10^{-5} M and 10^{-6} M were used, while COX-1 inhibitory activities were evaluated at 10^{-5} M concentration only. All the eight compounds tested here differ by the nature of C-5 substituent. It has been found that the variation in the C-5 substituent considerably changes the inhibitory activity of the compound towards COX-2, while this change has relatively less effect on COX-1 inhibition. All the compounds exhibit more inhibition of COX-2 than COX-1 at 10^{-5} M concentration. Diastereomers **1c** and **2c** with CH_2I group at C-5 show only 9.5% and 23.5% inhibition of COX-2 at 10^{-6} M concentration indicating the poor participation of small, non-polar group (CH_2I) in the interactions with active site residues. Compound **7**, with structural similarities to rofecoxib, shows COX-2 inhibition (100%) at 10^{-5} M concentration like rofecoxib but the COX-2 inhibition at 10^{-6} M concentration is considerably less (10%) than that of rofecoxib (75%). A very nice discrimination between the two diastereomers of tetrahydrofuran by COX-2 has been observed in the case of compounds **1d** and **2d** where compound **2d** with (S^*) configuration at C-5 exhibits significant inhibition of COX-2 with $IC_{50} < 1$ μM and COX-2 selectivity >10, while the second diastereomer (**1d**) shows no inhibition of COX-1 at 10^{-6} M concentration. Compounds **1a** and **2e** with respective CH_2OH and CH_2NH_2 groups at C-5 show considerable COX-2 inhibition at 10^{-5} M concentration. Maximum COX-2 inhibition (68%) has been observed in case of compound **1b** having COOH group at C-5 of tetrahydrofuran. At the measurable concentrations, **1b** exhibits $IC_{50} < 1$ μM and COX-2 selectivity >10. A comparison of percentage inhibition and IC_{50}s for **1b** and **2d** with the corresponding reported values for rofecoxib and celecoxib indicates that the percentage inhibition of COX-2 by **1b** and **2d** is in-between that of rofecoxib and celecoxib. But the less selectivity of **1b** and **2d** for COX-2 in comparison to rofecoxib may make them better substitutes of rofecoxib and celecoxib because in the latter cases too much selectivity (for COX-2) leads to the cardiac toxicity.

Table 1. In vitro percentage inhibition and IC_{50} values for COX-1 and COX-2 enzymes

Compound	% Inhibition			IC_{50} (μM)		COX-2 selectivity[a]
	COX-2		COX-1	COX-2	COX-1	
	1 μM	10 μM	10 μM			
1a	27.65	77	2.8	5.1	>10	>1.96
1b	68.05	69	−1.15	< 1	>10	>10
1c	9.5	61.05	1.9	7.5	>10	>1.33
1d	−5.93	68	11.5	7.56	>10	>1.32
2c	23.5	59.3	−6.45	7.85	>10	>1.27
2d	67.55	92.1	22.1	<1	>10	>10
2e	30.25	87.75	11.45	4.15	>10	>2.4
3	10.37	100	9.25	5	>10	>2
Rofecoxib[b]	75	100	75	0.3	40	~133
Celecoxib[b]	50	100	65	1.2	14	~10

[a] COX-2 selectivity = IC_{50}(COX-1)/IC_{50}(COX-2).
[b] Reported.[7a]

Further detailed investigations on compounds **1b**, **2d** and their analogues are under progress.

Therefore, amongst the eight compounds evaluated here, compound **1b** with COOH group at *C*-5 and compound **2d** with $CH_2SCH_2CH_3$ group at *C*-5 exhibit appreciable COX-2 inhibition and selection over COX-1. These two compounds could be selected as the leads and require further investigations at low concentrations. Moreover, role of the nature of *C*-5 substituent and the conformation at *C*-5 chiral centre (along with the *C*-2 and *C*-3 chiral centres, which are kept fixed here) towards the COX-2 inhibition, which is evident from the COX-2 inhibitory activities of **1b** and diastereomers **1d** and **2d**, invites further exploration for the synthesis of chiral COX-2 inhibitors, an area which so far has received little attention.

The interactions of **1b** and **2d** in the active site of COX-2 were investigated from their docking studies following the previously described procedure[14] taking the crystal structure of COX-2, with Sc-558 (close similarity to celecoxib) as the ligand, from the Protein Data Bank (pdb ID 6COX). To ensure the validity of the programme, before docking **1b** and **2d** in the active site of COX-2, Sc-558 was made to dock in the active site of COX-2. The close overlapping of the docked structure with the native ligand (X-ray crystal structure) ensures the validity of the programme (Fig. 2). The distance between one of the three fluorines of CF_3 group of Sc-558 and hydrogen of guanidine part of R120 is 2.3 Å.

Since the metabolic activity of COX-2 starts with the formation of a salt bridge between carboxylic group of arachidonic acid and the guanidine moiety of R120, an effective COX-2 inhibitor must be able to block R120. The dockings of **1b** in the active site of COX-2 show the proximity of carboxylic group of **1b** to the guanidine part of R120 and formation of H-bond between the two groups (Fig. 3) and thereby blocking the R120 amino acid residue of COX-2.

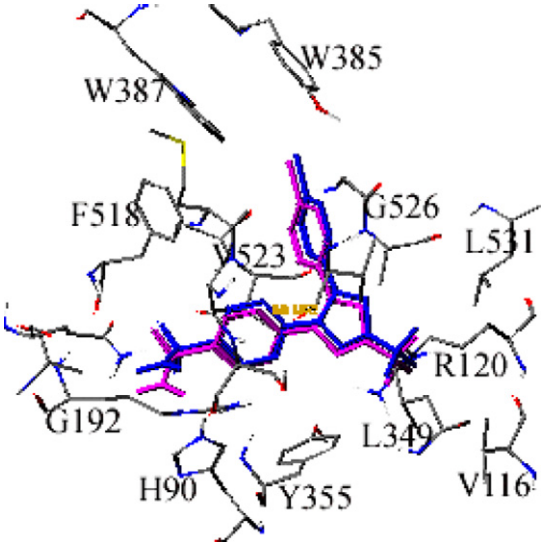


Figure 2. Close overlapping of docked structure of Sc-558 (magenta) with its crystal structure (blue, marked as native ligand) (rms error is 0.56).

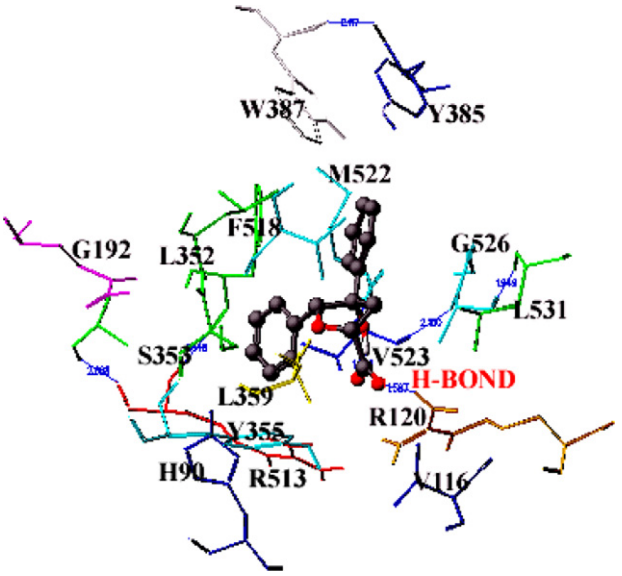


Figure 3. Compound **1b** docked in the active site of COX-2. H-bond formation between COOH group of **1b** and R120 is very clear. H's are omitted for clarity.

Similarly, compound **2d**, when docked in the active site of COX-2 orients in such a way that its *C*-5 substituent is placed in the vicinity of guanidine moiety of R120 (Fig. 4). The sulfur atom present in *C*-5 substituent of **2d** approaches the H of guanidine group with a distance of 2.1 Å. However, during the docking of **1d** (diastereomer of **2d**) in the active site of COX-2, the *C*-5 substituent is placed away from R120.

Therefore, in both the compounds **1b** and **2d**, the placements of C-5 substituent are nearer the guanidine moiety of R120 than in the case of Sc-558 (CF_3 group) and their interactions help in the inhibition of catalytic properties of COX-2.

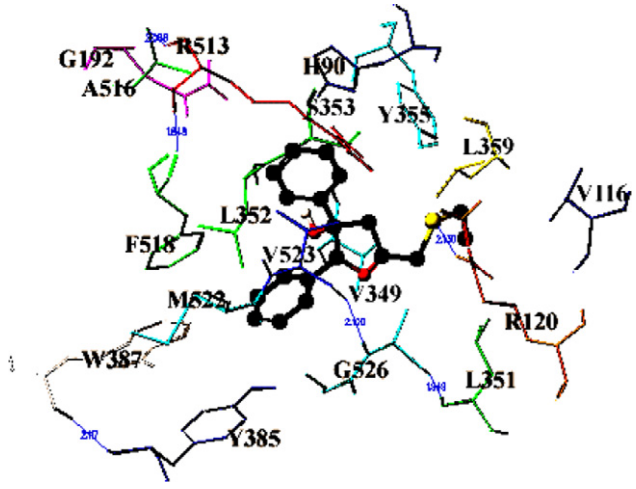


Figure 4. Compound **2d** docked in the active site of COX-2. A weak interaction between the S present with C-5 substituent of **2d** and guanidine H of R120 has been observed.

4. Conclusion

The COX-1 and COX-2 inhibitory activities of 2,3-diphenyltetrahydrofuran derivatives studied here remarkably point towards the role of *C*-5 substituent and the configuration at *C*-5 carbon for the inhibition of COX-2. Compound **1b** with COOH group and R^* configuration at *C*-5 and **2d** with $CH_2SCH_2CH_3$ group and S^* configuration at *C*-5 exhibit appreciable COX-2 inhibition and selectivity over COX-1 and could be explored further as lead molecules for COX-2 inhibition.

5. Experimental

5.1. General details

Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were run on JEOL 300 MHz and 75 MHz NMR, respectively, using $CDCl_3$ as solvent. Chemical shifts are given in ppm with TMS as an internal reference. *J* values are given in Hertz. Chromatography was performed with silica 100–200 mesh and reactions were monitored by thin-layer chromatography (TLC) with silica plates coated with silica gel HF-254. The bioassay kit was purchased from Cayman Chemical.

5.2. General procedure

5.2.1. Procedure A. Benzoin **4** (5 mmol), allyl bromide (7.5 mmol) and indium metal (5 mmol) were taken in THF–H_2O (2:1) mixture (10 ml) and the reaction mixture was stirred at 30 ± 2 °C until the indium metal was dissolved. The turbid reaction mixture was treated with 4N HCl and was extracted with $CHCl_3$ (3× 25 ml). The organic phase was dried over Na_2SO_4. The solvent was distilled off and the residue was column chromatographed (silica gel, 60–120 mesh) using ethyl acetate, hexane as eluents to isolate pure homoallylic alcohol.

5.2.2. (*1R, *2S**)-1,2-diphenyl-pent-4-ene-1,2-diol (5).** Yield 92%; White solid, mp 94–95 °C ($CHCl_3$); IR (KBr, cm^{-1}): 3620 (OH); ^1H NMR (300 MHz): δ 2.58 (s, 1H, OH, exchanges with D_2O), 2.59 (s, 1H, OH, exchanges with D_2O), 2.77 (dd, ^1J = 14.1 Hz, ^2J = 8.7 Hz, 1H, 1H of CH_2), 2.93 (dd, ^1J = 14.1 Hz, ^2J = 5.7 Hz, 1H, 1H of CH_2), 4.80 (s, 1H, CH), 5.06–5.26 (m, 2H, =CH_2), 5.50–5.63 (m, 1H, =CH), 6.96–7.23 (m, 10H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 42.45 (-ve, CH_2), 78.34 (ab, C), 80.44 (+ve, CH), 119.80 (-ve, CH_2), 126.53 (+ve, CH), 126.90 (+ve, CH), 127.43(+ve, CH), 127.60 (+ve, CH), 127.77 (+ve, CH), 133.24 (+ve, CH), 139.29 (ab, C), 141.465 (ab, C); M^+ *m/z* 237 (M^+−OH); Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.1%; H, 6.9%.

5.3. *m*-CPBA mediated cyclisation of homoallylic alcohol

m-CPBA (20 mmol) was added to an ice-cold solution homoallylic alcohol **5** (5 mmol) in $CHCl_3$ and the reaction mixture was stirred for 24 h at 0 °C (TLC monitoring). The reaction mixture was neutralized with sodium bicarbonate followed by extraction with $CHCl_3$. The organic layer was dried over anhydrous sodium sulfate and distilled off. The residue was column chromatographed (silica gel 100–200) using ethyl acetate, hexane as eluents to get mixture of diastereomers **1a** and **2a** which on further recrystallisation gave pure **1a**.[15]

5.4. PCC mediated oxidation of hydroxylmethyl tetrahydrofuran derivatives

The solution of pyridinium chloro chromate (PCC) (20 mmol) in dry DCM was added to the solution of hydroxylmethyl tetrahydrofuran derivatives in dry DCM and stirred for 48–76 h at 30 ± 1 °C (TLC monitoring). The reaction mixture was extracted with dry diethyl ether. The organic layer was dried over anhydrous sodium sulfate and was distilled off. The residue was column chromatographed (silica gel 100–200) to isolate the products.

5.4.1. 4-Hydroxy-5-methyl-4,5-diphenyl-tetrahydro-furan-2-carboxylic acid (1b). Yield 31%; white solid, mp 126 °C (C_2H_5OH); IR (KBr, cm^{-1}): 3580 (OH), 1710 (C=O). ^1H NMR (300 MHz): δ 1.59 (bs, 1H, exchanges with D_2O), 2.46 (d, *J* = 11.1 Hz, 1H, H-4), 3.02 (dd, ^1J = 11.1 Hz, ^2J = 2.1 Hz, 1H, H-4), 4.90 (d, *J* = 2.1 Hz, 1H, H-5), 5.27 (s, 1H, H-2), 6.91 (d, *J* = 6.6 Hz, 2H, ArH), 7.07–7.43 (m, 8H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 45.53 (-ve, C-4), 78.12 (+ve, C-5), 85.65 (+ve, C-2), 92.11 (ab, C-3), 125.47 (+ve, CH), 126.95 (+ve, CH), 127.89 (+ve, CH), 128.36 (+ve, CH), 128.61 (+ve, CH), 128.97 (+ve, CH), 132.04 (ab, C), 133.57 (ab, C), 171.60 (ab, C=O); NOE experiments: Irradiation of singlet at δ 5.27 (H-2) shows positive NOE with signals at δ 4.90 (5-H, 7.2%), 3.02 (H-4, 4.9%) and 6.91, 7.06–7.45 (ArH, 13.55%, 6.85%) and irradiation of doublet at δ 4.90 (H-5) shows positive NOE with dd at δ 3.02 (3.16%); M^+ *m/z* 267 (M^+−OH); Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.84%; H, 5.67%. Found: C, 72.13%; H, 5.97%.

5.4.2. 4-Hydroxy-4,5-diphenyl-dihydro-furan-2-one (3). Yield 15%; white solid, mp 131 °C; IR (KBr, cm^{-1}): 3610 (OH), 3520 (OH), 1820 (C=O); ^1H NMR (300 MHz): δ 1.90 (d, *J* = 1.8 Hz, 1H, exchanges with D_2O), 3.02 (d, *J* = 17.4 Hz, 1H, H-4), 3.21 (dd, ^1J = 17.4 Hz, ^2J = 1.8 Hz, 1H, H-4), 5.83 (s, 1H, H-2), 7.06–7.09 (m, 2H, ArH), 7.26–7.43 (m, 8H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 45.88 (-ve, C-4), 79.86 (ab, C-3), 88.79 (+ve, C-2), 125.17 (+ve, CH), 126.41 (+ve, CH), 128.26 (+ve, CH), 128.68 (+ve, CH), 128.84 (+ve, CH), 129.27 (+ve, CH), 131.45 (ab, C), 139.61 (ab, C), 174.05 (ab, C=O); FAB mass (M^++1) *m/z* 255; Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57%; H, 5.55%. Found: C, 75.34%; H, 5.48%.

5.5. Iodine mediated cyclisation of homoallylic alcohols

Sodium hydrogen carbonate (9 mmol) was added to an ice-cold solution of homoallylic alcohol (3 mmol) in dry acetonitrile and resulting suspension was stirred

for 15 min at 0 °C. Iodine (9 mmol) was added and stirring was continued for 72 h at 0 °C (TLC monitoring). The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous sodium thiosulfate to remove excess of iodine. The organic layer was dried over anhydrous sodium sulfate and was distilled off. The residue was column chromatographed (silica gel 100–200) to isolate substituted tetrahydrofuran derivatives **1c** and **2c**.[15]

5.6. Conversion of iodomethyl tetrahydrofuranol into ethylsulfanylmethyl tetrahydrofuranol

To the ice-cold solution of NaH (5.5 mmol) in DMF was added ethane thiol (5.5 mmol) and stirred for 2 min. followed by the addition of ice-cold solution of **1c**, **2c** (5 mmol). On completion of reaction (2–3 min, TLC monitoring), the reaction mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate and was distilled off. The residue was column chromatographed (silica gel 100–200) using ethyl acetate, hexane as eluents to isolate the product.

5.6.1. (*2R, *3S**, *5R**)-5-Ethylsulfanylmethyl-2,3-diphenyl-tetrahydro-furan-3-ol (1d).** Yield 72%; liquid; IR ($CHCl_3$, cm^{-1}): 3600 (OH); ^1H NMR (300 MHz): δ 1.34 (t, $J = 7.5$ Hz, CH_3), 2.17 (bs, 1H, exchanges with D_2O), 2.38 (dd, $^1J = 14.1$ Hz, $^2J = 4.8$ Hz, H-4), 2.76 (q, $J = 7.5$ Hz, SCH_2), 2.83 (dd, $^1J = 14.1$ Hz, $^2J = 9.0$ Hz, H-4), 2.97 (dd, $^1J = 13.8$ Hz, $^2J = 4.8$ Hz, 1H, 5-CH_2), 3.09 (dd, $^1J = 13.8$ Hz, $^2J = 5.4$ Hz, 1H, 5-CH_2), 4.65 (dq, $^1J = 9.9$ Hz, $^2J = 4.8$ Hz, 1H, H-5), 5.11 (s, 1H, H-2), 6.98–7.43 (m, 10H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.95 (+ve, CH_3), 27.48 (-ve, SCH_2), 37.11(-ve, 5-CH_2), 48.17 (-ve, C-4), 77.19 (+ve, C-5), 82.04 (ab, C-3), 90.38 (+ve, C-2), 125.40 (+ve, CH), 126.65 (+ve, CH), 127.02 (+ve, CH), 127.93 (+ve, CH), 127.96 (+ve, CH), 128.21 (+ve, CH), 135.09 (ab, C), 142.01 (ab, C). NOE experiments: Irradiation of singlet at δ 5.18 (H-2) shows positive NOE with signals at δ 4.65 (H-5), and 6.94, 7.43 (ArH) and irradiation of dq at δ 4. 65 (H-5) shows positive NOE with dd at δ 2.83 (5.46%); FAB mass (M^+-1) *m/z* 313 Anal. Calcd for $C_{19}H_{22}O_2S$: C, 72.57%; H, 7.05%. Found: C, 72.63%; H, 7.19%.

5.6.2. (*2R, *3S**, *5S**)-5-Ethylsulfanylmethyl-2,3-diphenyl-tetrahydro-furan-3-ol (2d).** Yield 72%; liquid, IR ($CHCl_3$, cm^{-1}): 3620 (OH), ^1H NMR (300 MHz): δ 1.31 (t, $J = 7.5$ Hz, CH_3), 2.46 (bs, 1H, exchanges with D_2O), 2.55 (d, $J = 7.8$ Hz, 2H, H-4), 2.69 (q, $J = 7.5$ Hz, SCH_2), 2.96 (q, $J = 2.4$ Hz, 2H, 5-CH_2), 4.86 (m, 1H, H-5), 5.43 (s, 1H, H-2), 7.02–7.44 (m, 10H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.98 (+ve, CH_3), 27.09 (-ve, SCH_2), 37.19 (-ve, CH_2-5), 47.92 (-ve, C-4), 78.44 (+ve, C-5), 83.25 (ab, C-3), 89.53 (+ve, C-2), 125.30 (+ve, CH), 125.87 (+ve, CH), 126.60 (+ve, CH), 127.26 (+ve, CH), 128.28 (+ve, CH), 128.35 (+ve, CH), 135.48 (ab, C), 141.66 (ab, C). NOE experiments: Irradiation of singlet at δ 5.43 (H-2) shows positive NOE with signals at δ 7.03 (19.8%), 7.38 (11.86%) (ArH) and shows no positive NOE with multiplet at δ 4.86 (H-5); FAB mass (M^+-1) *m/z* 313; Anal. Calcd for $C_{19}H_{22}O_2S$: C, 72.57%; H, 7.05%. Found: C, 72.36%; H, 6.89%.

5.7. (*2R**, *3S**, *5S**)-5-Aminomethyl-2-methyl-2,3-diphenyl-tetrahydro-furan-3-ol (2e)

To the solution of **2c** in C_2H_5OH/THF (1:1) was added aq NH_3 and the reaction mixture was stirred at room temperature for 48 h (TLC monitoring) followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and was distilled off. The residue was column chromatographed (silica gel 100–200) to isolate **2e**. Yield 60%; pale yellow liquid; ^1H NMR (300 MHz): δ 2.40 (dd, $^1J = 12.9$ Hz, $^2J = 9.9$ Hz, H-4), 2.53 (ddd, $^1J = 12.9$ Hz, $^2J = 2.9$ Hz, $^3J = 1.2$ Hz, H-4), 3.18 (d, $^1J = 2.7$ Hz, 2H of CH_2NH_2), 4.50–4.60 (m, 1H, H-5), 5.35 (s, 1H, H-2), 7.13–7.35 (m, 10H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 45.45 (-ve, CH_2NH_2), 48.01 (-ve, C-4), 77.54 (+ve, C-5), 83.19 (ab, C-3), 89.42 (+ve, C-2), 125.30 (+ve, CH), 126.64 (+ve, CH), 127.30 (+ve, CH), 128.27 (+ve, CH), 128.31 (+ve, CH), 128.39 (+ve, CH), 135.40 (ab, C), 141.54 (ab, C). NOE experiments: Irradiation of singlet at δ 5.35 (H-2) shows NOE for signals at δ 2.45 (H-4) and Ph (δ 7.45) but does not show NOE for H-5 (δ 4.50–4.59). Irradiation of signal at δ 2.55 (H-4) shows positive NOE with signal at H-5 (δ 4.55–4.60); FAB mass (M^+) *m/z* 269; Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81%; H, 7.11%. Found: C, 76.18%; H, 7.01%.

Acknowledgments

We thank DST (project no. SR/FTP/CS-20/2001), New Delhi, for financial assistance and CDRI, Lucknow, for FAB Mass and elemental analysis. Anu thanks CSIR for SRF.

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