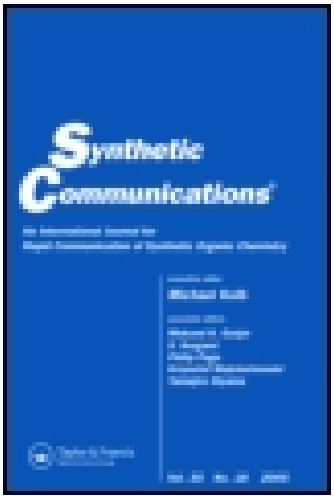

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C-C Bond Formation by Radical Cyclization: Regioselective Synthesis of [6,6] Pyrano pyran System

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C-C Bond Formation by Radical Cyclization: Regioselective Synthesis of [6,6] Pyrano pyran System

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Abstract: A number of 4-aryloxymethyl pyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones **3(a–f)** were prepared by refluxing 4-chloromethyl pyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones **1(a,b)** with *o*-bromophenols **2(a–c)** in acetone in the presence of anhydrous potassium carbonate and sodium iodide in 70–80% yield. Compounds **3(a–f)** were then subjected to radical cyclization by refluxing with tri-*n*-butyltin chloride, sodium cyanoborohydride, and azobisisobutyronitrile (AIBN) in dry benzene for 4–5 h to give a *cis*-diastereomeric mixture of [6,6]pyranopyran derivatives in 80–85% yield.

Keywords: azobisisobutyronitrile, *o*-bromophenol, *6-endo* cyclization, radical cyclization, sodium cyanoborohydride, tri-*n*-butyltin chloride

INTRODUCTION

In recent years, radical cyclization has emerged as a valuable tool for the construction of carbo- and heterocyclic compounds, including natural products.[1] An understanding of the kinetic and the structural information of these reactive intermediates paved the way for development of the modern synthetic radical chemistry.[2] During our work on the synthesis of heterocycles by the application of sigmatropic rearrangements,[3] we recently observed the unusual formation of [6,6]pyranopyrans in case of substrates containing 5-hydroxypyrimidine[4] and 3-hydroxy coumarin[5] in the second Claisen rearrangement step. The generation and subsequent reactions of

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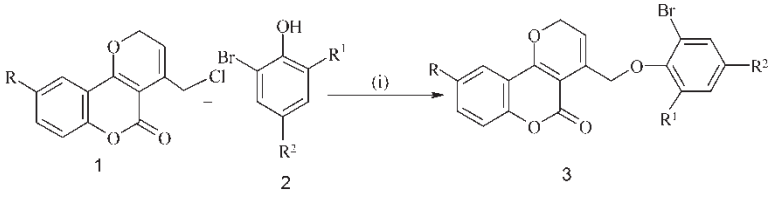
radicals formed from aryl halides using tri-*n*-butyltinhydride and azobisisobutyronitrile (AIBN) is now well established.[6] Aryl radical cyclization normally has a high 5-exo/6-endo ratios, indicating a stronger preference for *exo* cyclization than alkyl radicals. However, this preference was reversed in cyclizations involving stabilized radicals.[7] Coumarin and its derivatives are reported[8] to possess various physiological activities. 3-Alkyl and 4-alkyl coumarins are well known[9] for their hypnotic, insecticidal, and antifungal activities, their anticoagulant effect on blood, and diuretic properties. Various heterocyclic compounds have been synthesized using 4-hydroxy coumarin or its derivatives and analogues as starting materials.

Recently we reported[10] the synthesis of [6,6]pyranothiopyrano by the application of sequential Claisen rearrangement followed by pyridine hydrotribromide–mediated regioselective *6-endo* cyclization. However, [3,3] sigmatropic rearrangement of 4-aryloxymethyl pyrano[3,2-*c*]coumarin derivatives failed to afford any cyclic products.[11] We, therefore, explored the possibility of whether the [6,6]pyranopyran derivatives can be synthesized by tri-*n*-butyl tin hydride and AIBN-induced radical cyclization of appropriate substrates **3(a–f)**. Herein we report the results.

RESULTS AND DISCUSSION

4-Chloromethylpyrano [3,2-*c*][1]benzopyran-5-(2*H*)-ones **1(a,b)** were refluxed with *o*-bromophenols **2(a–c)** in acetone in the presence of anhydrous potassium carbonate and sodium iodide (Finkelstein condition) to afford a number of 4-aryloxymethyl pyrano[3,2-*c*][1] benzopyran-5-(2*H*)-ones **3(a–f)** (Scheme 1), which have been utilized as the starting material

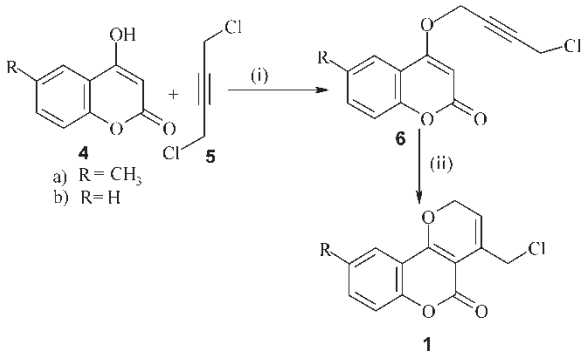


a) R = CH_3
b) R = H

2	R^1	R^2
a	CH_3	CH_3
b	H	CH_3
c	H	H

3	R	R^1	R^2	Yield(%)
a	CH_3	CH_3	CH_3	74
b	H	CH_3	CH_3	72
c	CH_3	H	CH_3	70
d	H	H	CH_3	75
e	CH_3	H	H	70
f	H	H	H	70

Scheme 1. Reagents and Conditions: i) $Me_2C{=}O/K_2CO_3$; NaI, 4-5 h.



Scheme 2. Reagents and Conditions: i) Me_2 C=O/K_2CO_3, Reflux, 20 h ii) Chlorobenzene, Reflux, 16 h.

of this study (Scheme 1). Compounds **1(a,b)** in turn were prepared by the following literature procedure,[12] that is, by alkylation of 4-hydroxycoumarin, followed by Claisen rearrangement (Scheme 2).

Compounds **3(a–f)** were characterized from their elemental analyses and spectral data. IR spectrum of the compound **3a** showed carbonyl absorption at 1700 cm^{-1}. The high field ^1H NMR (300-MHz) spectrum of the compound **3a** exhibited a two-proton doublet at δ 4.96 for -OCH_2, two-proton doublet at δ 5.13 for another -OCH_2, and one proton triplet at δ 6.14 for the vinylic proton among other signals for aromatic protons.

The substrate **3a** was then refluxed in benzene under a nitrogen atmosphere with tri-*n*-butyl tin chloride and sodium cyanoborohydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 4 h to give cyclic product **7a**. Thin-layer chromatography (TLC) indicated a single product. However, ^1H NMR revealed that it was actually a mixture of two compounds. In the aromatic region, the protons displayed chemical shifts at nearly similar positions whereas in the aliphatic region they showed different chemical shifts. The positions, splitting patterns, and coupling constants of the protons at the ring junctures implies that they are diastereomeric in nature, both with *cis* ring juncture,[13] as their coupling constant is less than 8 Hz. We tried our best to separate these two products, but all our efforts miserably failed. A few years ago, we reported the pyranopyran system obtained by thermal Claisen rearrangement with *cis*-fusion. However, there we obtained only one *cis* diastereomer.[14] We tried to obtain only one diastereomer by changing the reaction condition. At first, the reaction was carried out by refluxing a suspension of the compounds **3(a–f)** (0.46 mmol). Bu_3SnH (0.52 mmol) and AIBN (0.28 mmol) in dry benzene (12 ml) were refluxed for 4–5 h under a nitrogen atmosphere. In all the cases, diastereomeric mixtures were obtained except in case of **7a**. Next the compounds **3(a–f)** (0.46 mmol), $^nBu_3SnCl$ (1.8 mmol), $Na(CN)BH_3$ (3.7 mmol), and AIBN (0.12 mmol) were refluxed in dry benzene for 4–5 h under a nitrogen atmosphere. Here too, a mixture of diastereomers was

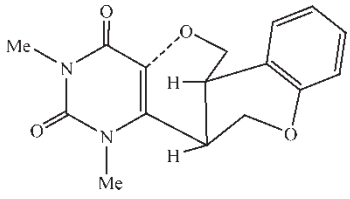


Figure 1. *cis*-[6,6]fused compounds.

obtained except in the case of **7a**. We therefore failed to produce a single diastereo isomer. However, in one case (**7a**), nearly pure (95:5) one diastereomer was obtained.

Compound **7a** was characterized from its elemental analysis and spectroscopic data. The IR spectrum of the compound **7a** (for the mixture) showed carbonyl absorption at 1703 cm^{-1}. ^1H NMR of the compound **7a** showed the following major signals: δ 2.18 (s, 3H, C**H**$_3$), 2.26 (s, 3H, C**H**$_3$), 2.42 (s, 3H, C**H**$_3$) 3.22–3.26 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11.5$ Hz), 3.38–3.42 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.71–3.78 (dd$\sim$t, 1H, $J = 11$ Hz), 4.12–4.20 (dd$\sim$t, 1H, $J = 11.5$ Hz), 4.61–4.66 (dd, 1H, $J = 3.9$ Hz, $J = 11.2$ Hz), 4.72–4.80 (dd, 1H, $J = 3.8$ Hz, $J = 10.5$ Hz), 6.7–7.36 (m, 4H, Ar**H**), 7.58 (s, 1H, Ar**H**). The ^1H NMR data for the other diastereomers that are formed in other cases are presented in the experimental section.

The *cis*-stereochemistry of the major diastereoisomer may be derived from the comparison of ^1H NMR data with the ^1H NMR data analysis result of our earlier published[14] *cis*-product (Fig. 1).

The minor diastereoisomer may also possess *cis*-stereochemistry as indicated by low coupling constants of the ring juncture protons. The two diastereoisomers may be represented by Fig. 2 and Fig. 3.

The generality of the reaction was tested by subjecting five other substrates **3(b–f)** under the same reaction conditions to give products **7(b–f)** (Scheme 3). The formation of products **7a–f** from **3a–f** may be easily explained by the generation of an aryl radical **8** in the tri-*n*-butyltinchloride, sodium cyanoborohydride, and azobisisobutyronitrile mediated reaction.

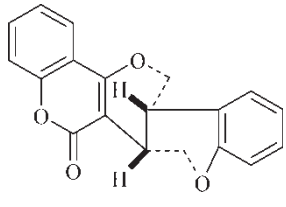


Figure 2. Another *cis*-diastereomer of compound **7**.

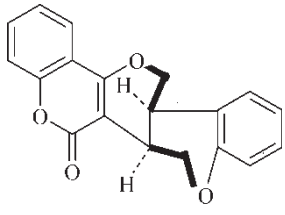
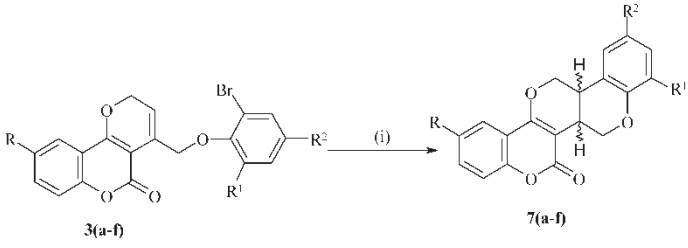


Figure 3.

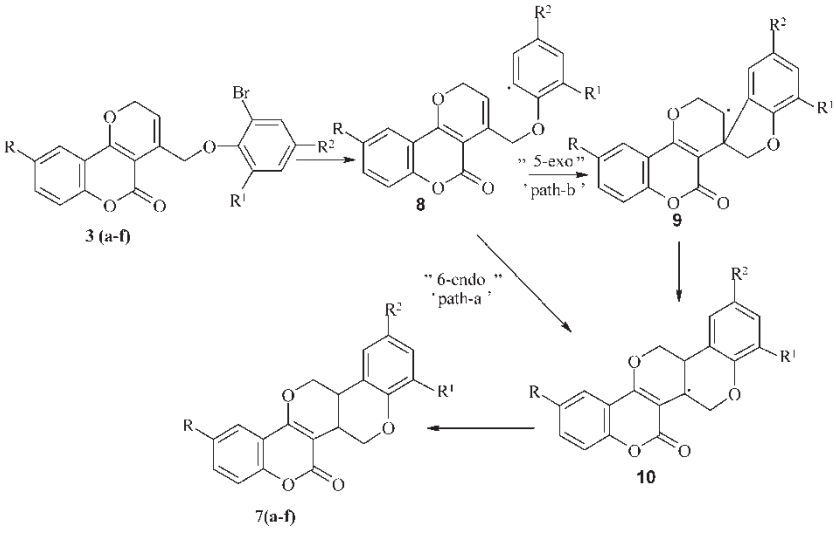
The aryl radical **8** may undergo cyclization by two different modes, a 6-*endo trig* cyclization[15] to afford the heterocyclic radical **10** (pathway a) or a 5-*exo trig* cyclization[16] to give the spiroheterocyclic radical **9** (not isolated, pathway b). The possibility of the formation of heterocyclic radical **10** via spirocylic radical **9** by a neophyl rearrangement[17] cannot be ruled out (Scheme 4).

It is known that radical cyclizations leading to six-membered rings are usually less general than cyclization leading to five-membered rings. Six-membered ring-forming reactions are also slower than five-membered ring-formation reactions and are subject to competitive formation of reduced uncyclized by-products. However, appropriately substituted 5-hexenyl radicals are known to undergo 6-*endo* cyclization to give six-membered rings. It is interesting to note that a regioselectively six-membered heterocyclic ring is formed in all the cases studied at present.



7	R	R^1	R^2	Yield(%)	Ratio of the diastereomeric mixture (A:B)
a	CH_3	CH_3	CH_3	82	95:5
b	H	CH_3	CH_3	79	47:53
c	CH_3	H	CH_3	76	50:50
d	H	H	CH_3	80	50:50
e	CH_3	H	H	70	45:55
f	H	H	H	75	50:50

Scheme 3. Reagents and conditions: i) Bu_3SnCl, $Na(CN)BH_3$; AIBN, C_6H_6, reflux, N_2 atmosphere, 4–5 h.



Scheme 4.

In conclusion, the reaction is mild, regioselective, but not stereoselective. This is an attractive and simple methodology for the synthesis of a [6, 6]pyranopyran ring system.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm) and IR spectra in KBr discs on a Perkin Elmer L 120 000A apparatus (ν_{max} in cm^{-1}). ^1H NMR spectra were run in $CDCl_3$ with TMS as an internal standard on a Bruker DPX 300-MHz instrument at the Indian Institute of Chemical Biology, Kolkata (chemical shifts in ppm). Silica gel (60–120 mesh) was obtained from Spectrochem, India. Extracts were dried over anhydrous sodium sulfate. Petroleum ether refers to the fraction boiling between 60°C and 80°C.

General Procedure for the Preparation of Compounds 3(a–f)

Compounds **(1a,b)** (1 mmol) in acetone (100 ml) were refluxed with several *o*-bromophenols **2(a–c)** (1 mmol) in the presence of anhydrous potassium carbonate (1 g) and a catalytic amount of Nal for 3–4 h. The reaction mixture was then cooled and filtered, and the solvent was removed. The residual mass was subjected to column chromatography over silica gel

using petroleum ether–ethyl acetate (19:1) as eluant to give compounds **3(a–f)**, which were then recrystallized from chloroform.

Data

Compound 3a: Yield: 74%; white solid; mp 159°C; IR (KBr): $\nu_{max} = 1725$, 1571, 1467, 1276 cm^{-1}; UV (EtOH): $\lambda_{max} = 206$, 280, 351 nm; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.25$ (s, 3H, C**H**$_3$), 2.28 (s, 3H, C**H**$_3$), 2.41 (s, 3H, C**H**$_3$), 4.96 (d, 2H, $J = 2.1$ Hz, OC**H**$_2$), 5.13 (d, 2H, $J = 1.9$ Hz, OC**H**$_2$), 6.14 (t, 1H, $J = 1.9$ Hz, =C**H**), 6.91–6.94 (1H, dt, $J = 1.2$ Hz, $J = 7.6$, Ar**H**), 7.16–7.35 (m, 4H, Ar**H**); MS: $m/z = 426$, 428 (M^+, M^{+2}). Anal. calcd. for $C_{22}H_{19}O_4Br$: C, 61.83; H, 4.45%. Found C, 61.58; H, 4.21%.

Compound 3b: Yield: 72%; white solid; mp 90°C; IR (KBr): $\nu_{max} = 1699$, 1608, 1454, 1271 cm^{-1}; UV (EtOH): $\lambda_{max} = 208$, 283, 344 nm; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.36$ (s, 3H, C**H**$_3$), 2.41 (s, 3H, C**H**$_3$), 4.94 (d, 2H, $J = 2.1$ Hz, OC**H**$_2$), 5.16 (d, 2H, $J = 1.8$ Hz, OC**H**$_2$), 6.12 (t, 1H, $J = 1.9$ Hz, =C**H**), 7.26–7.57 (m, 5H, Ar**H**), 7.79–7.81 (d, 1H, $J = 6$ Hz, Ar**H**); MS: $m/z = 413$, 415 (M^+, M^{+2}). Anal. calcd. for $C_{21}H_{17}O_4Br$: C, 60.87; H, 4.12%. Found C, 60.76; H, 4.16%.

Compound 3c: Yield: 70%; white solid; mp 115°C; IR (KBr): $\nu_{max} = 1699$, 1601, 1567, 1496 cm^{-1}; UV (EtOH): $\lambda_{max} = 217$, 289, 344 nm; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.27$ (s, 3H, C**H**$_3$), 2.41 (s, 3H, C**H**$_3$), 5.10 (d, 2H, $J = 2.1$ Hz, OC**H**$_2$), 5.15 (d, 2H, $J = 1.8$ Hz, OC**H**$_2$), 6.07 (t, 1H, $J = 1.9$ Hz, =C**H**), 6.91–6.94 (dt, 1H, $J = 1.2$ Hz, $J = 7.5$ Hz, Ar**H**), 7.04–7.07 (1H, dd, $J = 1.2$ Hz, $J = 8.1$ Hz, Ar**H**), 7.18–7.36 (m, 3H, Ar**H**), 7.58 (dd, 1H, $J = 1.3$ Hz, $J = 7.8$ Hz, Ar**H**); MS: $m/z = 413$, 415 (M^+, M^{+2}). Anal. calcd. for $C_{21}H_{17}O_4Br$: C, 60.87; H, 4.12%; Found C, 60.57; H, 4.09%.

Compound 3d: Yield: 75%; white solid; mp 120°C; IR (KBr): $\nu_{max} = 1698$, 1601, 1495, 1255 cm^{-1}; UV (EtOH): $\lambda_{max} = 206$, 283, 310, 323 nm; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.28$ (s, 3H, C**H**$_3$), 5.13 (d, 2H, $J = 2.03$ Hz, OC**H**$_2$), 5.16 (d, 2H, $J = 1.8$ Hz, OC**H**$_2$) 6.08 (t, 1H, $J = 1.9$ Hz, =C**H**), 6.84–6.91 (dt, 1H, $J = 1.2$ Hz, $J = 7.6$ Hz, Ar**H**), 7.03–7.11 (dd, 1H, $J = 1.1$ Hz, $J = 8.2$ Hz, Ar**H**), 7.26–7.58 (m, 4H, Ar**H**) 7.78–7.81 (d, 1H, $J = 7.8$ Hz, Ar**H**); MS: $m/z = 398$, 400 (M^+, M^{+2}). Anal. calcd. for $C_{20}H_{15}O_4Br$: C, 60.15; H, 3.76%. Found C, 60.06; H, 3.54%.

Compound 3e: Yield: 70%; white solid; mp 181°C; IR (KBr): $\nu_{max} = 1709$, 1619, 1565, 1497, 1448, 1202 cm^{-1}; UV (EtOH): $\lambda_{max} = 211$, 283, 340 nm; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.41$ (s, 3H, C**H**$_3$), 5.11 (d, 2H, $J = 2.1$ Hz, OC**H**$_2$), 5.19 (d, 2H, $J = 1.8$ Hz, OC**H**$_2$), 6.10 (t, 1H,

$J = 1.9$ Hz, =C**H**), 6.86–6.90 (dt, 1H, $J = 1.2$ Hz, $J = 7.5$ Hz, Ar**H**), 7.17–7.21 (dd, 1H, $J = 1.1$ Hz, $J = 8.1$ Hz, Ar**H**) 7.33–7.35 (m, 2H, Ar**H**), 7.50–7.54 (dd, 1H, $J = 1.2$ Hz, $J = 7.9$ Hz, Ar**H**), 7.58 (d, 1H, $J = 6$ Hz, Ar**H**); MS: $m/z = 398$, 400 (M^+, M^{+2}). Anal. calcd. for $C_{20}H_{15}O_4Br$: C, 60.15; H, 3.76%. Found C, 60.35; H, 3.54%.

Compound 3f: Yield: 70%; white solid; mp 160°C; IR (KBr): $\nu_{max} = 1702$, 1611, 1480, 1031 cm^{-1}; UV (EtOH): $\lambda_{max} = 205$, 273, 281 nm; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 5.13$ (d, 2H, $J = 2.1$ Hz, OC**H**$_2$), 5.19 (d, 2H, $J = 1.8$ Hz, OC**H**$_2$), 6.10 (t, 1H, $J = 1.9$ Hz, =C**H**), 6.82–6.88 (dt, 1H, $J = 1.2$ Hz, $J = 7.6$ Hz, Ar**H**), 7.03–7.06 (dd, 1H, $J = 1.1$ Hz, $J = 8.2$ Hz, Ar**H**), 7.26–7.32 (m, 3H, Ar**H**) 7.52–7.58 (m, 2H, Ar**H**), 7.78–7.81 (dd, 1H, $J = 1.2$ Hz, $J = 7.9$ Hz, Ar**H**); MS: $m/z = 384$, 386 (M^+, M^{+2}). Anal. calcd for $C_{19}H_{13}O_4Br$: C, 59.22; H, 3.38%. Found C, 59.40; H, 3.26%.

General Procedure for the Preparation of Compounds 7(a–f) by Radical Cyclization

A suspension of the compound **3a–f** (0.46 mmol), $^nBu_3SnCl$ (1.8 mmol), $Na(CN)BH_3$ (3.7 mmol), and AIBN (0.12 mmol) in 10 ml of dry benzene was refluxed for 4–5 h under a nitrogen atmosphere. The solvent was evaporated under reduced pressure, and the residue was taken in water (10 ml) and was extracted with $CHCl_3$ (3 × 10 ml). The combined organic extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished a residue, which was magnetically stirred with a saturated solution of potassium fluoride (5 ml) for 24 h. It was then extracted with $CHCl_3$ (3 × 10 ml) and was washed with water for several times, and dried (Na_2SO_4). The residual mass after removal of the solvent ($CHCl_3$) was subjected to column chromatography over silica gel using petroleum ether–ethylacetate (97:3) as eluant to give cyclized products **7(a–f)**, which were then recrystallized from chloroform-petroleum ether.

Data

Compound 7a: Yield: 82%; diastereomeric ratio (A : B) 95:5; white solid; mp 272–275°C; IR (KBr): $\nu_{max} = 1703$, 1630, 1584, 1486 cm^{-1}; UV (EtOH): $\lambda_{max} = 207$, 273, 284 nm; ^1H NMR ($CDCl_3$, 300 MHz) of the diastereomer (A): $\delta_H = 2.18$ (s, 3H, C**H**$_3$), 2.26 (s, 3H, C**H**$_3$), 2.42 (s, 3H, C**H**$_3$), 3.22–3.26 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11.5$ Hz), 3.38–3.42 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.71–3.78 (dd∼t, 1H, $J = 11$ Hz), 4.12–4.20 (dd∼t, 1H, $J = 11.5$ Hz), 4.61–4.66 (dd, 1H, $J = 3.9$ Hz, $J = 11.2$ Hz), 4.72–4.80 (dd, 1H, $J = 3.8$ Hz, $J = 10.5$ Hz), 6.7–7.36 (m, 4H, Ar**H**), 7.58 (s, 1H, Ar**H**).

Compound 7b: Yield: 79%; diastereomeric ratio (A : B) 47:53; white solid; mp 106–110°C; IR (KBr): $\nu_{max} = 1704$, 1613, 1572, 1403 cm^{-1}; UV (EtOH): $\lambda_{max} = 208$, 271, 281, 294 nm.^{1}H NMR ($CDCl_3$, 300 MHz) of the diastereomer (A): $\delta_H = 2.26$ (s, 3H, C**H**$_3$), 2.30 (s, 3H, C**H**$_3$) 3.23–3.25 (m, ring juncture proton, 1H, overlap with other peaks), 3.40–3.46 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.72–3.79 (dd∼t, 1H, $J = 11$ Hz), 4.13–4.20 (dd∼t, 1H, $J = 11$ Hz), 4.63–4.67 (dd, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 4.71–4.77 (dd, 1H, $J = 3.8$ Hz, $J = 10.6$ Hz), 6.70–7.81 (m, 6H, Ar**H**).

^{1}H NMR of other diastereomer (B): $\delta_H = 2.26$ (s, 3H, C**H**$_3$), 2.30 (s, 3H, C**H**$_3$), 3.00–3.09 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.23–3.25 (m, ring juncture proton, 1H, overlap with other peaks), 3.94–3.96 (dd∼t, 1H, $J = 10.8$ Hz), 4.17–4.21 (dd∼t, 1H, $J = 11$ Hz), 5.13–5.18 (dd, 1H, $J = 3.8$ Hz, $J = 10.6$ Hz), 5.19–5.37 (dd, 1H, $J = 3.8$ Hz, $J = 10.5$ Hz), 6.70–7.81 (m, 6H, Ar**H**).

Compound 7c: Yield: 76%; diastereomeric ratio (A : B) 50:50; white solid; mp 245–250°C; IR (KBr): $\nu_{max} = 1709$, 1631, 1584, 1500 cm^{-1}; UV (EtOH): $\lambda_{max} = 207$, 274, 285 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) of the diastereomer (A): $\delta_H = 2.30$ (s, 3H, C**H**$_3$), 2.42 (s, 3H, C**H**$_3$), 3.20–3.27 (m, ring juncture proton, 1H, overlap with other peaks), 3.41–3.46 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.72–3.80 (dd ∼ t, 1H, $J = 10.8$ Hz), 4.13–4.20 (dd∼t, 1H, $J = 11$ Hz), 4.61–4.67 (dd, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 4.70–4.75 (dd, 1H, $J = 3.8$ Hz, $J = 10.6$ Hz), 6.8–7.6 (m, 6H, Ar**H**).

δ_H ^{1}H NMR of other diastereomer (B): = 2.30 (s, 3H, C**H**$_3$), 2.42 (s, 3H, C**H**$_3$) 2.98–3.07 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.20–3.27 (m, ring juncture proton, 1H, overlap with other peaks), 3.89–3.97 (dd∼t, 1H, $J = 10.8$ Hz), 4.16–4.24 (dd∼t, 1H, $J = 11$ Hz), 5.18–5.23 (dd, 1H, $J = 3.8$ Hz, $J = 10.6$ Hz), 5.67–5.72 (dd, 1H, $J = 3.8$ Hz, $J = 10.5$ Hz), 6.8–7.6 (m, 6H, Ar**H**).

Compound 7d: Yield: 80%; diastereomeric ratio (A : B) 50:50; white solid; mp 167–170°C; IR (KBr): $\nu_{max} = 1703$, 1615, 1501, 1404 cm^{-1}; UV (EtOH): $\lambda_{max} = 205$, 272, 282 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) of the diastereomer (A): $\delta_H = 2.30$ (s, 3H, C**H**$_3$), 3.20–3.30 (m, ring juncture proton, 1H, overlap with other peaks), 3.41–3.47 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.73–3.80 (dd∼t, 1H, $J = 11$ Hz), 4.14–4.21 (dt∼t, 1H, $J = 11$ Hz), 4.63–4.69 (dd, 1H, $J = 1.2$ Hz, $J = 11$ Hz), 4.71–4.76 (dd, 1H, $J = 1$ Hz, $J = 11$ Hz), 6.8–7.84 (m, 7H, Ar**H**).

^{1}H NMR of other diastereomer (B): $\delta_H = 2.30$ (s, 3H, C**H**$_3$), 3.00–3.08 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.20–3.30 (m, ring juncture proton, 1H, overlap with other peaks), 3.90–3.97 (dd∼t, 1H, $J = 10.8$ Hz), 4.18–4.26 (dd∼t, 1H, $J = 11$ Hz), 5.20–5.25 (dd, 1H,

$J = 3.8$ Hz, $J = 10.6$ Hz), 5.67–5.72 (dd, 1H, $J = 3.8$ Hz, $J = 10.5$ Hz), 6.8–7.84 (m, 7H, Ar**H**).

Compound 7e: Yield: 70%; diastereomeric ratio (A : B) 45 : 55; white solid; mp 225–228°C; IR (KBr): $\nu_{max} = 1703, 1632, 1581, 1463, 1443\ cm^{-1}$; UV (EtOH): $\lambda_{max} = 205, 274, 282, 306$ nm; ^{1}H NMR ($CDCl_3$, 300 MHz) of the diastereomer (A): $\delta_H = 2.42$ (s, 3H, C**H**$_3$), 3.22–3.36 (m, ring juncture proton, 1H, overlap with other peaks), 3.43–3.50 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.82–3.89 (dd∼t, 1H, $J = 11$ Hz), 4.13–4.21 (dd∼t, 1H, $J = 11$ Hz), 4.61–4.67 (dd, 1H, $J = 1.3$ Hz, $J = 3.3$ Hz), 4.89–4.94 (dd, 1H, $J = 3.24$ Hz, $J = 6$ Hz), 6.76–7.60 (m, 7H, Ar**H**).

^{1}H NMR of other diastereomer (B): $\delta_H = 2.42$ (s, 3H, C**H**$_3$), 3.00–3.09 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.22–3.36 (m, ring juncture proton, 1H, overlap with other peaks), 4.01–4.09 (dd∼t, 1H, $J = 10.8$ Hz), 4.16–4.24 (dd∼t, 1H, $J = 11$ Hz), 5.18–5.23 (dd, 1H, $J = 3.8$ Hz, $J = 10.6$ Hz), 5.85–5.90 (dd, 1H, $J = 3.8$ Hz, $J = 10.5$ Hz), 6.76–7.60 (m, 7H, Ar**H**).

Compound 7f: Yield: 75%; diastereomeric ratio (A:B) 50:50; white solid; mp 158–161°C; IR (KBr): $\nu_{max} = 1710, 1626, 1492, 1405\ cm^{-1}$; UV (EtOH): $\lambda_{max} = 205, 273, 282, 306, 319$ nm; ^{1}H NMR ($CDCl_3$, 300 MHz) of the diastereomer (A): $\delta_H = 3.24–3.35$ (m, ring juncture proton, 1H, overlap with other peaks), 3.43–3.48 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.76–3.84 (dd∼t, 1H, $J = 10.8$ Hz), 4.15–4.23 (dd∼t, 1H, $J = 11$ Hz), 4.64–4.69 (dd, 1H, $J = 3.67$ Hz, $J = 11$ Hz), 5.70–5.75 (dd, 1H, $J = 3.4$ Hz, $J = 10.8$ Hz), 6.9–7.8 (m, 8H, Ar**H**).

^{1}H NMR of other diastereomer (B) δ_H: = 3.01–3.10 (dt, ring juncture proton, 1H, $J = 3.8$ Hz, $J = 11$ Hz), 3.24–3.35 (m, ring juncture proton, 1H, overlap with other peaks), 3.94–4.01 (dd∼t, 1H, $J = 10.8$ Hz), 4.19–4.27 (dd∼t, 1H, $J = 11$ Hz), 5.22–5.27 (dd, 1H, $J = 3.7$ Hz, $J = 10.6$ Hz), 5.70–5.75 (dd, 1H, $J = 3.8$ Hz, $J = 10.5$ Hz), 6.9–7.8 (m, 8H, Ar**H**).

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