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Diastereoselective Synthesis of the Model Insect Antifeedants Related to Azadiradione and Epoxyazadiradione Based on Intramolecular Insertion of α-Aryl-α-Diazoketones

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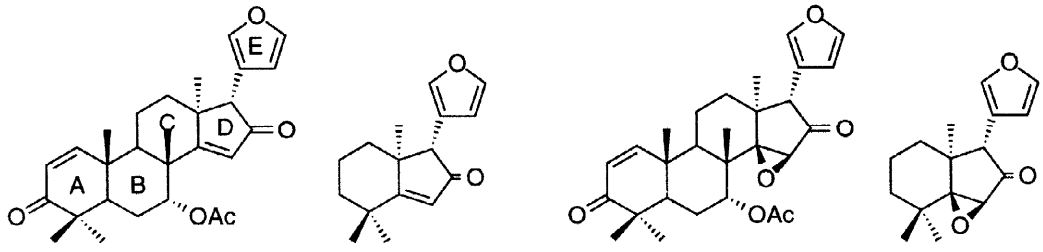
Abstract: A new practical and stereoselective method for the synthesis of the model insect antifeedant CDE fragment of azadiradione and epoxyazadiradione, based on intramolecular insertion of α-aryl-α-diazoketones, has been developed. The procedure can be applied to complex systems. A short SAR study is reported

In the course of our search for the synthesis of limonoid model insect antifeedants we have found that after treatment with Rh(II) some α-aryl-α-diazo ketones afford insertion products in good yields.[1] Cyclization of such aryldiazo ketones should be a useful method for the construction of aryl indanones related to the CDE fragment of azadiradione and epoxyazadiradione. Among this kind of compound the keto epoxide **II**, deserves special mention, which has shown high antiviral activity against HIV-replication "*in vitro*" and also strong antifeedant activity against *Spodoptera littoralis*.[2] This promising biological activity has stimulated interest in defining stucture-activity relationships (SAR) and makes the insertion reaction an easy and practical synthetic method. With the aim of developing safe, selective and less persistent pest control agents, we have designed simple structural mimics of azadiradione and epoxyazadiradione to investigate the resulting effects on biological activity .



Azadiradione I Epoxyazadiradione II

Here we wish to report a convenient synthesis and the biological aspects related to compounds **9a-c**, **16** and **19a-d**. The simplest compounds, **9a-c**, were prepared according to the route shown in scheme 1. The starting unsaturated ester **1** was readily available from cyclohexanone by a Wadsworth-Emmons reaction.[3] Alkaline hydrolysis produced the corresponding acid **2**. Treatment of the sodium salts of acid with oxalyl

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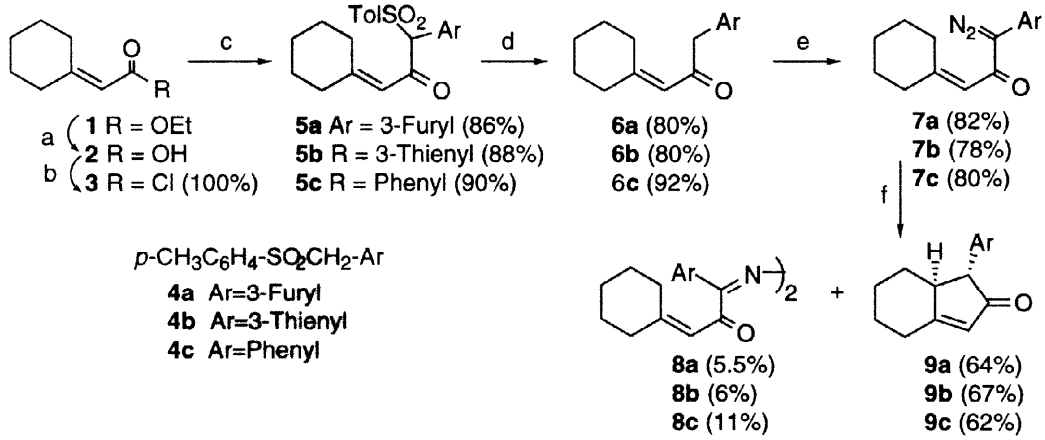
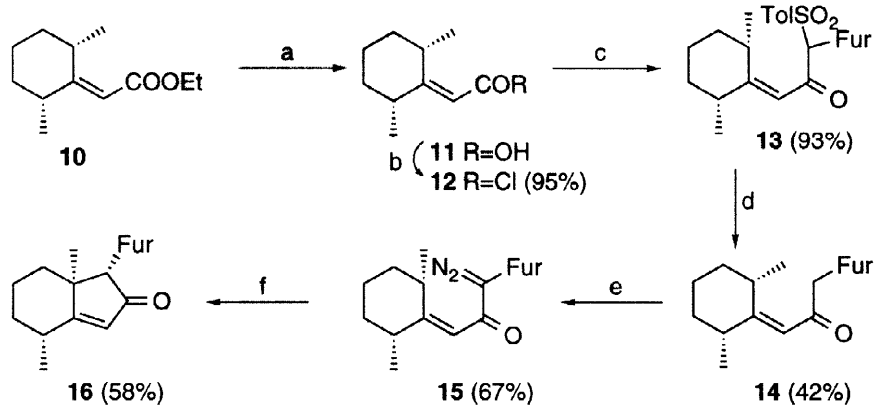
chloride gave acid chloride **3**. Condensation of the acid chloride **3** with sulfonyl dianions of **4** separately afforded the corresponding keto sulfones **5**. The sulfones **4** were obtained from the corresponding bromides by nucleophilic displacement with sodium *p*-toluenesulfinate[4] in DME at 80 °C. The dianions were generated by treatment of sulfones **4** with 2.2 equivalents of butyllithium.[5] Reductive desulfurization[6] of keto sulfones **5** was carried out with zinc and ammonum chloride in THF to give the unsaturated ketones **6**. Diazo transfer[7] to the ketones was accomplished with N-acetylsulfanilyl azide and DBU in acetonitrile to afford diazo ketones **7**.[8]



Scheme 1

Decomposition of diazo ketones **7** with dirhodium tetraacetate[9] led to diastereomerically pure indenones **9** in 62-67 % yield. The stereochemical assignment of the indenones rests tentatively on interpretation of their ^{1}H NMR spectra. The diedral angle H_1-C-C-H_{7a} when H_{7a} and Ar keep a *cis* relationship is approximately 130°, and the coupling constant J H_1-H_{7a} should be around 3 Hz. If H_{7a} and Ar are *trans*, the diehdral angle H_1-C-C-H_{7a} is 20° and J H_1-H_{7a} should be larger, around 7 Hz. All three indenones **9** obtained from the insertion process have a coupling constant of J H_1-H_{7a} = 3 Hz, which indicates a *cis* relationship between the angular H_{7a} and the aryl group. This stereochemistry is supported by the mechanism proposed by Doyle[10] to explain diastereoselctivity in the C-H insertion reactions of α-aryl-α-diazo ketones.

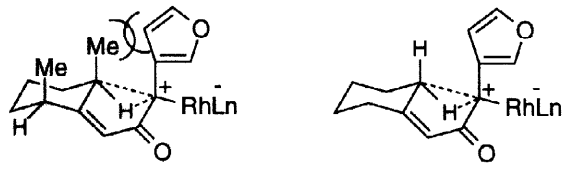
In keeping with the above sequence, we obtained the dimethyl derivative **16**, as described in the scheme 2. The starting unsaturated ester **10** was obtained following the method described by Curini et al.[9] The overall yield from **10** to **16** was 13 %. The diastereoselectivity found in the insertion reaction **15** →**16** is remarkable. In the only indenone obtained, the angular methyl group and the furan keep a *cis* relationship. This assignment is based on the well known diamagnetic shielding effect induced by the furan on the methyl group.[11]



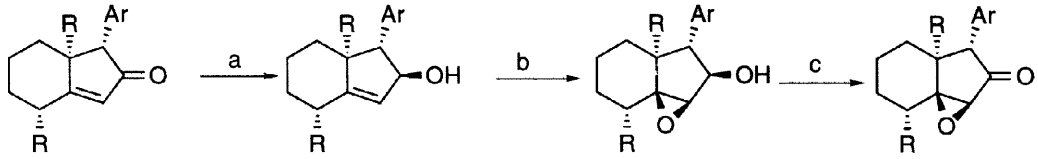
a) KOH, EtOH/H_2O; b) $(COCl)_2$, benzene, 0°C; c) **4a**, BuLi, THF, -78°C;d) Zn, THF-NH_4Cl, r.t.; (e) N-acetylsulfanilyl azide, DBU, CH_3CN, 0°C; f) $Rh_2(OAc)_4$, CH_2Cl_2, r.t.

Scheme 2

The facility of the insertion reaction process in the dimethyl derivative **15** extends the scope of the reaction for α-aryl-α-diazoketones α',β'-unsaturated with a tertiary γ'-carbon. Until now this reaction has only been achieved with secondary γ'-carbon. The issue is important because in the intermediate **A** the general mechanism proposed by Doyle,[10] is followed, a strong non-bonding interaction between a methyl group and the furan is observed. This interaction is not found in the intermediate **B** corresponding to insertion **7** → **9**. The ease of insertion in **A** reinforces the argument that insertion must be due to the C-H allylic activation, which prevails over steric impediments.



Transformation of indenones **9** and **16** into the corresponding keto epoxides **19** was accomplished in a three step sequence (scheme 3). Direct epoxidation with hydrogen peroxide was unsuccesful: in all cases, the oxidant promotes degradation of the compound.



9a-c R = H	**17a** R=H, Ar=3-Furyl (88%)	**18a** (94%)	**19a** (80%)
16 R = Me	**17b** R=H, Ar=3-Thienyl (91%)	**18b** (92%)	**19b** (78%)
	17c R=H, Ar=Phenyl (89%)	**18c** (96%)	**19c** (92%)
	17d R=Me, Ar=3-Furyl (91%)	**18d** (94%)	**19d** (40%)

a)$LiAlH_4$, diethyl ether, 0°C; b) *m*-CPBA, CH_2Cl_2, 0°C; c) PCC, CH_2Cl_2, r.t.

Scheme 3

Reduction of the unsaturated ketones **9** and **16** with LAH was completely diastereoselective. The major alcohol always come from the exo hydride attack. The epoxidation of **17** with *m*-CPBA is *syn*, directed by the hydroxyl group. Oxidation with PCC of each epoxy alcohol **18** separately afforded the corresponding keto epoxides **19** in yields ranging 80 %.

The stereochemical assignment of the epoxy alcohols **18** and epoxy ketones **19** are based on the γ-effect observed in the ^{13}C NMR of the benzyl carbon of keto epoxides as compared to that found for the unsaturated compounds.[2,12]

Biological Results

Larvae of the African leafworm *Spodoptera frugiperda* were used to assess the antifeedant activity of our molecular fragments.[13] In the series related to azadiradione, racemic demethyl derivatives **9a** and **9c** were found to be more active than the racemic trimethyl analog **I**, while the thienyl derivative **9b** was less active. In the ketoepoxide series the racemic dimethyl compound **19d** had almost the same activity as racemic trimethyl analog **II**, and one of the demethyl derivatives, **19b**, was sligthly more active than racemic **II**, while the other one, **19c**, was a phagostimulant.

Table I. Effects of synthesized compounds **9a-c** and **19b-c**, and **I** (±), **II** (±), **II** (+), **II** (-), azadiradione and epoxyazadiradione on the feeding behaviour of larvae of *Spodoptera frugiperda* and *Spodoptera littoralis*.

	Antifeedant index at 100 ppm[a#]		
Compound	*Spodoptera littoralis*	Compound	*Spodoptera frugiperda*
Azadiradione	1	**9a** (±)	42*
Epoxyazadiradione	22	**9b** (±)	1
I (±)	16	**9c** (±)	40*
II (±)	28	**19b** (±)	36
II (+)	55*	**19c** (±)	-12
II (-)	32	**19d** (±)	29

[a]Antifeedant index = [(C-T)/(C +T)]%,
* = significant activity $p < 0.05$ (Wilcoxon matched pairs test, n = 10).
# Structures of I and II are on page 1.

Experimental

General Methods. Commercial reagents were used as received. Dichloromethane was distilled under nitrogen over calcium hydride. Benzene, diethyl ether, and tetrahydrofuran were distilled from sodium. Ethanol and acetonitrile were distilled before use. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50 MHz respectively. IR spectra were obtained as thin films. All reactions were carried out under an atmosphere of argon in glassware dried overnight and cooled under argon. Reactions were monitored by TLC. Flash column chromatographies were carried out using silica gel 60 (0.040-0.063 mm Merck). Organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure with the aid of a rotary evaporator.

Cyclohexylidenyl acid chloride 3. A solution of unsaturated ester **1**[3] (3.06 g, 18.23 mmol) and potassium hydroxide (1.02 g, 18.23 mmol) in ethanol-water (1:1, 55 mL) was heated under reflux for 5 h. The reaction mixture was evaporated under reduced pressure. A suspension of the dry salt in benzene (15 mL) was teated with oxalyl chloride (7.35 mL, 84.5 mmol) at 0 °C for 1 h. The reaction mixture was filtered

and the solvent and excess of oxalyl chloride were evaporated under reduced presure. Acid chloride **3**[11] was obtained (2.88 g) in quantitative yield: IR 2938, 1788, 1759, 1611 cm^{-1}.

Dimethyl-cyclohexylidenyl acid chloride 12. A solution of potassium hydroxide (0.86 g, 15.3 mmol) in ethanol-water (1:1, 50 mL) was added into unsaturated ester **10** (3.0 g, 15.3 mmol) and was heated under reflux, with magnetical stirring for 6 h. The reaction mixture was evaporated and the residue was disolved in bencene and cooled until 0 °C. Oxalyl chloride (4.25 mL, 49 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was filtered and the solvent and excess of oxalyl chloride are evaporated under reduced pressure. Acid chloride **12**[11] (2.71 g, 95 %) was obtained as a colourless oil: IR 2950, 1800, 1620 cm^{-1}.

General procedure. Reaction of acid chlorides with sulfones 4.- Butyllithium (2.2 mmol, 1.6 M in hexane) was added slowly with efficient stirring, to a solution of 3-aryl-*p*-toluenesulfonyl methane **4** (1 mmol) in THF (5 mL) at -30 °C. After 1 h acid chloride (1 mmol) in THF (1 mL) was slowly added by syringe and stirred for 45 min. Then, the reaction mixture was poured into a saturated NH_4Cl solution, stirred and gradually warmed to room temperature. Extraction with diethyl ether followed by washing, drying and evaporation of the solvent afforded an oil that was purified by chromatography (6/4, hexane/diethyl ether).

1-Cyclohexylidenyl-3-(3-furyl)-3-(toluene-4-sulfonyl)-propan-2-one 5a.- The acid chloride **3** (0.62 g, 3.91 mmol) was treated as the general procedure with 3-furyl-*p*-toluenesulfonyl methane **4a** to obtain the keto sulfone **5a** (1.21 g, 86%) as a very viscous, brown oil: IR 3012, 1670, 1619, 1440 cm^{-1}; ^1H NMR δ 1.59 (m, 6H), 2.20 (t, 2H, J=6 Hz), 2.40 (s, 3H), 2.70 (t, 2H, J=6 Hz), 5.15 (s, 1H), 6.25 (s, 1H), 6.45 (d, 1H, J=2 Hz), 7.21 (s, 1H), 7.43 (m, 5H) ppm; Anal. Calcd. for $C_{20}H_{22}O_4S$: C, 67.01; H, 6.19. Found: C, 67.07; H, 6.15.

1-Cyclohexylidenyl-3-(3-thienyl)-3-(toluene-4-sulfonyl)-propan-2-one 5b.- The acid chloride **3** (0.69 g, 4.35 mmol) was treated as the general procedure with of 3-thienyl-*p*-toluenesulfonyl methane **4b** to afford the keto sulfone **5b** (1.43 g, 88%) as a very viscous, brown oil: IR 3010, 1675, 1612, 1330 cm^{-1}; ^1H NMR δ 1.60 (m, 6H), 2.19 (t, 2H, J=6 Hz), 2.40 (s, 3H), 2.70 (t, 2H, J=6 Hz), 5.41 (s, 1H), 6.20 (s, 1H), 7.10 (m, 1H), 7.18-7.48 (m, 6H) ppm; Anal. Calcd. for $C_{20}H_{22}O_3S_2$: C, 64.14; H, 5.92. Found: C, 64.19; H, 5.98.

1-Cyclohexylidenyl-3-phenyl-3-(toluene-4-sulfonyl)-propan-2-one 5c.- The acid chloride **3** (0.58 g, 3.66 mmol) was treated as the general procedure with phenyl-*p*-toluenesulfonyl methane **4c** afforded the keto sulfone **5c** (1.21 g, 90%) as a very viscous, brown oil: IR 2990, 1660, 1630, 1420 cm^{-1}; ^1H NMR δ 1.60 (m, 6H), 2.18 (t, 2H, J=6 Hz), 2.40 (s, 3H), 2.70 (t, 2H, J=6 Hz), 5.40 (s, 1H), 6.22 (s, 1H), 7.35 (m, 9H) ppm; Anal. Calcd. for $C_{22}H_{24}O_3S$: C, 71.71; H, 6.56. Found: C, 71.77; H, 6.53.

1-(2,6-Dimethyl-cyclohexylidenyl)-3-(3-furyl)-3-(toluene-4-sulfonyl)-propan-2-one 13.- The acid chloride **12** (2.31 g, 12.38 mmol) was treated as the general procedure with 3-furyl-*p*-toluenesulfonyl methane **4a** afforded the keto sulfone **13** (4.44 g, 93 %) as a very viscous, brown oil: IR 3040, 1672, 1610, 1330 cm^{-1}; ^1H NMR δ 1.12 (d, 3H, J=7 Hz), 1.19 (d, 3H, J=7 Hz), 2.40 (s, 3H), 5.18 (s, 1H), 6.24 (s, 1H), 6.47 (m, 1H), 7.48 (m, 6H) ppm; Anal. Calcd. for $C_{22}H_{26}O_4S$: C, 68.37; H, 6.78. Found: C, 68.35; H, 6.81.

General procedure. Desulfurization of keto sulfones.- To a solution of β-keto sulfones **5** (1 mmol) in THF (15 mL) was added activated zinc (400 mg) and saturated aqueous NH_4Cl (15 mL). The mixture was stirred vigorously at room temperature for 2 h. The mixture was diluted with ethyl acetate and filtered. The

filtrate was washed with sodium bicarbonate solution and brine, dried and evaporated. Chromatography (9:1, hexane-diethyl ether) of the residue afforded the unsaturated ketone.

1-Cyclohexylidenyl-3-(3-furyl)-propan-2-one 6a. According to the general procedure, reaction of β-keto sulfone **5a** (0.97 g, 2.71 mmol) afforded ketone **6a** (442 mg, 80%), as a viscous, colourless liquid: IR 3148, 2932, 1688, 1620 cm^{-1}; ^1H NMR δ 1.57 (m, 6H), 2.16 (m, 2H), 2.81 (m, 2H), 3.52 (s, 2H), 6.02 (s, 1H), 6.33 (s, 1H), 7.38 (m, 2H) ppm; ^{13}C NMR δ 26.1, 27.8, 28.7, 29.9, 38.0, 40.5, 111.5, 118.1, 119.9, 140.3, 142.8, 163.0, 197.7 ppm; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.49; H, 7.84.

1-Cyclohexylidenyl-3-(3-thienyl)-propan-2-one 6b. According to the general procedure, reaction of β-keto sulfone **5b** (0.62 g, 1.67 mmol) afforded ketone **6b** (292 mg, 80%), as a viscous, colourless liquid: IR 2930, 1682, 1616 cm^{-1}; ^1H NMR δ 1.59 (m, 6H), 2.14 (m, 2H), 2.80 (m, 2H), 3.72 (s, 2H), 6.00 (s, 1H), 6.97 (m, 1H), 7.09 (m, 1H), 7.28 (m, 1H) ppm; ^{13}C NMR δ 26.2, 27.6, 28.8, 29.9, 38.1, 45.7, 120.2, 122.4, 125.4, 128.6, 134.8, 163.1, 197.7 ppm; Anal. Calcd. for $C_{13}H_{16}OS$: C, 70.87; H, 7.32. Found: C, 70.83; H, 7.36.

1-Cyclohexylidenyl-3-phenyl-propan-2-one 6c. According to the general procedure, reaction of β-keto sulfone **5c** (1.02 g, 2.77 mmol) afforded ketone **6c** (546 mg, 92%), as a viscous, colourless liquid: IR 2932, 1688, 1613 cm^{-1}; ^1H NMR δ 1.57 (m, 6H), 2.13 (m, 2H), 2.80 (m, 2H), 3.69 (s, 2H), 6.00 (s, 1H), 7.26 (m, 5H) ppm; ^{13}C NMR δ: 26.1, 27.7, 28.6, 29.7, 37.9, 51.3, 120.2, 126.5, 128.4 (2), 129.3 (2), 135.0, 162.7, 198.1 ppm; Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.10; H, 8.42.

1-(2,6-Dimethyl-cyclohexylidenyl)-3-(3-furyl)-propan-2-one 14.- According to the general procedure, reaction of β-keto sulfone **13** (4.13 g, 10.70 mmol) afforded ketone **14** (1.08 g, 42%), as a viscous, colourless liquid: IR 3144, 2930, 1680, 1603 cm^{-1}; ^1H NMR δ 1.19 (d, 6H, J=7 Hz), 3.53 (s, 2H), 6.03 (s, 1H), 6.33 (d, 1H, J=2 Hz), 7.36 (br s, 1H), 7.39 (m, 1H) ppm; ^{13}C NMR δ 15.5, 20.8, 22.2, 30.5, 31.5, 32.1, 38.2, 40.1, 111.2, 117.6, 121.2, 139.9, 142.3, 170.1, 196.8 ppm; Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.59; H, 8.64.

General procedure. Preparation of diazo ketones.- A solution of the ketone (1 mmol), N-acetylsulfanilyl azide (1.25 mmol) and DBU (2.50 mmol) in dry acetonitrile (5 ml) was stirred at 0 °C away from light for 90 min. The mixture was filtered through a short column of Florisil and eluted with a mixture of 9:1 hexane-diethyl ether. Removal under vacuo of the solvent afforded α-diazo ketone.

1-Cyclohexylidenyl-3-diazo-3-(3-furyl)-propan-2-one 7a.- Ketone **6a** (404 mg, 1.98 mmol) afforded α-diazo ketone **7a** (372 mg, 82%), as a viscous, yellow oil: IR 3148, 2932, 2064, 1645, 1615 cm^{-1}; ^1H NMR δ 1.63 (m, 6H), 2.20 (m, 2H), 2.78 (m, 2H), 6.02 (s, 1H), 6.29 (d, 1H, J=2 Hz), 7.46 (m, 2H) ppm.

1-Cyclohexylidenyl-3-diazo-3-(3-thienyl)-propan-2-one 7b.- Ketone **6b** (243 mg, 1.10 mmol) afforded α-diazo ketone **7b** (212 mg, 78%), as a viscous, yellow oil: IR 2930, 2060, 1642, 1611 cm^{-1}; ^1H NMR δ 1.64 (m, 6H), 2.21 (m, 2H), 2.79 (m, 2H), 6.05 (s, 1H), 7.07 (m, 1H), 7.39 (m, 2H) ppm.

1-Cyclohexylidenyl-3-diazo-3-phenyl-propan-2-one 7c.- Ketone **6c** (535 mg, 2.50 mmol) afforded α-diazo ketone **7c** (480 mg, 80%), as a viscous, yellow oil: IR 2932, 2068, 1642, 1613 cm^{-1}; ^1H NMR δ 1.84 (m, 6H), 2.19 (m, 2H), 2.77 (m, 2H), 6.05 (s, 1H), 7.44 (m, 5H) ppm.

1-(2,6-Dimethyl-cyclohexylidenyl)-3-diazo-3-(3-furyl)-propan-2-one 15.- Ketone **14** (1.08 g, 4.65 mmol) afforded α-diazo ketone **15** (800 mg, 67%) as a viscous, yellow oil: IR 3130, 2939, 2062, 1640 cm^{-1}; ^1H NMR δ 1.21 (d, 3H, J=7 Hz), 1.26 (d, 3H, J=7 Hz), 2.46 (m, 1H), 3.65 (m, 1H), 6.01 (s, 1H), 6.29 (d, 1H, J=2 Hz), 7.46 (m, 2H) ppm.

General procedure. Diazo ketone decomposition.- A solution of α-diazo ketone (1 mmol) in anhydrous CH_2Cl_2 (30 ml) was slowly added dropwise to a suspension of dirhodium tetraacetate (5 mg) in dry CH_2Cl_2 (6 ml) and stirred for 1 h. The mixture was evaporated under vacuo. Chromatography of the residue afforded the indenones.

1-(3-Furyl)-1,4,5,6,7,7a-hexahydro-2H-inden-2-one 9a.- α-Diazo ketone **7a** (221 mg, 0.96 mmol) afforded azine **8a** (11 mg, 5.5%) as a viscous oil, followed by indenone **9a** (124 mg, 64%) as a colourless liquid.

8a: IR: 2980, 1667, 1647 cm^{-1}; ^1H NMR δ 1.66 (m, 6H), 2.31 (t, 2H, J=6 Hz), 2.92 (t, 2H, J=6 Hz), 6.71 (s, 1H), 6.87 (s, 1H), 7.43 (s, 1H), 8.51 (s, 1H) ppm; Anal. Calcd. for $C_{26}H_{28}O_4N_2$: C, 72.20; H, 6.52; N, 6.48. Found: C, 72.25; H, 6.57; N, 6.42.

9a: IR 3138, 2936, 1703, 1622 cm^{-1}; ^1H NMR δ 1.2-2.9 (m, 9H), 3.06 (d, 1H, J=3 Hz), 5.88 (s, 1H), 6.27 (m, 1H), 7.36 (m, 2H) ppm; ^{13}C NMR δ 25.2, 26.7, 30.8, 34.2, 50.1, 50.3, 109.7, 122.0, 125.7, 139.5, 143.2, 181.9, 206.6 ppm; MS m/z (relative intensity) 202 (43, M^+), 173 (14), 131 (49), 115 (30), 103 (16), 91 (52), 77 (70), 51 (100); Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.23; H, 6.95.

1-(3-Thienyl)-1,4,5,6,7,7a-hexahydro-2H-inden-2-one 9b.- α-Diazo ketone **7b** (193 mg, 0.78 mmol) afforded azine **8b** (12 mg, 6%) as a viscous oil, followed by indenone **9b** (114 mg, 67%) as a white solid.

8b: IR: 2957, 1680, 1603 cm^{-1}; ^1H NMR δ 1.8 (m, 6H), 2.30 (m, 2H), 2.91 (m, 2H), 6.45 (s, 1H), 6.95 (m, 1H), 7.26 (m, 1H), 7.45 (m, 1H) ppm; Anal. Calcd. for $C_{26}H_{28}O_2S_2N_2$: C, 67.21; H, 6.07; N, 6.03. Found: C, 67.26; H, 6.04; N, 6.08.

9b: mp. 66 °C; IR 2934, 1697, 1622 cm^{-1}; ^1H NMR δ 1.3-3.0 (m, 9H), 3.26 (d, 1H, J=3 Hz), 5.91 (s, 1H), 6.93 (m, 1H), 7.10 (m, 1H), 7.29 (m, 1H) ppm; ^{13}C NMR δ 25.1, 26.6, 30.6, 34.2, 50.6, 54.8, 121.1, 125.6, 125.7, 126.7, 138.6, 182.0, 206.5 ppm; MS m/z (relative intensity) 218 (65, M^+), 189 (38), 161 (26), 147 (88), 115 (23), 91 (32), 77 (42), 65 (31); Anal. Calcd. for $C_{13}H_{14}OS$: C, 71.52; H, 6.46. Found: C, 71.55; H, 6.48.

1-Phenyl-1,4,5,6,7,7a-hexahydro-2H-inden-2-one 9c.- α-Diazo ketone **7c** (340 mg, 1.41 mmol) afforded azine **8c** (34 mg, 11%) as a viscous oil, followed by indenone **9c** (186 mg, 62%), as a white solid

8c: IR 2941, 1680, 1609 cm^{-1}; ^1H NMR δ 0.8-8.6 (m, 6H), 2.31 (m, 2H), 2.90 (m, 2H), 6.42 (s, 1H), 7.35 (m, 4H), 7.97 (m, 1H) ppm; Anal. Calcd. for $C_{30}H_{32}O_2N_2$: C, 79.61; H, 7.13; N, 6.19. Found: C, 79.66; H, 7.15; N, 6.16.

9c: mp. 48 °C; IR 2934, 1703, 1622 cm^{-1}; ^1H NMR δ 1.3-3.0 (m, 9H), 3.13 (d, 1H, J=3 Hz), 5.94 (s, 1H), 7.25 (m, 5H) ppm; ^{13}C NMR δ 24.9, 26.2, 30.6, 33.7, 51.6, 59.7, 125.6, 126.4, 127.6 (2), 128.4 (2), 139.2, 182.8, 207.5 ppm; MS m/z (relative intensity) 212 (75, M^+), 183 (39), 169 (13), 155 (24), 141 (100), 115 (55), 102 (13), 91 (52), 77 (47), 65 (30), 51 (49); Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.84; H, 7.66.

1-(3-Furyl)-4α,7aα-dimethyl-1,4,5,6,7,7a-hexahydro-2H-inden-2-one 16.- α-Diazo ketone **15** (800 mg, 3.10 mmol) afforded **indenone 16** (413 mg, 58 %) as a colourless liquid: IR 3148, 2934, 1705 cm^{-1}; ^1H NMR δ 0.98 (s, 3H), 1.29 (d, 3H, J=7 Hz), 3.10 (m, 1H), 3.40 (s, 1H), 5.91 (s, 1H), 6.21 (d, 1H, J=1 Hz), 7.39 (m, 2H) ppm; ^{13}C NMR δ 17.0, 20.0, 24.4, 32.1, 33.1, 39.1, 47.0, 59.1, 111.0, 118.7, 126.0, 141.0, 142.2, 188.0, 205.3 ppm; Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.28; H, 7.85.

General procedure. Reduction with LAH.- LAH (0.3 mmol) was added to a solution of ketone (1 mmol) in dry diethyl ether (5 mL) at 0 °C. The solution was stirred under argon at this temperature for 45 min and quenched by the addition of $Na_2SO_4 \cdot 10\ H_2O$. The resulting mixture was then stirred at 25 °C and filtered. Evaporation of the solvent afforded the alcohols.

1α-(3-Furyl)-1,4,5,6,7,7a-hexahydro-2H-inden-2β-ol 17a.- Unsaturated ketone **9a** (35 mg, 0.17 mmol) afforded alcohol **17a** (31 mg, 88%) as a viscous oil: IR 3358, 3046, 2928 cm^{-1}; ^1H NMR δ 1.1-2.1 (m, 8H), 2.58 (m, 1H), 4.70 (m, 1H), 5.35 (d, 1H, J=2 Hz), 6.33 (s, 1H), 7.31 (s, 1H), 7.38 (m, 1H) ppm; ^{13}C NMR δ 25.6, 26.5, 28.7, 34.3, 50.9, 53.1, 83.3, 109.8, 123.7, 126.4, 138.7, 143.3, 148.3 ppm; Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.49; H, 7.84.

1α-(3-Thienyl)-1,4,5,6,7,7a-hexahydro-2H-inden-2β-ol 17b.- Unsaturated ketone **9b** (100 mg, 0.46 mmol) afforded alcohol **17b** (92 mg, 91%) as a viscous oil: IR 3455, 3031, 2924 cm^{-1}; ^1H NMR δ 1.1-2.6 (m, 9H), 2.93 (m, 1H), 4.79 (m, 1H), 5.33 (d, 1H, J=2 Hz), 6.89 (m, 1H), 7.00 (m, 1H), 7.25 (m, 1H) ppm; ^{13}C NMR δ 25.5, 26.4, 28.6, 34.5, 51.4, 57.9, 83.5, 119.6, 123.5, 125.6, 126.6, 144.0, 148.0 ppm; Anal. Calcd. for $C_{13}H_{16}OS$: C, 70.86; H, 7.32. Found: C, 70.82; H, 7.36.

1α-Phenyl-1,4,5,6,7,7a-hexahydro-2H-inden-2β-ol 17c.- Unsaturated ketone **9c** (100 mg, 0.47 mmol) afforded alcohol **17c** (85 mg, 89%), as a vicous oil: IR 3455, 3031, 2925 cm^{-1}; ^1H NMR δ 1.1-2.6 (m, 9H), 2.67 (1H, t, J=6.2 Hz), 4.84 (m, 1H), 5.37 (d, 1H, J=2 Hz), 7.27 (m, 5H) ppm; ^{13}C NMR δ 25.6, 26.6, 28.7, 34.7, 52.1, 63.1, 84.5, 123.3, 126.3, 127.6 (2), 129.2 (2), 143.7, 148.6 ppm; Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.03; H, 8.49.

1α-(3-Furyl)-4α,7aα-dimethyl-1,4,5,6,7,7a-hexahydro-2H-inden-2β-ol 17d.- Unsaturated ketone **16** (195 mg, 0.85 mmol) afforded alcohol **17d** (180 mg, 91%), as a viscous oil: IR 3368, 3130 cm^{-1}; ^1H NMR δ 0.86 (s, 3H), 1.13 (d, 3H, J=7 Hz), 2.70 (d, 1H, J=8 Hz), 4.91 (d, 1H, J= 8 Hz), 5.40 (s, 1H), 6.29 (s, 1H), 7.32 (s, 1H), 7.39 (s, 1H) ppm; ^{13}C NMR δ 17.2, 21.3, 22.2, 31.5, 32.3, 40.1, 47.4, 60.6, 78.5, 111.1, 122.3, 125.1, 139.9, 142.6, 155.8 ppm; Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.59; H, 8.63.

General procedure. Epoxidation with MCPBA.- *m*-Chloroperoxybenzoic acid (1 mmol) was added at 0 °C to a solution of the allylic alcohol (1 mmol) in dry CH_2Cl_2 (5 mL), and the resulting mixture was stirred at this temperature for 3 h. A solution of $NaHSO_3$ (10%) was added and the resulting heterogeneous mixture was stirred and gradually warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with diethyl ether. The combined extracts were washed with 0.5 N NaOH, water and brine and then dried. Removal of the solvent afforded epoxy alcohols.

1α-(3-Furyl)-3β,3aβ-epoxy-octahydro-indan-2β-ol 18a.- Alcohol **17a** (31 mg, 0.15 mmol) afforded oxirane **18a** (31 mg, 94%), as a colourless oil: IR 3426 cm^{-1}; ^1H NMR δ 1.2-1.9 (m, 9H), 2.26 (t, 1H, J=8 Hz), 3.55 (s, 1H), 4.02 (d, 1H, J=8 Hz), 6.31 (s, 1H), 7.28 (s, 1H), 7.38 (s, 1H) ppm; ^{13}C NMR

δ 23.8, 25.3, 27.4, 28.9, 43.0, 45.5, 63.5, 65.9, 78.9, 109.4, 124.2, 139.1, 143.2 ppm; Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.84; H, 7.29.

1α-(3-Thienyl)-3β,3aβ-epoxy-octahydro-indan-2β-ol 18b.- Alcohol **17b** (85 mg, 0.39 mmol) afforded oxirane **18b** (84 mg, 92%) as a white solid: mp. 55 °C; IR 3426, 3030, 2930 cm^{-1}; ^1H NMR δ 1.2-1.9 (m, 9H), 2.48 (t, 1H, J=9 Hz), 3.56 (s, 1H), 4.09 (d, 1H, J=8 Hz), 6.99 (m, 2H), 7.27 (m, 1H) ppm; ^{13}C NMR δ 23.6, 25.3, 27.6, 29.0, 46.1, 47.6, 63.6, 65.8, 79.2, 120.4, 125.7, 126.9, 141.5 ppm; Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 66.10; H, 6.85.

1α-Phenyl-3β,3aβ-epoxy-octahydro-indan-2β-ol 18c.- Alcohol **17c** (50 mg, 0.23 mmol) afforded oxirane **18c** (52 mg, 96%), as a white solid: mp. 90 °C; IR 3450, 3035, 2924 cm^{-1}; ^1H NMR δ 1.2-2.1 (m, 9H), 2.37 (t, 1H, J=9 Hz), 3.61 (s, 1H), 4.19 (t, 1H, J=8 Hz), 7.28 (m, 5H) ppm; ^{13}C NMR δ 23.9, 25.3, 27.4, 29.1, 46.6, 52.7, 63.6, 65.8, 79.6, 126.7, 128.0 (2), 128.5 (2), 140.4 ppm; Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.26; H, 7.84.

1α-(3-Furyl)-4α,7aα-dimethyl-3β,3aβ-epoxy-octahydro-indan-2β-ol 18d.- Alcohol **17d** (180 mg, 0.77 mmol) afforded oxirane **18d** (180 mg, 94%) as a colourless oil: IR 3418, 3142, 2930 cm^{-1}; ^1H NMR δ 0.80 (s, 3H), 1.16 (3H, d, J=8 Hz), 1.6-2.9 (m, 7H), 2.57 (d, 1H, J=9 Hz), 3.55 (s, 1H), 4.19 (d, 1H, J=9 Hz), 6.22 (d, 1H, J=2 Hz), 7.25 (s, 1H), 7.38 (m, 1H) ppm; ^{13}C NMR δ 16.9, 17.5, 18.0, 29.6, 33.2, 34.1, 42.0, 48.1, 62.6, 71.2, 75.4, 111.0, 121.2, 140.1, 142.7 ppm; Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.59; H, 8.17.

General method.Oxidation with PCC.- A solution of alcohol (1 mmol) in CH_2Cl_2 (3.5 mL) was added to a slurry of PCC (1.5 mmol) in CH_2Cl_2 (10 mL) at room temperature and the mixture was stirred for 3 h. The reaction mixture was diluted with diethyl ether and filtered through a short column of silica gel. Excess solvent was removed under vacuo to afforded the epoxy ketones.

1α-(3-Furyl)-3β,3aβ-epoxy-octahydro-indan-2-one 19a.- Epoxy alcohol **18a** (30 mg, 0.14 mmol) afforded epoxy ketone **19a** (24 mg, 80%), as a colourless oil: IR 3021, 2928, 1753 cm^{-1}; ^1H NMR δ 0.8-2.1 (m, 9H), 3.29 (d, 1H, J=9 Hz), 3.46 (s, 1H), 6.24 (d, 1H, J=2 Hz), 7.31 (s, 1H), 7.40 (d, 1H, J=2 Hz) ppm; ^{13}C NMR δ 24.6, 25.3, 28.8, 29.7, 44.6, 45.3, 60.7, 66.5, 110.1, 119.4, 140.3, 143.3, 209.0 ppm; MS m/z (relative intensity) 218 (2, M^+), 205 (6), 147 (12), 135 (15), 124 (42), 109 (9), 97 (61), 79 (32), 69 (31), 45 (100); Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.58; H, 6.43.

1α-(3-Thienyl)-3β,3aβ-epoxy-octahydro-indan-2-one 19b.- Epoxy alcohol **18b** (50 mg, 0.21 mmol) afforded epoxy ketone **19b** (38 mg, 78%), as a white solid: mp. 73 °C; IR 3104, 2934, 1750 cm^{-1}; ^1H NMR δ 1.2-2.3 (m, 9H), 3.47 (s, 1H), 3.48 (d, 1H, J=9 Hz), 6.88 (d, 1H, J=2 Hz), 7.02 (s, 1H), 7.31 (m, 1H) ppm; ^{13}C NMR δ:24.6, 25.4, 28.1, 28.9, 45.8, 49.1, 60.7, 68.3, 122.4, 125.8, 127.6, 136.0, 209.0 ppm; MS m/z (relative intensity) 234 (9, M^+), 205 (6), 177 (9), 147 (12), 135 (15), 124 (42), 109 (9), 97 (61), 79 (32), 69 (31), 45 (100); Anal. Calcd. for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02. Found: C, 66.69; H, 6.09.

1α-Phenyl-3β,3aβ-epoxy-octahydro-indan-2-one 19c.- Epoxy alcohol **18c** (26 mg, 0.11 mmol) afforded epoxy ketone **19c** (24 mg, 92%) as a white solid: mp. 97 °C; IR 3021, 2940, 1748 cm^{-1}; ^1H NMR δ 1.6-2.3 (m, 9H), 3.36 (d, 1H, J=9 Hz), 3.49 (s, 1H), 7.20 (m, 5H) ppm; ^{13}C NMR δ 24.6, 25.4, 27.6, 28.9, 46.3, 54.1, 60.8, 68.2, 127.2, 128.6 (2), 129.1 (2), 136.1, 209.3 ppm; MS m/z (relative intensity)

229 (3, M^+), 228 (53), 199 (11), 171 (70), 141 (16)129 (72), 118 (100), 91 (86), 77 (33); Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.95; H, 7.03.

1α-(3-Furyl)-4α,7aα-dimethyl-3β,3aβ-epoxy-octahydro-indan-2-one 19d.- Epoxy alcohol **18d** (160 mg, 0.64 mmol) afforded epoxy ketone **19d** (63 mg, 40%), as a colourless oil: IR 3156, 2930, 1753 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 1.21 (d, 3H, J=8 Hz), 3.41 (s, 1H), 3.76 (s, 1H), 6.19 (d, 1H, J=3 Hz), 7.37 (m, 2H) ppm; ^{13}C NMR δ 17.4, 17.6, 18.9, 30.6, 33.4, 33.7, 42.6, 50.5, 59.8, 73.2, 111.3, 116.3, 141.5, 142.3, 209.3 ppm; MS m/z (relative intensity) 246 (13, M^+), 203 (39), 190 (17), 175 (11), 161 (12), 133 (12), 108 (100), 91 (64), 77 (73), 67 (69), 55 (75); Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.17; H, 7.40.

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