Synthesis of Insect Antifeedants Related to Azadiradione

A. Fernández Mateos,* A. López Barba, G. Pascual Coca, R. Rubio González, C. Tapia Hernández
Departamento de Química Orgánica, Facultad de C. Químicas, Universidad de Salamanca, Salamanca, Spain
Fax +34(23)294574; E-mail: afmateos@gug.usal.es
Received 30 April 1997; revised 27 June 1997

An efficient synthesis of a model insect antifeedant based on the C, D and E rings of the limonoid azadiradione has been developed. (8 steps ≥ 18% overall yield). The key steps were an electrocyclization induced by acids **4** → **5** and a dyotropic rearrangement from epoxide **7** to ketone **8**.

Recently limonoids have attracted much attention because of the marked insect antifeedant and growth regulating activity exhibited by some members of this naturally occurring family.[1] Though structure–activity relationship studies have been carried out, motivated by the desire to find useful compounds for specific agricultural applications, much further research in the field is needed. The present work reports the chemical synthesis of several CDE molecular fragments related to azadiradione.

The synthetic approach to the CDE fragment of azadiradione **9** involves eight steps, and allows the preparation of the multigram quantities necessary for further SAR studies. Starting from the readily available β-cyclocitral **(1)** we have developed a successful strategy for the preparation of **9** based on the Nazarov cyclization[2] which is outlined in the Scheme.

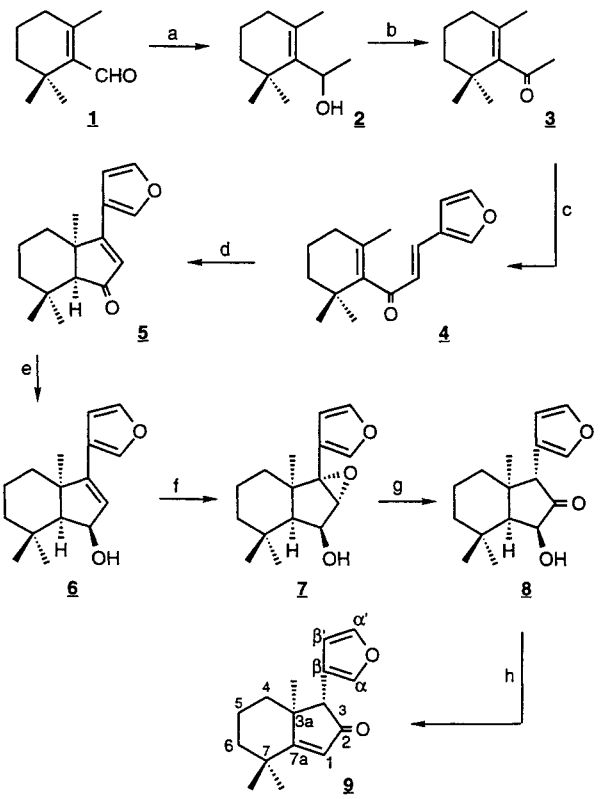
Treatment of **1** with MeLi in diethyl ether at −10 °C gave an epimeric mixture of allylic alcohols **2**.[3a] Subsequent oxidation using manganese dioxide in hexane, afforded the required methyl ketone **3**[3] in excellent overall yield (86%). Aldol condensation[4] of **3** with 3-furaldehyde at room temperature in the presence of NaOH in ethanol gave exclusively the divinyl ketone **4** in 68% yield.[5]

The Nazarov cyclization[2c] of **4** was performed with concentrated sulfuric acid, phosphoric acid (85%) or a mixture of formic acid/phosphoric acid,[6] in each case yielding only the bicyclic enone **5** in approximately 70% yield. The yield and selectivity of this cationic electrocyclization is of merit in view of the extreme sensitivity of furan to hard protonic acids.

The enone **9**, the CDE fragment of azadiradione, was obtained in a four-step sequence from the byciclic enone **5**.

Reduction of **5** with lithium aluminum hydride in diethyl ether at 0 °C afforded the allylic alcohol **6** in quantitative yield. Structure **6** was assigned to the allylic β-alcohol based on nucleophilic attack from the least hindered face of the cyclopentenone,[7] and NOE experiments.[8]

Epoxidation of the allylic alcohol **6** was carried out by reaction with 3-chloroperoxybenzoic acid. To avoid destruction of the extremely sensitive furan ring, oxidation was performed under very mild conditions, to give 60% of the α-epoxide **7** as the only reaction product. Although the influence of the *syn* effect of the hydroxy group was expected, no β-epoxide from the reaction was detected. In this case, the steric factor seems to prevail over hydrogen bonding. The α configuration assigned to the oxiranic oxygen is based on the upfield shift of the ^{13}C NMR signal for the homoallylic carbon bearing an axial hydrogen *cis* to the oxygenated function of the epoxide **7** ($\delta = 55.16$) with respect to the unsaturated precursor **5** ($\delta = 63.58$).



(a) MeLi, Et_2O, −10 °C, 97%; (b) MnO_2, hexane, 86%; (c) 3-furaldehyde, NaOH, EtOH, 68%; (d) $HCOOH$-H_3PO_4, 75 °C, 70%; (e) $LiAlH_4$, Et_2O, 98%; (f) MCPBA, CH_2Cl_2, −40 °C, 60%; (g) $BF_3 \cdot Et_2O$, CH_2Cl_2, −30 °C, 95%, (h) $SOCl_2$, CH_2Cl_2, 82%.

Scheme

Rearrangement of epoxide **7** was carried out with boron trifluoride–diethyl ether complex in dichloromethane at −30 °C to give only the hydroxy ketone **8** in 95% yield. A "concerted" mechanism seems to operate, starting with a slow epoxide opening to give a carbenium ion and followed by a rapid 1,2 hydrogen shift.[9] This dyotropic rearrangement of epoxide **7** set the required α furan stereochemistry in the target compound.[10]

Dehydration of the hydroxy ketone **8** with thionyl chloride in pyridine at 0 °C afforded the CDE fragment of azadiradione **9** in 82% yield. The overall yield of **9** was 18% over eight steps starting from β-cyclocitral **(1)**. The spectroscopical and physical properties of **9** were in agreement with those reported in the literature.[11]

Table 1. ^{13}C NMR Chemical Shifts (δ) for **5–8**

	5	6	7	8
C-1	209.7	77.1	73.3	75.1
C-2	126.9	127.1	64.7	218.3
C-3	173.9	146.8	67.4	56.7
C-3a	46.0	47.6	30.8	39.5
C-4	30.7	37.0	33.5	36.5
C-5	17.0	17.8	17.9	18.7
C-6	34.0	36.2	36.2	35.2
C-7	35.6	31.6	42.6	32.0
C-7a	63.6	65.5	55.2	56.4
C-α	142.5	138.8	141.3	141.0
C-β	119.5	120.2	119.3	119.8
C-α′	143.4	142.4	142.4	142.8
C-β′	109.8	110.1	110.6	111.1
CH_3 (C-3a)	28.8	25.7	21.1	25.1
CH_3 (C-7)	24.4	29.9	29.3	29.7
CH_3 (C-7)	32.6	31.6	31.0	30.4

Commercial reagents were used as received. CH_2Cl_2 and pyridine were distilled under N_2 over CaH_2. Et_2O and THF were distilled from sodium. Hexane was distilled before use. Melting points were determined on a hot-stage apparatus and are not corrected. The ^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. Mass spectra were obtained on a VG-TS 250 instrument. All reactions were carried out under an atmosphere of N_2 in glassware dried overnight and cooled under N_2. Reaction were monitored by TLC. Flash column chromatography was carried out using silica gel 60 (0.0400.063 mm Merck). Organic extracts were dried with anhyd Na_2SO_4 and concentrated under reduced pressure with the aid of a rotary evaporator.

1-(2,6,6-Trimethylcyclohex-1-enyl)ethan-1-ol (2):
To a stirred solution of β-cyclocitral (**1**, 5.3 g, 35 mmol) in Et_2O (180 mL) at −10 °C under N_2, was gradually added 1.5 M MeLi in Et_2O (25 mL, 38 mmol). The mixture was stirred at −10 °C for 30 min. Then, satd aq NH_4Cl was added, the organic phase was separated and the aqueous phase was extracted with Et_2O. Extracts were washed with brine and dried. Distillation at reduced pressure afforded an oily product identified as **2**[3a] (5.7 g, 97%).

IR: ν = 3200, 2980 cm^{-1}.

Table 2. $^1H/^{13}C$ Long Range Correlations

Compound	H	C
5	α-CH_3 (C-7)	CH_3 (C-7), 6, 7a
	β-CH_3 (C-7)	CH_3 (C-7), 6, 7a
	CH_3 (C-3a)	4, 7a, 3
	H-7a	CH_3 (C-7), CH_3 (C-3a), 3a, 3, 1
6	α-CH_3 (C-7)	6, 7a
	β-CH_3 (C-7)	6, 7a
	CH_3 (C-3a)	4, 7a, 3
	H-7a	CH_3 (C-3a), CH_3 (C-7), 7, 3a, 1
	H-1	CH_3 (C-7), 2, 3
7	α-CH_3 (C-7)	CH_3 (C-7), 6, 7a
	β-CH_3 (C-7)	CH_3 (C-7), 6, 7a
	CH_3 (C-3a)	4, 7a, 3
	H-2	7a, 1
	H-1	3a
8	α-CH_3 (C-7)	6, 7a, CH_3 (C-7)
	β-CH_3 (C-7)	6, 7a, CH_3 (C-7)
	CH_3 (C-3a)	4, 7a, 3
	H-3	4, 3a, 7a, 2, C-β, C-β′, C-α
	H-1	7, 7a, 2
	H-7a	CH_3 (C-7), CH_3 (C-3a), 4, 3a, 1

^1H NMR: δ = 0.94 (s, 3 H, CH_3-6′), 1.08 (s, 3 H, CH_3-6′), 1.39 (d, 3 H, J = 7 Hz, CH_3-2), 1.84 (s, 3 H, CH_3-2′), 4.49 (q, 1 H, J = 7 Hz, H-1).

MS: m/z (%) = 168 (30, M^+), 153 (30), 135 (72), 123 (70), 109 (78), 93 (50), 79 (60), 69 (65), 55 (100).

1-(2,6,6-Trimethylcyclohex-1-enyl)ethanone (3):
Manganese dioxide (53 g) was added to a solution of **2** (5.3 g, 31.5 mmol) in hexane (100 mL). The mixture was shaken vigorously for 15 h at r.t. and the brown precipitate was collected and washed with Et_2O. The combined solvent portions were concentrated in vacuo to afford a crude product identified as the ketone **3**[3b] (4.5 g, 86%).

IR: ν = 2980, 1700 cm^{-1}.

^1H NMR: δ = 1.06 (s, 6 H, CH_3-6′), 1.57 (s, 3 H, CH_3-2′), 2.27 (s, 3 H, CH_3-2).

MS: m/z (%) = 166 (25, M^+), 151 (35), 135 (26), 123 (30), 109 (38), 95 (46), 81 (52), 69 (78), 61 (100), 55 (85).

(*E*)-1-(2,6,6-Trimethylcyclohex-1-enyl)-3-(3-furyl)prop-2-en-1-one (4):
To a solution of the ketone **3** (4.5 g, 27 mmol) in EtOH (32 mL) were gradually added 3-furaldehyde (2.6 g, 27.10 mmol) and NaOH (2.17 g, 54 mmol). The reaction mixture was vigorously stirred for 2 h at r.t. The mixture was concentrated in vacuo to afford a residue which was dissolved in water and extracted with Et_2O. The organic layers were washed with brine, dried and filtered. The solvent was evaporated and the residue was purified by flash chromatography using hexane/Et_2O (95:5), to give an oily product identified as **4** (4.5 g, 68%).

IR: ν = 2980, 1640 cm^{-1}.

^1H NMR: δ = 1.02 (s, 6 H, CH_3-6′), 1.51 (s, 3 H, CH_3-2′), 6.41 (d, 1 H_a, J = 16 Hz, H-2), 6.58 (m, 1 H, H-β′), 7.23 (d, 1 H_b, J = 16 Hz, H-3), 7.40 (m, 1 H, H-α), 7.64 (1 H, m, H-α′).

^{13}C NMR: δ = 18.85, 21.02, 28.69 (2), 31.09, 33.42, 38.78, 107.40, 122.90, 129.07, 130.40, 134.60, 140.30, 144.30, 144.70, 201.00.

MS: m/z (%) = 244 (31, M^+), 229 (18), 201 (12), 187 (8), 161 (16), 147 (21), 135 (18), 121 (64), 107 (25), 93 (64), 81 (78), 69 (100).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.69; H, 8.21.

3-(3-Furyl)-3a,7,7-trimethyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one (5):
Divinyl ketone **4** (1.5 g, 6.1 mmol) was dissolved in 85% phosphoric acid (3 mL) and 90% formic acid (3 mL), and the mixture was heated at 75 °C for 30 min under a N_2 atmosphere. After cooling, the reaction was treated with water and extracted with Et_2O. The organic layer was washed with 2% NaOH and brine, dried and evaporated. Chromatography of the residue and elution with hexane/Et_2O (7:3) left a crystalline product identified as **5** (1 g, 70%); mp 58–59 °C.

IR: ν = 2980, 1690, 1600 cm^{-1}.

^1H NMR: δ = 0.91 (s, 3 H, CH_3-7), 1.22 (s, 3 H, CH_3–7), 1.37 (s, 3 H, CH_3-3a), 1.93 (s, 1 H, H-7a), 6.13 (s, 1 H, H-2), 6.57 (m, 1 H, H-β′), 7.48 (m, 1 H, H-α), 7.77 (m, 1 H, H-α′).

MS: m/z (%) = 244 (16, M^+), 229 (16), 175 (25), 162 (42), 145 (20), 131 (3), 115 (51), 91 (100), 77 (75), 63 (78).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.69; H, 8.18.

3-(3-Furyl)-3a,7,7-trimethyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-ol (6):
$LiAlH_4$ (72 mg, 2 mmol) was added to a solution of ketone **5** (1.2 g, 5 mmol) in dry Et_2O (40 mL) at 0 °C. The solution was stirred under N_2 at this temperature for 15 min and quenched by the addition of $Na_2SO_4 \cdot 10\,H_2O$ (72 mg, 0.2 mmol). The mixture was then stirred for 20 min at 25 °C and filtered. Removal of the solvent afforded an oily compound identified as **6** (1.2 g, 98%).

IR: ν = 3400, 2980, 1640 cm^{-1}.

^{1}H NMR: δ = 1.10 (s, 6H, CH_3-7), 1.35 (s, 3H, CH_3-3a), 4.67 (d, 1H, J = 8 Hz, H-1), 5.66 (s, 1H, H-2), 6.42 (m, 1H, H-β'), 7.35 (m, 1H, H-α), 7.42 (m, 1H, H-α').

MS: m/z (%) = 246 (35, M^+), 229 (38), 213 (42), 203 (20), 175 (30), 163 (20), 147 (22), 128 (28), 109 (40), 91 (52), 81 (54), 69 (100).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.04; H, 8.92.

2,3-Epoxy-3-(3-furyl)-3a,7,7-trimethyl-perhydro-inden-1-ol (7):
A solution of MCPBA (523 mg, 3 mmol) in dry CH_2Cl_2 (9 mL) was added dropwise at −40 °C to a solution of the allylic alcohol **6** (245 mg, 1 mmol) in dry CH_2Cl_2, and the resulting mixture was stirred at this temperature for 15 min. A solution of 10% $NaHSO_3$ was added and the resulting heterogenous mixture was stirred and gradually warmed to r.t. The organic layer was separated, and the aqueous phase was extracted twice with Et_2O. The combined extracts were washed with 0.5 N NaOH, water and brine and then dried and filtered. Evaporation of the solvent afforded a residue, which was flash chromatographed using hexane/Et_2O (6:4) as the eluting solvent to give the epoxide alcohol **7** (157 mg, 60%).

IR: ν = 3300, 2980 cm^{-1}.

^{1}H NMR: δ = 1.04 (s, 6H, CH_3-7), 1.24 (s, 3H, CH_3-3a), 3.54 (s, 1H, H-2), 4.07 (br s, 1H, H-1), 6.37 (m, 1H, H-β'), 7.35 (m, 1H, H-α), 7.43 (m, 1H, H-α').

MS: m/z (%) = 262 (31, M^+), 247 (24), 219 (10), 192 (8), 179 (14), 161 (18), 137 (20), 109 (85), 95 (100), 81 (50), 69 (66).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.27; H, 8.39.

1-Hydroxy-3-(3-furyl)-3a,7,7-trimethylperhydroindan-2-one (8):
A solution of the epoxide alcohol **7** (116 mg, 0.4 mmol) in CH_2Cl_2 (19 mL) was treated with $BF_3 \cdot Et_2O$ (0.04 mL) left 5 min at −30 °C, and then water (6 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined extracts were washed with brine and then dried and filtered. Removal of the solvent afforded a residue identified as hydroxy ketone **8** (110 mg, 95%).

IR: ν = 3400, 2980, 1720 cm^{-1}.

^{1}H NMR: δ = 0.97 (s, 3H, CH_3-7), 1.08 (s, 3H, CH_3-7), 1.11 (s, 3H, CH_3-3a), 3.22 (s, 1H, H-3), 4.16 (d, 1H, J = 10 Hz, H-1), 6.21 (m, 1H, H-β'), 7.28 (m, 1H, H-α), 7.36 (m, 1H, H-α').

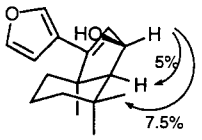
MS: m/z (%) = 262 (42, M^+), 161 (6), 139 (100), 123 (14), 109 (65), 91 (30), 81 (45), 69 (30).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.27; H, 8.41.

1-(3-Furyl)-4,4,7a-trimethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one (9):
$SOCl_2$ (0.01 mL, 1.5 mmol) was added at 0 °C with stirring under N_2 to a solution of the corresponding hydroxy ketone **8** (73 mg, 0.3 mmol) in dry CH_2Cl_2 (2 mL) and dry pyridine (0.05 mL, 0.7 mmol). The mixture was stirred at 0 °C for 5 min and then poured onto ice. The heterogenous mixture was gradually warmed to r.t.; it was then extracted three times with CH_2Cl_2. The combined extracts were washed with aq 2 N HCl, 5% $NaHCO_3$ and brine and then dried. The solvent was evaporated and the residue was purified by flash chromatography using hexane/Et_2O (8:2) to yield a solid identified as ketone **9** (55 mg, 82%).[10]

Financial support of this work by the Ministerio de Educación y Ciencia of Spain PB 95-0943 and the Junta de Castilla y León SA 45/97 is gratefully acknowledged.

(1) Kraus, W. Biologically active compounds from Meliaceae. In *Chemistry and Biotechnology of Biologically Active Natural Products*; Proceedings of the Second International Conference; Budapest, 15–19 August, 1983. Szantay, Cs., Ed.; Studies in Organic Chemistry. 17; Elsevier: Amsterdam, 1984; pp 331–345.
Champagne, D.E.; Koul, O.; Isman, M.B.; Scudder, G.E.; Towers, G.H. *Phytochemistry* **1992**, *31*, 377.
Taylor, D.A.H. *Prog. Chem. Org. Nat. Prod.* **1984**, *45*, 1.
Van Beek, T.A.; de Groot, A. *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 513.
Kulkarni, R.A. *Pure Appl. Chem.* **1986**, *58*, 917.
(2) (a) Santelli-Rouvier, S.; Santelli, M. *Synthesis* **1983**, 429.
(b) Habermas, K.L.; Denmark, S. E.; Jones, T.K. *Org. React.* **1994**, *45*, 1.
(c) Fernández-Mateos, A.; López Barba, A.; Pascual Coca, G.; Rubio González, R.; Tapia Hernández, C. *Synlett.* **1995**, 409.
(3) (a) Henbest, H.B.; Woods, G. *J. Chem. Soc.* **1952**, 1150.
(b) Müller, E.P.; Jeger, O. *Helv. Chim. Acta* **1975**, *58*, 2173.
(4) Wattanasin, S.; Murphy, W.S. *Synthesis* **1980**, 647.
(5) Unless otherwise stated, all compounds synthesized are racemic modifications, although only one enantiomer is depicted.
(6) Hirano, S.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1974**, 1429.
Hirano, S.; Takagi, T.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 169.
(7) Bürgi, H.B.; Dunitz, J.D. *Acc. Chem. Res.* **1983**, *16*, 153.
(8)



(9) Coxon, J.M.; Lim, C.E. *Aust. J. Chem.* **1977**, *30*, 1137.
Blackett, B.N.; Coxon, J.M.; Hartshorn, M.P.; Richards, K.E. *Aust. J. Chem.* **1970**, *23*, 2077.
(10) The ^{1}H and ^{13}C NMR spectra of compounds **5–8** were assigned with the aid of ^{1}H-^{13}C correlation experiments and were found to be in complete agreement with the proposed structure and stereochemistry.
(11) Fernández-Mateos, A.; de la Fuente Blanco, J. *J. Org. Chem.* **1990**, *55*, 1349.
Fernández-Mateos, A.; López Barba, A. *J. Org. Chem.* **1995**, *60*, 3580.