The Absolute Stereochemical Characterization of Two New Jatrophane Diterpenes from *Euphorbia esula*

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The structures and absolute stereochemistry of two moderately toxic jatrophane diterpenes of potential taxonomic importance, esulone A [(E)-(−)-(1R,3S,8R,9S,11R,12S,13R,14R)-1,13-diacetoxy-9,11-dibenzoyloxy-8,14-dihydroxy-3,6,6,14-tetramethyl-10-methylene-*trans*-bicyclo[10.3.0]pentadec-4-ene-2,7-dione] and esulone B [(E)-(−)-(1R,3S,8R,9S,11R,12S,13R,14R)-1,8,13-triacetoxy-9,11-dibenzoyloxy-14-hydroxy-10-methylene-3,6,6,14-tetramethyl-*trans*-bicyclo[10.3.0]pentadec-4-ene-2,7-dione], isolated from *Euphorbia esula* roots were determined utilizing n.m.r. spectroscopy, X-ray crystallography, and exciton chirality techniques. Stereochemical assignment corrections for previously reported lathyrane and jatrophane diterpenes are discussed.

The deep-rooted perennial noxious weed *Euphorbia esula* (leafy spurge) is toxic to cattle,[1] allelopathic[2] to desired forage species, and has seriously impacted open-range livestock production in the upper great plains states of the United States. Control of this plant by chemical means is costly and eradication in open-range situations has not been achieved. Biological control methods successfully applied to European *E. esula*[3] have not been effective in North America.

Previously chemical investigations of leafy spurge have identified hydrocarbons,[4] long-chain alcohols,[4,5] long-chain aldehydes,[6] triterpenes,[4,7,8] flavonoids,[9] and toxic ingenane diterpenes[10-12] in this plant; however, chemical investigations related to allelopathy are minimal.[2] Jatrophane diterpenes have not previously been described in *E. esula*, although twelve of these compounds have been described in other species of *Euphorbia*[13-19] and in *Jatropha gossypiifolia*.[20,21] The unique structural character of these diterpenes and their exclusive distribution in the family Euphorbiaceae suggest their potential taxonomic importance within this plant family.

We now report the isolation and characterization of two new jatrophane diterpenes from the roots of *E. esula*. Biological assay of one of these compounds (esulone A) showed it to be moderately phytotoxic [29% root-length reduction (lettuce seeds) at 250 p.p.m.], and also to be moderately toxic (LD_{50} 78 ± 23 mg kg^{-1}) and mildly inflammatory (10^{-5} to 10^{-6} M) to mammals, but without causing hyperplasia.

Esulone A (**2**) [3,15-diacetoxy-5,7-dibenzoyloxy-2,8-dihydroxyjatropha-6(17),11-diene-9,14-dione]* was obtained by preparative absorption chromatography of a neutral fraction of the ether extract of *E. esula* roots, followed by fractional crystallization. The ^{1}H n.m.r. spectrum (Table 1) of esulone A (**2**) showed distinct resonances for the following groups: three tertiary methyls, one secondary methyl, one isolated methylene, two acetates, and two benzoates. The molecular formula ($C_{20}H_{30}O_4$) (excluding diacetate, dibenzoate esterification) suggested esulone A to be a bicyclic diterpene. The compound formed its diacetate (**4**), confirming the presence of two hydroxy groups in esulone A, and two carbonyl signals in its ^{13}C n.m.r. spectrum (Table 2) accounted for the remaining oxygen functionality in the compound. The spectrum also showed
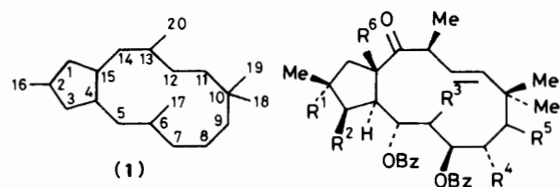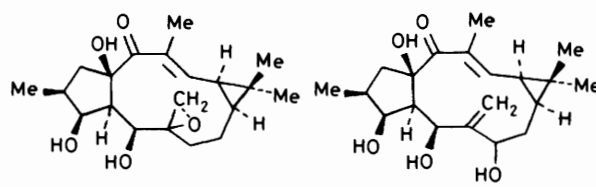

(1)

(2) R^1 = R^4 = OH, R^2 = R^6 = OAc, R^3 = =CH$_2$, R^5 = =O

(3) R^1 = OH, R^2 = R^4 = R^6 = OAc, R^3 = =CH$_2$, R^5 = =O

(4) R^1 = R^2 = R^4 = R^6 = OAc, R^3 = =CH$_2$, R^5 = =O

(5) R^1 = R^4 = OH, R^2 = R^6 = OAc, R^3 = Me,H, R^5 = =O

(6) R^1 = R^4 = R^5 = OH, R^2 = R^6 = OAc, R^3 = =CH$_2$
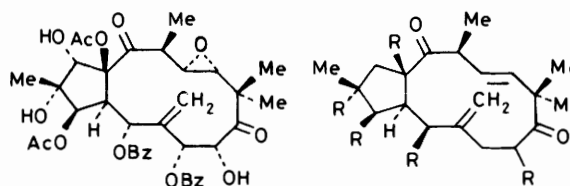
(7)

(8) R = OAc (3 x), OBz, nicotinoyl

(9) R = OAc (3 x), (E)-2-methyl but-
-2-enoyl, nicotinoyl

(10)   (11)

signals for four methyl carbons, one alkyl methylene carbon, two oxygen-substituted quaternary carbons, one alkyl-substituted quaternary carbon, four oxygen-substituted tertiary carbons, two alkyl-substituted tertiary carbons, two tertiary unsaturated carbons, one unsaturated methylene carbon, and a single quaternary unsaturated carbon. Four acetate and fourteen benzoate carbon signals completed the spectrum.

Acetylation of esulone A to form the tetra-acetate (**4**) produced downfield shifts of one tertiary methyl resonance ($\Delta\delta_H$

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* Compounds described in this presentation were named in accord with IUPAC recommendations ('International Union of Pure and Applied Chemistry, Nomenclature of Organic Chemistry: 1979 Edition,' Pergamon, New York, 1979, Section F, p. 491 *et seq.*) as derivatives of a parent jatrophane (**1**) stucture and were numbered according to the previously established jatrophane numbering systems.[20]

Table 1. ^{1}H N.m.r. chemical shifts and multiplicity values of jatrophane diterpenes and derivatives from *E. esula* [δ (*J*/Hz)]. Locants for H atoms refer to the non-crystallographic numbering scheme shown in structure (1)

	(2)	(3)	(4)	(5)	(6)
H(1$_a$)	2.47 (ddd)	2.46 (dd)	2.58 (d)	2.37 (ddd)	2.41 (d)
	(16.5, 1.5, 0.5)	(16.5, 0.5)	(16.5)	(16.5, 1.5, 0.5)	(16.5)
H(1$_e$)	2.93 (dd)	2.92 (dd)	3.62 (d)	2.93 (dd)	2.80 (d)
	(16.5, 1.0)	(16.5, 1.0)	(16.5)	(16.5, 1.0)	(16.5)
H(3)	5.43 (dd)	5.48 (dd)	5.82 (dd)	5.19 (dd)	5.43 (dd)
	(4.0, 1.0)	(4.0, 1.0)	(11.0, 1.5)	(4.0, 11.0)	(4.0, 1.0)
H(4)	3.70 (dd)	3.76 (dd)	3.50 (dd)	3.71 (dd)	3.64 (dd)
	(4.0, 9.0)	(4.0, 9.0)	(4.0, 8.0)	(4.0, 11.0)	(4.0, 4.0)
H(5)	5.98 (d)	5.98 (d)	5.92 (d)	5.74 (d)	5.80 (dd)
	(9.0)	(9.0)	(8.0)	(11.0, 1.5)	(4.0, 1.0)
H(6)				2.07 (dq)	
				[6.5(3), 1.5, 1.0]	
H(7)	6.00 (br s)	6.27 (br s)	6.23 (br s)	5.72 (d)	5.16 (br s)
				(1.0)	
H(8)	4.82 (d)	5.54 (br s)	5.51 (br s)	4.46 (d)	3.73 (br m)
	(9.5)			(9.5)	
H(9)					4.69 (br m)
H(11)	6.03 (d)	6.13 (d)	6.03 (d)	6.07 (d)	5.96 (d)
	(16.0)	(16.0)	(16.0)	(16.0)	(16.0)
H(12)	5.86 (dd)	5.98 (dd)	5.97 (dd)	5.84 (dd)	5.61 (dd)
	(16.0, 9.0)	(16.0, 9.0)	(16.0, 8.0)	(16.0, 9.0)	(16.0, 9.0)
H(13)	4.34 (dq)	4.55 (dq)	3.69 (dq)	4.42 (dq)	4.29 (dq)
	[9.0, 6.5 (3)]	[9.0, 16.5 (3)]	[8.0, 6.5 (3)]	[9.0, 6.5 (3)]	[9.0, 6.5 (3)]
H(17$_A$)*	5.74 (d)	5.69 (d)	5.69 (d)		5.11 (d)
	(1.0)	(1.0)	(1.0)		(1.0)
H(17$_B$)*	6.05 (br s)	5.67 (d)	5.59 (d)		5.38 (d)
	(1.0)	(1.0)	(1.0)		(1.0)
OH(2)	2.32 (d)	2.84 (br s)		2.03 (d)	2.13 (br s)
	(1.5)			(1.5)	
OH(8)	3.30 (d)			3.10 (d)	2.78 (br s)
	(9.5)			(9.5)	
OH(9)					2.73 (br s)
Me(16)	1.31 (s)	1.30 (s)	1.58 (s)	1.31 (s)	1.33 (s)
Me(17)				1.34 (d)	
				(6.5)	
Me(18)	1.34 (s)	1.34 (s)	1.36 (s)	1.17 (s)	1.15 (s)
Me(19)	1.23 (s)	1.23 (s)	1.23 (s)	1.25 (s)	1.23 (s)
Me(20)	1.39 (d)	1.36 (d)	1.39 (d)	1.43 (d)	1.25 (d)
	(6.5)	(6.5)	(6.5)	(6.5)	(6.5)
OAc(2)			2.12 (s)		
OAc(3)	1.94 (s)	1.95 (s)	1.95 (s)	1.89 (s)	1.73 (s)
OAc(8)		2.07 (s)	2.30 (s)		
OAc(15)	2.13 (s)	2.12 (s)	2.13 (s)	2.20 (s)	2.14 (s)
OBz	6.97—7.37 (m)	7.09—7.50 (m)	7.04—7.50 (m)	6.86—7.30 (m)	7.40—7.68 (m)
	7.58—7.69 (m)	7.60—7.73 (m)	7.60—7.70 (m)	7.45—7.75 (m)	7.98—8.12 (m)

* Assignment may be reversed.

0.27 p.p.m.), two geminal-coupled methylene proton resonances (0.11 and 0.69 p.p.m.), and an esterified carbinol methine [H(3)] resonance (0.39 p.p.m.). These observations are consistent with acetylation of a tertiary hydroxy group on a methyl-substituted quarternary carbon between an isolated methylene and an esterified carbinol carbon centre as in the five-membered ring of esulone A. Decoupling experiments confirmed the connectivity of C(4) to C(3) and C(5).

Catalytic reduction of esulone A (2) gave compound (5) whose ^{1}H n.m.r. spectrum displayed an additional secondary methyl signal (δ_H 1.34) compared with that of esulone A. Irradiation of a new secondary methyl methine proton resonance (δ_H 2.07) revealed coupling to two esterified carbinol methine protons (δ_H 5.72 and 5.74), thus indicating the presence of an exo-methylene at C(6) in esulone A between two esterified carbinol carbons [C(5) and C(7)].

Addition of D_2O to the ^{1}H n.m.r. sample of esulone A (2) eliminated a sharp doublet at δ_H 3.30 in the spectrum and

reduced a low-field (δ_H 4.82) doublet to a singlet, clearly defining the existence of a hydrogen-bonded secondary alcohol group in the compound. Decoupling of the low-field carbinol methine doublet also sharpened a low-field [δ_H 6.00, H(7)] esterified carbinol methine proton singlet, thus locating the secondary hydroxy group vicinal to the secondary ester.

Sodium borohydride reduction of esulone A (2) produced compound (6) whose ^{1}H n.m.r. spectrum showed no hydrogen-bonded hydroxy group resonances and one additional carbinol proton signal (δ_H 4.69). After deuterium exchange, the broad resonances at δ_H 3.73 and 4.69 became singlets and irradiation of the δ_H 3.73 resonance sharpened the δ_H 4.69 resonance and that of an esterified carbinol methine resonance (δ_H 5.16) which was unaffected by the deuterium exchange. Since the esterified carbinol methine [C(7)] had been placed adjacent to a secondary alcohol [C(8)] in compound (2), the occurrence of a vicinal diol in compound (6) required a carbonyl group at C(9) in esulone A.

Table 2. ^{13}C N.m.r. chemical shift values for esulone A (2), esulone B (3), and dihydroesulone A (5) (δ_C/p.p.m.).

	(2)	(3)	(4)
C(1)	50.4	51.4	50.3
C(2)	79.0	78.8	79.1
C(3)	80.6	81.0	81.0
C(4)	46.6	47.4	47.6
C(5)	65.9	65.0	66.7
C(6)	137.4	138.3	38.7
C(7)	72.5	73.8	73.3
C(8)	72.5	74.3	74.6
C(9)	211.2	211.6	205.7
C(10)	48.4	49.6	48.3
C(11)	134.1	135.1	132.8
C(12)	134.7	136.2	134.5
C(13)	42.0	42.4	42.0
C(14)	204.9	205.5	207.5
C(15)	90.9	91.0	90.5
C(16)	25.1	25.0	26.0
C(17)	124.0	124.7	13.5
C(18)	23.0	22.6	23.0
C(19)	19.8	19.8	19.8
C(20)	23.5	23.4	24.5
OAc (Me) (3)	21.3	21.2	21.2
OAc (Me) (8)		20.4	
OAc (Me) (15)	20.7	20.7	20.7
OAc (CO) (3)	169.5	169.4	169.5
OAc (CO) (8)		170.3	
OAc (CO) (15)	169.4	169.8	169.7
OBz (CO) (5)	165.9	165.2	165.9
OBz (CO) (7)	164.8	166.2	165.9
Bz(1′)	128.9, 128.6	128.9, 130.0	128.8, 128.8
Bz(2′,6′)	129.2(2 ×),	129.2(2 ×),	129.2(2 ×),
	129.5(2 ×)	129.5(2 ×)	129.5(2 ×)
Bz(3′,5′)	127.7(2 ×),	127.7(2 ×),	127.7(2 ×),
	127.9(2 ×)	127.9(2 ×)	127.9(2 ×)
Bz(4′)	132.7, 132.7	133.6, 133.8	132.5, 132.8

Irradiation of the C(13) methine resonance of compounds (2) and (5) produced a broad doublet from a vinyl double doublet resonance while reducing the C(20) secondary methyl doublet to a broad singlet, thus confirming the allylic relationship of the methyl to the C(11)—C(12) *trans* vinyl group. The proton spin multiplicities of the C(13) methine and the C(11) vinyl proton determined their adjacency to quaternary carbon centres. The low-field position (δ_H 4.34) of the C(13) methine resonance in esulone A (2) suggested the C(13) carbon to be vicinal to the second carbonyl in esulone A and established the C(11)—C(14) fragment of the molecule.

The location of two quaternary carbon centres and two tertiary alkyl methyl groups and the definition of the bicyclic ring system remained in order to complete the structure of esulone A. The high-field position of one quaternary carbon (δ_H 90.9) in the ^{13}C spectrum indicated ester substitution. Moreover, the lack of a high-field methyl resonance (δ_H *ca.* 1.60) in the ^1H n.m.r. spectrum of esulone A (2), as observed for the C(2) methyl in compound (4), indicated that the two unassigned methyls must occur as a gem dimethyl group on the alkyl-substituted quarternary carbon and that the ester-substituted quaternary centre must be a bridgehead carbon. The diamagnetic shift of one tertiary methyl group in compound (6) is consistent with reduced shielding (reduction of an adjacent carbonyl) and placed the gem dimethyl-substituted quaternary centre at C(10). Since C(4) must be a bridgehead carbon it is bonded to the ester-substituted quaternary carbon C(15). Application of terpene biosynthetic considerations requires

attachment of the isolated methylene atom C(1) to C(15), thus forming a cyclopentanol ring and placing the C(11)—C(14) fragment between C(10) and C(15) to define structure (2) for esulone A, exclusive of ester substitution and stereochemistry. The proposed structure is of the same jatrophane structural type described for kansuinine B[14] (7) and the partial structure proposed for jatrophane diterpenes (8) and (9) obtained from *E. characias*.[19] The complete structure and relative stereochemistry of esulone A were determined by single-crystal X-ray analysis, and the absolute stereochemistry was determined by the exciton chirality method.

Esulone B (3) [3,8,15-*Triacetoxy*-5,7-*dibenzoyloxy*-2-*hydroxy-jatropha*-6(17),11-*diene*-9,14-*dione*].—A second diterpene was obtained from absorption chromatography of the mother liquors of esulone A. Esulone B (3) had a ^1H n.m.r. spectrum (Table 1) similar to that of esulone A, with the addition of a third acetate resonance and the absence of hydrogen-bonded hydroxy group/carbinol methine resonances. The spectral data suggested the compound to be the C(8) acetate of esulone A. Mild acetylation of esulone A yielded synthetic compound (3) totally comparable with the natural product and established structure (3) for esulone B.

X-Ray Analysis of Esulone A (2).—The perspective view of esulone A (Figure) depicts the absolute stereochemistry of the
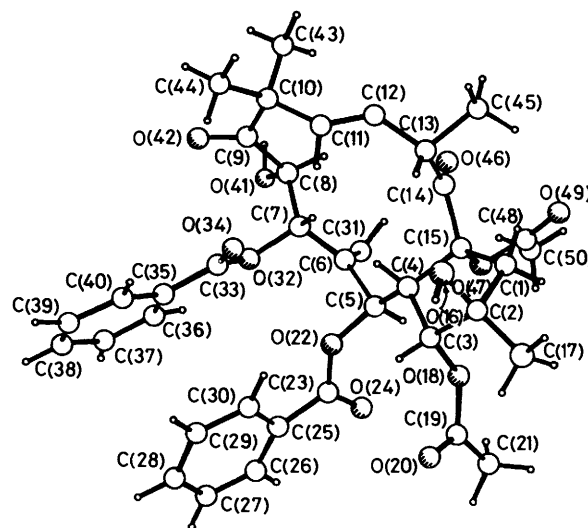

Figure. Perspective view of esulone A (2) with crystallographic numbering scheme. The shaded circles represent oxygen atoms. H(12) and H(31B) occur directly behind the carbons to which they are bonded in this perspective view and are thus not shown.

compound and the atom-numbering system used in the crystallographic analysis. The final atomic co-ordinates and their estimated standard deviation appear in Table 3. The precise molecular geometry of the five- and twelve-membered rings can be seen from the endocyclic torsional angles in Table 4. The observed bond lengths and angles are reported in Tables 5 and 6 respectively. All values are generally within normal accepted ranges except for those of the disordered phenyl ring of the C(5) benzoate group. Aside from the short intermolecular distance between O(16)•••O(20) = 2.85 Å, close contacts in the crystal structure exceed 3.1 Å. An attempt to establish the absolute configuration of the structure by least-square refinement of the parameters of both enantiomers using

Table 3. Non-hydrogen atom co-ordinates ($\times 10^4$) for compound (2). The crystallographic numbering scheme (Figure) is used

Atom	x	y	z
C(1)	2 163(12)	7 483(5)	1 953(5)
C(2)	2 065(12)	7 499(5)	1 236(5)
C(3)	785(11)	6 981(5)	1 118(4)
C(4)	1 042(11)	6 407(4)	1 572(4)
C(5)	−316(13)	5 914(5)	1 641(4)
C(6)	−20(11)	5 251(5)	2 015(4)
C(7)	1 217(13)	4 768(5)	1 765(4)
C(8)	1 862(12)	4 291(5)	2 240(5)
C(9)	3 267(13)	3 923(5)	1 970(5)
C(10)	4 784(13)	4 241(6)	2 002(6)
C(11)	4 074(12)	5 040(5)	1 911(5)
C(12)	4 672(12)	5 476(5)	2 375(5)
C(13)	4 298(12)	6 208(5)	2 276(5)
C(14)	2 732(12)	6 326(4)	2 545(4)
C(15)	1 571(11)	6 765(5)	2 190(4)
O(16)	3 439(8)	7 171(4)	1 018(3)
C(17)	1 812(13)	8 215(5)	988(5)
O(18)	−657(8)	7 308(3)	1 268(3)
C(19)	−1 521(12)	7 549(6)	803(5)
O(20)	−1 194(10)	7 488(5)	266(3)
C(21)	−2 944(13)	7 866(7)	1 045(6)
O(22)	−677(10)	5 700(4)	1 005(3)
C(23)	−2 113(19)	5 745(7)	827(6)
O(24)	−3 089(11)	6 036(6)	1 125(5)
C(25)	−2 380(13)	5 436(5)	186(5)
C(26)	−3 773(13)	5 267(5)	−78(5)
C(27)	−3 828(13)	4 938(5)	−655(5)
C(28)	−2 492(13)	4 778(5)	−968(5)
C(29)	−1 100(13)	4 947(5)	−704(5)
C(30)	−1 044(13)	5 276(5)	−127(5)
C(31)	−818(13)	5 156(5)	2 531(5)
O(32)	535(7)	4 344(3)	1 284(3)
C(33)	1 319(13)	4 295(5)	749(5)
O(34)	2 460(10)	4 619(4)	652(3)
C(35)	621(13)	3 796(5)	310(4)
C(36)	−716(13)	3 501(5)	420(5)
C(37)	−1 298(15)	3 055(6)	−15(5)
C(38)	−467(1)	2 873(5)	−539(5)
C(39)	912(14)	3 175(7)	−641(6)
C(40)	1 453(14)	3 659(6)	−225(5)
O(41)	822(9)	3 797(4)	2 443(4)
O(42)	3 086(10)	3 350(4)	1 765(4)
C(43)	5 408(16)	4 052(6)	2 623(7)
C(44)	5 851(16)	3 962(6)	1 492(7)
C(45)	5 427(12)	6 663(5)	2 643(5)
O(46)	2 408(8)	6 083(4)	3 045(3)
O(47)	260(7)	6 842(3)	2 579(3)
C(48)	452(14)	7 154(6)	3 134(5)
O(49)	1 540(10)	4 493(4)	3 262(3)
C(50)	−902(13)	7 042(6)	3 562(5)

Table 4. Endocyclic torsional angles (°) for 5- and 12-membered rings in compound (2) (e.s.d.s 0.1°)

C(15)–C(1)–C(2)–C(3)	26.1
C(1)–C(2)–C(3)–C(4)	−40.0
C(2)–C(3)–C(4)–C(15)	39.0
C(3)–C(4)–C(15)–C(1)	−21.1
C(4)–C(15)–C(1)–C(2)	−3.7
C(15)–C(4)–C(5)–C(6)	−67.9
C(4)–C(5)–C(6)–C(7)	−59.8
C(5)–C(6)–C(7)–C(8)	158.2
C(6)–C(7)–C(8)–C(9)	−170.3
C(7)–C(8)–C(9)–C(10)	85.8
C(8)–C(9)–C(10)–C(11)	−36.4
C(9)–C(10)–C(11)–C(12)	96.2
C(10)–C(11)–C(12)–C(13)	−167.9
C(11)–C(12)–C(13)–C(14)	108.0
C(12)–C(13)–C(14)–C(15)	−137.4
C(13)–C(14)–C(15)–C(4)	67.8
C(14)–C(15)–C(4)–C(5)	87.8

Table 5. Bond lengths (Å) for compound (2) (crystallographic numbering scheme)

C(1)–C(2)	1.540(15)	C(1)–C(15)	1.580(14)
C(2)–C(3)	1.538(15)	C(2)–O(16)	1.451(13)
C(2)–C(17)	1.509(15)	C(3)–C(4)	1.501(13)
C(3)–O(18)	1.462(13)	C(4)–C(5)	1.545(14)
C(4)–C(15)	1.570(12)	C(5)–C(6)	1.544(14)
C(5)–O(22)	1.461(12)	C(6)–C(7)	1.540(15)
C(6)–C(31)	1.326(14)	C(7)–C(8)	1.492(15)
C(7)–O(32)	1.454(12)	C(8)–C(9)	1.548(16)
C(8)–O(41)	1.402(13)	C(9)–C(10)	1.480(16)
C(9)–O(42)	1.211(13)	C(10)–C(11)	1.571(15)
C(10)–C(43)	1.489(19)	C(10)–C(44)	1.544(19)
C(11)–C(12)	1.308(15)	C(12)–C(13)	1.479(13)
C(13)–C(14)	1.518(15)	C(13)–C(45)	1.550(15)
C(14)–C(15)	1.537(14)	C(14)–O(46)	1.208(12)
C(15)–O(47)	1.436(11)	O(18)–C(19)	1.342(13)
C(19)–O(20)	1.193(14)	C(19)–C(21)	1.495(17)
O(22)–C(23)	1.330(18)	C(23)–O(24)	1.215(19)
C(23)–C(25)	1.519(18)	C(26)–C(27)	1.395(3)
C(25)–C(26)	1.395(3)	C(27)–C(28)	1.395(3)
C(28)–C(29)	1.395(3)	C(29)–C(30)	1.395(3)
C(30)–C(25)	1.395(3)	O(32)–C(33)	1.343(13)
C(33)–O(34)	1.209(14)	C(33)–C(35)	1.489(15)
C(35)–C(36)	1.337(16)	C(35)–C(40)	1.389(15)
C(36)–C(37)	1.375(16)	C(37)–C(38)	1.390(17)
C(38)–C(39)	1.372(19)	C(39)–C(40)	1.383(17)
O(47)–C(48)	1.347(12)	C(48)–O(49)	1.201(15)
C(48)–C(50)	1.525(16)		

acentrically sorted data proved inconclusive, probably because of the molecular disorder of the C(5) benzoate phenyl group.

The absolute configuration of esulone A was determined by the exciton chirality method[22] which has been extensively applied to various natural and synthetic chiral compounds. The interaction of the C(5) and C(7) benzoate chromophores of esulone A produce a negative first (longer wavelength) Cotton effect ($\Delta\varepsilon_{242}$ −15.7) which reflects negative chirality for compound (2). The observed negative chirality coupled with an observed intramolecular dihedral angle of 21.9° between the C(5)–O(22) and C(7)–O(32) bonds and the molecular conformation determined in the X-ray analysis of esulone A clearly specifies the 5R,7S configurations in compound (2) and the absolute molecular configuration (2R,3R,4R,5R,7S,8R,-13S,15R) as shown in the Figure. A negative first c.d.

Cotton effect ($\Delta\varepsilon_{241}$ −15.7) observed for dihydroesulone A (5) establishes the dibenzoate chromophore interaction of esulone A to be exclusively with the C(17) methylene group.

The X-ray analysis confirmed the proposed structure (2) for esulone A and established a trans C(4)–C(15) ring junction in the compound as described in the absolute stereochemical description of kansuinine B and the euphoscopins.[18] The carbonyls at C(9) and C(14) and the exo-methylene as C(6) are also observed in kansuinine B (7), and the trans C(11)–C(12) double bond occurs in the euphoscopins.

Consideration of the absolute configuration of the asymmetric centres of esulone A showed the C(5) and C(7) benzoates as α and β respectively while both acetates [C(3), C(15)] occur as β substituents. The methyl groups at C(2) and C(13) are β substituted and the hydroxy groups at C(2) and C(8) occur as α substituents. The planar stereochemical representation of

Table 6. Bond angles (°) for compound (2) (crystallographic numbering scheme)

C(2)–C(1)–C(15)	108.7(8)	C(1)–C(2)–C(3)	101.1(8)
C(1)–C(2)–O(16)	105.4(8)	C(3)–C(2)–O(16)	105.9(8)
C(1)–C(2)–C(17)	112.3(9)	C(3)–C(2)–C(17)	116.1(9)
O(16)–C(2)–C(17)	114.7(9)	C(2)–C(3)–C(4)	105.8(8)
C(2)–C(3)–O(18)	108.7(8)	C(4)–C(3)–O(18)	108.3(8)
C(3)–C(4)–C(5)	114.1(8)	C(3)–C(4)–C(15)	105.1(7)
C(5)–C(4)–C(15)	115.3(7)	C(4)–C(5)–C(6)	115.9(9)
C(4)–C(5)–O(22)	105.0(7)	C(6)–C(5)–O(22)	106.4(7)
C(5)–C(6)–C(7)	116.9(8)	C(5)–C(6)–C(31)	117.4(9)
C(7)–C(6)–C(31)	125.7(9)	C(6)–C(7)–C(8)	114.5(8)
C(6)–C(7)–O(32)	107.5(8)	C(8)–C(7)–O(32)	106.8(7)
C(7)–C(8)–C(9)	109.9(9)	C(7)–C(8)–O(41)	113.0(9)
C(9)–C(8)–O(41)	108.9(8)	C(8)–C(9)–C(10)	121.1(9)
C(8)–C(9)–O(42)	117.2(10)	C(10)–C(9)–O(42)	121.6(10)
C(91)–C(10)–C(11)	111.7(9)	C(9)–C(10)–C(43)	105.9(10)
C(11)–C(10)–C(43)	111.9(9)	C(9)–C(10)–C(44)	112.0(10)
C(11)–C(10)–C(44)	106.8(9)	C(43)–C(10)–C(44)	108.6(10)
C(10)–C(11)–C(12)	123.4(10)	C(11)–C(12)–C(13)	121.5(10)
C(12)–C(13)–C(14)	107.2(8)	C(12)–C(13)–C(45)	109.6(8)
C(14)–C(13)–C(45)	108.0(8)	C(13)–C(14)–C(15)	120.4(8)
C(13)–C(14)–O(46)	119.6(9)	C(15)–C(14)–O(46)	119.9(9)
C(1)–C(15)–C(4)	102.7(7)	C(1)–C(15)–C(14)	115.6(8)
C(4)–C(15)–C(14)	111.7(7)	C(1)–C(15)–O(47)	111.2(7)
C(4)–C(15)–O(47)	107.2(7)	C(14)–C(15)–O(47)	108.1(7)
C(3)–O(18)–C(19)	119.1(8)	O(18)–C(19)–O(20)	122.9(10)
O(18)–C(19)–C(21)	111.4(10)	O(20)–C(19)–C(21)	125.5(11)
C(5)–O(22)–C(23)	117.2(9)	O(22)–C(23)–O(24)	124.0(12)
O(22)–C(23)–C(25)	113.5(11)	O(24)–C(23)–C(25)	123.4(14)
C(27)–C(26)–C(25)	120.0(1)	C(26)–C(27)–C(28)	120.0(1)
C(27)–C(28)–C(29)	120.0(1)	C(28)–C(29)–C(30)	120.0(1)
C(29)–C(30)–C(25)	120.0(1)	C(23)–C(25)–C(26)	126.7(8)
C(23)–C(25)–C(30)	113.1(8)	C(26)–C(25)–C(30)	120.0(1)
C(7)–O(32)–C(33)	115.6(8)	O(32)–C(33)–O(34)	122.8(10)
O(32)–C(33)–C(35)	111.9(9)	O(34)–C(33)–C(35)	125.3(10)
C(33)–C(35)–C(36)	122.4(10)	C(33)–C(35)–C(40)	115.4(10)
C(36)–C(35)–C(40)	122.2(10)	C(35)–C(36)–C(37)	118.9(10)
C(36)–C(37)–C(38)	120.8(12)	C(37)–C(38)–C(39)	119.3(11)
C(38)–C(39)–C(40)	119.8(11)	C(35)–C(40)–C(39)	118.7(11)
C(15)–O(47)–C(48)	117.3(8)	O(47)–C(48)–O(49)	123.6(10)
O(47)–C(48)–C(50)	111.6(9)	O(49)–C(48)–C(50)	124.7(10)

esulone A, as determined by X-ray crystallography, is shown in structure (2).

A comparison of the X-ray analyses of esulone A (2) and kansuinine B (7) showed the same absolute stereochemistry at C(2)—C(5), C(8), C(13), and C(15) and opposite stereochemistry at C(7). The observed stereochemistry of the C(2), C(3), C(4), and C(15) carbons and the *trans* cyclopentane ring junction were in accord with those determined for two lathyrane diterpenes [6,17-epoxylathyrol[23] (10) and 7-hydroxylathyrol[24] (11)] which served as reference compounds for the designation of proposed relative stereochemistry of the lathyrane and jatrophane diterpenes obtained from *E. characias*.[19,25] The observed α substitution of C(5) in esulone A and kansuinine B is contrary to the proposed C(5) β substitution of the *E. characias* diterpenes established by comparison to the reference lathyranes obtained from *E. lathyris*.

The lathyrane and jatrophane diterpenes are considered to originate biogenetically from a common parent diterpene (cembrene) and the lathyrane diterpenes are postulated as biogenetic precursors of the ingenol diterpenes.[26] The occurrance of stereochemically identical samples of the ingenol diterpene ingenol 3,5,17-triacetate in *E. lathyris*[27] and *E. esula*[12] suggests that the lathyrane, and related jatrophane, diterpene precursors should be stereochemically similar. The opposing stereochemistry at C(5) of the *E. lathyris* lathyranes

and *E. esula* jatrophanes was biogenetically inconsistent and prompted a close examination of the published stereochemical data for the lathyrane reference compounds.

Our examination of the published stereochemical perspective views of the lathyrane reference compounds and consideration of corresponding molecular models clearly suggested α substitution at C(5) as observed in esulone A and kansuinine B. A similar examination by Uemura *et al.*[16] may have led to the stereochemical description of the lathyrane diterpene jolkinols, which were chemically converted into hydroxylathyrol, to include α substitution at C(5). These authors, in a biogenetic scheme, include stereochemical representations of 7-hydroxylathyrol and 6,17-epoxylathyrol which are in accord with our interpretation of the original perspectives of these compounds [α at C(5) and β at C(7)], but opposed to the earlier stereochemical designation of C(5) and C(7) in the reference lathyranes.

Although the original X-ray analysis of the reference lathyrane diterpenes established their absolute configuration, no specific configurational data were reported and most planar representations of these compounds did not show the stereochemistry at C(5) and C(7). The contrary interpretation of the X-ray stereochemical perspectives of these compounds emphasizes the necessity for a specific configurational description of the two lathyrane compounds to provide an accurate stereochemical basis for relative stereochemical proposals for related compounds. Precise relative or specific configuration of asymmetric centres in the lathyrane and jatrophane diterpenes would, of course, require X-ray analysis or equivalent physical data for individual compounds.

Esulones A and B from *E. esula* are the first jatrophane diterpenes reported in this plant. The co-occurrence of these compounds establishes the biosynthesis of a stabilized keto–enol tautomer (esulone A) in this plant, which undergoes further esterification (esulone B). Based upon biological assay results, these compounds do not appear to be major factors in the reported allelopathy or toxicity of leafy spurge.

The exclusive distribution of jatrophane diterpenes in Euophorbiaceae and this report of their occurrence in *E. esula* may aid the biological control of leafy spurge in North America. The inability to control *E. esula* in North America with insects predatory to European leafy spurge may be attributed to many factors (*e.g.*, environment, climate, competition); taxonomic evidence, however, suggests that the two leafy spurge species may be different. Morphological definition of the North American species is difficult and has led to the recognition of several morphologically different accessions[28] and the subsequent proposed naming of the North American spurge as *E. esula-virgata*. A chemical analysis of leaf wax triterpenes[8] supports the variability within the North American species and recognizes distinct differences between the European and North American species. The higher yield, exclusive family distribution, location in the plant, and unique structural character of the jatrophane diterpenes seems to provide a more precise chemical basis for the taxonomic differentiation of *Euphorbia* species. The presence (or absence) of these compounds may accurately define predator-susceptible European leafy spurge and aid in the location of similar spurge species in North America which can be subjected to the European predators for an accurate evaluation of predator susceptibility and the potential for biological control.

Experimental

M.p.s are uncorrected. ^1H and ^{13}C n.m.r. spectra were obtained for $CDCl_3$ or $(CD_3)_2CO$ solutions on a Nicolet NMC-200 (200 MHz) spectrophotometer and a Joel Model PS-100

spectrophotometer respectively. ^{13}C n.m.r. assignments were determined on the basis of substitution character as obtained from inversion-recovery ^{13}C spectra and ^{13}C–^{1}H multiplicity/chemical shift relationships observed in variable single-frequency off-resonance decoupling experiments. Optical rotations were run on a Perkin-Elmer Model 241 polarimeter. Ammonia/C.I. (chemical ionization) mass spectra were obtained on a VG-micromass 70/70 spectrophotometer. C.d. measurements were obtained on a Cary Model 60 spectro-polarimeter with a 6003 CD attachment. Analytical and semi-preparative h.p.l.c. was performed on silica gel columns on a Waters h.p.l.c. system utilizing u.v. detection.

Extraction of Euphorbia esula.—Root material of flowering *E. esula* was collected near Fargo, North Dakota in June 1983. The material was air dried (4.3 kg), hammermilled to pass a $\frac{1}{8}''$ screen and sequentially extracted with n-hexane, diethyl ether, acetone, and methanol for one-week periods in a soxhlet extractor. The resulting extracts were concentrated to dryness under reduced pressure and stored (0 °C).

Ether Extract

A portion (5 g) of the ether extract (28.1 g) was dissolved/suspended in diethyl ether (300 ml) and the mixture was extracted with aqueous 10% NaOH (2 × 100 ml). The ether-soluble layer was separated from an emulsified aqueous layer and washed with water (2 × 100 ml), dried (MgSO$_4$), and concentrated to dryness (1.9 g). The ether-soluble material was redissolved in minimal CHCl$_3$–MeOH (1:1) and applied to an LH-20 chromatographic colum (2.5 cm × 50 cm). The column was eluted with CHCl$_3$ and twenty 125-ml fractions were collected. The fractions were concentrated to dryness under reduced pressure and fractions 5—7 contained crystalline material. These fractions were recombined and crystallization (acetone–MeOH) gave crude crystals. The mother liquors were further crystallized (3 ×) to obtain similar crystalline material. The final mother liquors were concentrated for semi-preparative h.p.l.c. chromatography (see Esulone B, below).

Esulone A (**2**) [(E)-(−)-(2R,3R,4S,5R,7S,8R,13S,15R)-3,15-Diacetoxy-5,7-dibenzoyloxy-2,8-dihydroxyjatropha-6(17),11-diene-9,14-dione]. The crude crystals obtained from the fractional crystallization of the LH-20 chromatographic fractions were recrystallized (MeOH, with carbon) to obtain *esulone A* (**2**) as needles (343 mg), m.p. 288—292 °C (Found: C, 66.2; H, 6.2. C$_{38}$H$_{42}$O$_{12}$ requires C, 66.1; H, 6.13%); [α]$_D^{20}$ +10.6° (c 10.4 in acetone); c.d. (MeOH) Δε$_{242}$ −15.7, Δε$_{228}$ +11.6; λ$_{max.}$ (MeOH) 210 (ε$_{max.}$ 12 000), 232 (17 000), and 276 nm (1 500); ν$_{max.}$ (KBr) 3 500s (OH), 3 000s (OH), 1 740s br (ester CO), 1 712s (CO), 1 603m (phenyl), 1 589m (phenyl), 1 460w, 1 385w, 905w, and 715s cm^{-1}; M^+ + NH$_4$, 708.2983; m/z (%) 708 (57), 569 (31), 466 (15), 449 (8), 140 (76), and 122 (100). ^{1}H and ^{13}C N.m.r. data (Tables 1 and 2).

Esulone B (**3**) [(E)-(−)-(2R,3R,4S,5R,7S,8R,13S,15R)-3,8,15-Triacetoxy-5,7-dibenzoyloxy-2-hydroxyjatropha-6(17),11-diene-9,14-dione]. The concentrated mother liquors from crystallization of esulone A were applied to a preparative silica gel chromatographic column (5.0 cm × 50 cm) and eluted with CHCl$_3$ (200-ml fractions). Fraction 4 (178 mg) was rechromatographed on a silica gel semi-preparative h.p.l.c. column [hexane–EtOAc (3:1), 2-ml fractions]. Fractions 41—46 were combined and rerun on the same column [hexane–propan-2-ol (50:1.5)] monitored by u.v. spectroscopy. The fraction (R_t 2.7) containing esulone B (**3**) was concentrated to dryness and *esulone B* was recrystallized (MeOH) as needles (21 mg), m.p. 274—276 °C; [α]$_D^{20}$ −8.3° (c 5.05 in acetone); c.d. (MeOH) Δε$_{241}$ −15.7, Δε$_{223}$ +2.59 (Found: C, 65.4; H, 6.1. C$_{40}$H$_{44}$O$_{13}$ requires C, 65.5; H, 6.05%); M^+ + NH$_4$, 750.3021;

m/z (%) 751 (12), 733 (2), 672 (1), 630 (1), 611 (2), 550 (1), 490 (2), 122 (24), and 105 (100). ^{1}H and ^{13}C N.m.r. data (Tables 1 and 2).

Synthesis of Esulone B.—Esulone A (15 mg) was acetylated (Ac$_2$O–pyridine; 25 °C; 4 h) and the resulting acetylation mixture was semi-preparatively chromatographed [h.p.l.c.; hexane–propan-2-ol (50:1)] to obtain esulone B (**3**) (8 mg). The synthetic esulone B was identical in all physical and spectral properties with natural esulone B, and a mixed m.p. showed no depression.

Esulone A Diacetate (**4**) (2,3,8,15-*Tetraacetoxy-5,7-dibenzoyl-oxyjatropha*-6,(17),11-*diene*-9,14,*dione*).—Acetylation of esulone A (**2**) (20 mg) (Ac$_2$O–pyridine; 80 °C; 2 h) yielded the diacetate (**4**) as needles (from MeOH) (17 mg), m.p. 198—200 °C (Found: C, 65.1; H, 6.0. C$_{42}$H$_{46}$O$_{14}$ requires C, 65.1; H, 5.98%); Isobutane C.I., MH^+ 775.2943; m/z (%) 775 (2), 715 (3), 653 (6), 593 (2), 551 (3), 533 (2), 473 (2), 413 (2), 355 (3), 353 (3), 295 (3), 293 (2), 123 (100), and 105 (16). ^{1}H N.m.r. data (Table 1).

Dihydroesulone A (**5**) (3,15-*Diacetoxy-5,7-dibenzoyloxy-2,8-dihydroxyjatroph*-11-*ene*-9,14-*dione*).—Esulone A (20 mg) was dissolved in EtOAc (4 ml), 5% Pd–carbon was added, and the mixture was hydrogenated (48 p.s.i.) with agitation for 6 h. The hydrogenation mixture was filtered, concentrated to dryness, and recrystallized from MeOH to yield the *title compound* (**5**) as crystals (15 mg), m.p. 289—292 °C (Found: C, 66.0; H, 6.4. C$_{38}$H$_{44}$O$_{12}$ requires C, 65.9; H, 6.40%); M^+ + NH$_4$, 710.3201; m/z (%) 710 (35), 590 (7), 588 (7), 571 (4), 530 (3), 451 (2), 408 (3), 315 (9), 313 (8), 140 (46), 122 (61), and 105 (100). ^{1}H and ^{13}C N.m.r data (Tables 1 and 2).

NaBH$_4$-*reduced Esulone A,* (**6**) (3,15-*Diacetoxy-5,7-dibenzoyl-oxy-2,8,9-trihydroxyjatropha*-6(17),11-*dien*-14-*one*).—Esulone A (**2**) (18 mg) was dissolved in EtOH (8 ml), the solution was cooled to 0 °C, and NaBH$_4$ (30 mg) was added. The mixture was stirred while being allowed to attain room temperature during 4 h. It was then acidified and extracted with ether and the ether-soluble portion was dried (MgSO$_4$), concentrated to dryness, and semi-preparatively chromatographed [h.p.l.c.; hexane–propan-2-ol (100:7)] and fractions were collected according to u.v. absorption. A fraction (R_t 6.2) was concentrated and recrystallized (acetone–MeOH) to yield the *triol* (**6**) as needles (6 mg), m.p. 154—157 °C (Found: M^+ + NH$_4$, 710.3180. C$_{38}$H$_{48}$NO$_{12}$ required m/z, 710.3177); m/z (%) 710 (13), 571 (8), 555 (3), 511 (1), 449 (8), 299 (5), 297 (5), 271 (5), 165 (14), 140 (40), 105 (88), and 35 (100). ^{1}H N.m.r. data (Table 1).

X-Ray Analysis

Crystal Data.—Esulone A (**2**), C$_{38}$H$_{42}$O$_{12}$, M = 690.8, or-thorhombic, space group $P2_12_12_1$, a = 8.847(3), b = 19.496(4), c = 21.445(5) Å, V = 3 699(1) Å^3, Z = 4, D_c = 1.24 g cm^{-3}, $F(000)$ = 1 464, (Cu-K_α) = 7.29 cm^{-1}. Esulone A yielded poor crystals and the crystals used gave limited diffraction data.

Intensity data were measured on a Nicolet R3 diffractometer with graphite-monochromatized Cu-K_α radiation (λ 1.5418 Å) by θ–2θ scan technique with variable scan speed at room temperature. Of the 2 968 independent reflections measured within the range 3 ≤ 2θ ≤ 114°, 2 203 were considered as observed with $|F_o| \geq 3\sigma|F_o|$. The data were corrected for background, Lorentz, and polarization effects, but not for absorption or extinction. The crystal structure was solved by direct methods and refined by a 'blocked cascade' full-matrix least-squares procedure with the SHELXTL[29] program package. Structure refinement disclosed a minor molecular disorder in the crystal. Atoms [C(26)—C(30)] of the phenyl unit exhibit extremely high thermal vibrational motions and assume partial

occupancies at different crystallographic positions. This effect suggests that the [C(23)–C(25)] single bond is undergoing a significant degree of oscillation. Convergence of this partially disordered structure was accomplished by applying a constrained least-squares refinement in which the disordered phenyl unit was input as a rigid planar ring with C–C bond lengths of 1.395 Å. In the final cycles of refinement, the six C atoms of the disordered phenyl ring were refined with individual isotropic temperature factors and all other non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in their calculated positions with a common fixed temperature factor of $U = 0.08$ Å^2. The weighted scheme applied was $w = [\sigma^2(F_0) + 0.001 \, F^2_0]^{-1}$, and the final R value was $R = 0.090$, $R' = 0.093$. A final difference Fourier map showed five peaks, each of about 1 e Å^{-3}, lying in close proximity to the disordered phenyl ring. These peaks are consistent with a possible vibrational disorder in the plane of the ring. Tables of isotropic and anisotropic thermal parameters of the non-hydrogen atoms have been deposited as Supplementary Publication No. SUP 56302 (3 pp.)* The X-ray molecular structure is shown in the Figure, together with the crystallographic numbering scheme.

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* For details of the Supplementary Publications Scheme, see Instructions for Authors (1985), J. Chem. Soc., Perkin Trans. 1, issue 1. Structure factors are available from the editorial office on request.

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