Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.56; H, 9.53.

General Procedure for the Lewis Acid Catalyzed Rearrangement of 10 and 11. **10** or **11** (8.6 g, (0.05 mol) is dissolved in 100 mL of CH_2Cl_2 and cooled to -78 °C. $BF_3{\cdot}Et_2O$ (1 mL) is added, and the reaction mixture is stirred for 3 h at -78 °C. Then the reaction mixture is poured into 100 mL of aqueous K_2CO_3 solution. The organic layer is washed twice with K_2CO_3 solution, and the aqueous layer is extracted with 20 mL of CH_2Cl_2. The combined organic layers are dried (K_2CO_3). After filtration and evaporation of the solvent the crude products are distilled in vacuo. Analytically pure samples are obtained by spinning band distillation. **(2*R**,3*R**)-2,3-Dimethyl-3,4-(isopropylidenedioxy)butanal (12)**: colorless liquid (7.6 g, 88%, 79% ds); bp 70 °C/10 Torr; IR (film) 2995, 2940, 2880, 2730, 1725, 1455, 1380, 1370, 1250, 1215, 1120, 1110, 985, 950, 925, 905, 870, 845, 800 cm^{-1}; ^1H NMR (CCl_4) δ 9.62 (1, d, J = 1.6 Hz, CHO), 3.85, 3.72 (2, 1 each, d, J = 9 Hz, CH_2), 2.51 (1, qd, J = 7.2, 1.6 Hz, O=CC*H*CH_3), 1.35, 1.30 (6, 3 each, q, J = 0.6 Hz, CH_3CCH_3), 1.24 (3, br s, CH_2CCH_3) 1.16 (3, d, J = 7.2 Hz, O=CCCH_3); ^{13}C NMR (C_6D_6) δ 202.12 (CO), 109.04 (CH_3CCH_3), 81.18 (*C*HOC), 72.91 (CH_2OC), 54.16 (O=*C*C), 27.21, 26.69 (CH_3CCH_3), 22.81 ($OCCH_3$), 9.23 (O=CCCH_3). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.55; H, 9.44. **(2*S**,3*R**)-2,3-Dimethyl-3,4-(isopropylidenedioxy)butanal (13)**: colorless liquid (7.5 g, 87%, 73% ds); bp 75-76 °C/16 Torr, IR (film) 3080, 2990, 2940, 2875, 1650, 1460, 1425, 1410, 1380, 1375, 1275, 1240, 1225, 1180, 1160, 1110, 1070, 1055, 995, 920, 890, 865, 830, 795 cm^{-1}; ^1H NMR (CCl_4) δ 9.70 (1, d, J = 1.6 Hz, CHO), 3.85, 3.66 (2, 1 each, d, J = 9 Hz, CH_2), 2.50 (1, qd, J = 7.2, 1.6 Hz, O=CC*H*CH_3), 1.37, 1.37 (6, 3 each, q, J = 0.6 Hz, CH_3CCH_3) 1.22 (3, br s, CH_2CCH_3), 1.01 (3, d, J = 7.2 Hz, O=CCCH_3); ^{13}C NMR (C_6D_6) δ 202.12 (CO), 109.78 (CH_3CCH_3), 81.89 (*C*HOC), 72.16 (CH_2OC), 54.08 (O=*C*C), 27.21, 26.97 (CH_3CCH_3), 22.20 ($OCCH_3$), 9.63 (O=CCCH_3). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.50; H, 9.36.

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Registry No. **8**, 19358-05-5; **9**, 113273-97-5; **10**, 113273-98-6; **11**, 113273-99-7; **12**, 113274-00-3; **13**, 113274-01-4; allyl alcohol, 107-18-6.

Intra- and Intermolecular Diels-Alder Reactions of Glutaconaldehyde Derivatives

Jan Becher,* Helle Chris Nielsen, Jens Peter Jacobsen, Ole Simonsen, and Helen Clausen

Odense University, Department of Chemistry, DK-5230 Odense M, Denmark

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The intramolecular Diels-Alder reaction of the alcohols **10a-d** and maleic anhydride gave the cis-fused cycloadducts **12a-d**, whereas the esters **13a** and **13c** prepared from **10a** and fumaric acid ethyl or methyl ester monochloride produced trans-fused adducts **14a** and **14c**, respectively. The trienes **16-22** did not undergo intramolecular Diels-Alder reaction even at 240 °C, whereas the acetylene system **24** (corresponding to the olefin system **16**) underwent Diels-Alder reaction to **26** at 60 °C. The acid group in **12a** or **12b** could be esterified to **27-30** and the cyclohexene unit in **14a** or **27a** was brominated. The alcohol **10a** with protection of the hydroxy group was able to participate in the intermolecular Diels-Alder reaction with a range of dienophiles.

Introduction

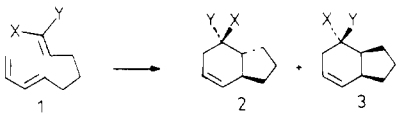
Compared to the intramolecular version, the IMDA (intramolecular Diels-Alder) reaction is more effective due to entropy, reactivity, and regio-, stereo-, and diastereoselectivity. As a result there has been an explosive growth in the study and application of the IMDA reaction.[1]

Normally trans dienes give the fused products[2] exclusively, in the majority of intramolecular Diels-Alder reactions.

Trans dienes containing chains of three or four atoms constitute the majority of substrates known to undergo the IMDA reaction. These may cyclize via either the syn transition state to give the cis-fused product or the anti transition state to give the trans-fused product. Chain length, substitutents on the chain, type of diene, type of dienophile, and catalysts are factors that influence the stereochemistry.

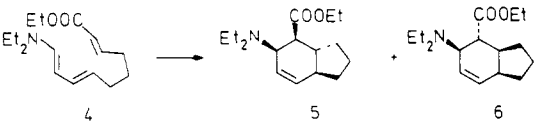
Trans dienes with three carbon atoms in the chain connecting the diene and the dienophile and an electron-withdrawing substituent on the terminal carbon atom of the dienophile (an activated dienophile) cyclize preferentially via the anti transition state to give mainly the trans-fused cycloadducts. Roush[3] found that **1a** (Scheme I) underwent cycloaddition to give a mixture of trans-fused hydroindane **2a** and the cis-fused isomer **3a** in the ratio 60:40, indicating that the anti transition state prevailed

Scheme I

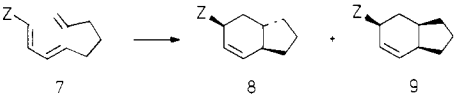


a: X = COOMe, Y = H
b: X = H, Y = COOMe

Scheme II



Scheme III



a: Z = H
b: Z = COOEt

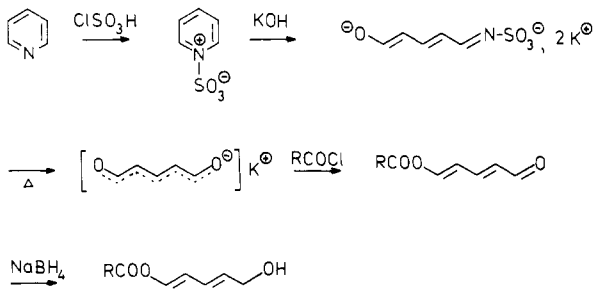
(1) For recent reviews, see: (a) Carlson, R. G. *Ann. Rep. Med. Chem.* **1974**, *9*, 270. (b) Oppolzer, W. *Angew. Chem.* **1977**, *89*, 10. (C) Brieger, G.; Bennett, J. *Chem. Rev.* **1980**, *80*, 63. (d) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (e) Taber, D. F. *Intramolecular Diels-Alder Reactions and Alder-Ene Reactions*; Springer Verlag: New York, 1984. (f) Ciganek, E. *Org. React. (N.Y.)* **1984**, *23*, 5-355.

(2) Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, *30*, 2537.

(3) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.

0022-3263/88/1953-1862$01.50/0

Scheme IV



in this instance. The stereoselectivity was independent of the stereochemistry of the dienophile as **1b** also preferred cyclization via the anti transition state to afford a mixture of the trans-fused **2b** and the cis-fused **3b** in the ratio 65:35; this result was one of many violations of the Alder endo rule. A possible reason for the preference of the anti transition state in both cases has been explained in terms of nonsynchronous bond formation.[1f]

An electron-donating substituent situated on the diene will cause an increased selectivity in favor of anti addition. Houk[4] observed that **4** underwent cyclization to afford a mixture of trans-fused **5** and cis-fused **6** (Scheme II) in the ratio 85:15 (where the triene **1a** gave a trans:cis ratio of 60:40).

Houk[5,6] also found that nonactivated dienophiles gave preference for the cis-fused product. Thus, **7a** afforded cis-fused **9a** in a threefold excess over the corresponding trans-fused product **8a** (Scheme III) while **7b** gave a mixture of trans-fused **8b** and cis-fused **9b** in the ratio 43:57, showing the lesser selectivity when the diene was substituted with an ester group. This result also demonstrated that an ester group on the diene caused the same effect in stereoselectivity, as it did when situated on the dienophile, but the effect in the latter case was considerably more significant.

Results

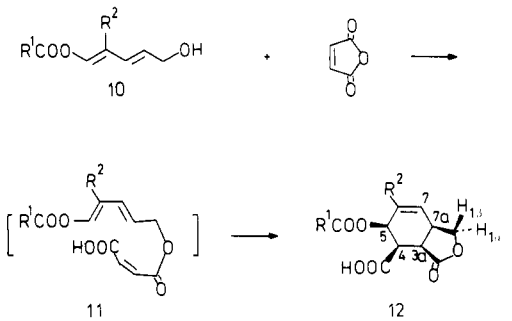
The inviting prospect of employing the IMDA reaction for assembling functionalized cyclohexene rings common to certain terpenoids led us to examine the thermal reaction of the *all*-trans-1-(acyloxy)-1,3-pentadien-5-ols bearing an appropriate dienophile moiety.[7]

The *all-trans*-1-(acyloxy)-1,3-pentadien-5-ols **10a–d** were readily prepared in few steps from pyridines in high yields. The first step was the preparation of the glutaconaldehyde anion[8] (Scheme IV). The anion reacted with acid chlorides to give the thermodynamically stable all-trans enol esters.[9] These were reduced by sodium borohydride to give the alcohols.[10]

A number of suitable dienophiles could be connected to the pentadienols, thus making it possible in a convergent route to prepare diene and dienophile separately followed by ester bond formation prior to IMDA cyclization.

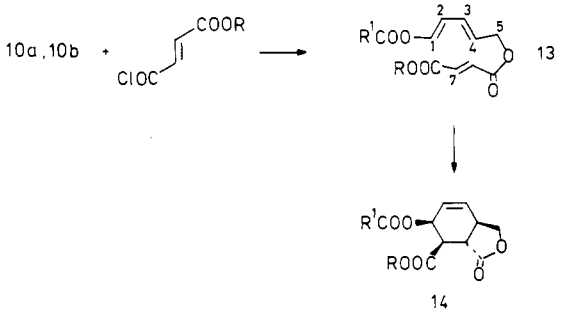
When the mixture of pentadienol **10** and maleic anhydride was heated at reflux in chloroform for 4 h, a single crystalline product (**12a**) was formed in good yield. The

Scheme V



	R^1	R^2
a	C_6H_5	H
b	$C_6H_5CH{=}CH$	H
c	C_6H_5	CH_3
d	C_2H_5O	H

Scheme VI



	R^1	R
a	C_6H_5	Et
b	$C_6H_5CH{=}CH$	Et
c	C_6H_5	Me

intermediate half-ester **11a** could not be isolated (Scheme V).

The IR spectrum of **12a** showed the carbonyl frequency (1770 cm^{-1}) expected for a γ-lactone. The configuration of the four, newly generated chiral centers of the product could be deduced from careful analysis of the NMR spectra (Tables I and II). Thus, a coupling constant of J(3a7a) = 8.5 Hz between H(3a) and H(7a) is consistent only with a cis-fused ring system[11,12] while the appearance of the coupling constants J(45) 4.0 Hz and J(3a4) = 4.8 Hz showed that the protons H(4), H(5), and H(3a) are situated at the same side of the ring system. An investigation of the mother liquor showed that the trans-fused isomer was not formed at all. It therefore appeared that **11a** underwent IMDA reaction exclusively via the syn transition state.

The same reactions were carried out with the pentadienols **10b–d** and maleic anhydride. This resulted in clean formation of the cis-fused lactones **12b–d**, indicating cyclization via the syn transition state.

With fumaric acid ethyl ester monochloride,[13] as the dienophile, the triene ester **13a** could be isolated (Scheme VI). Exposure of **13a** to refluxing xylene for 18 h gave the cycloadduct **14a** in high yield. The IR spectrum showed again a γ-lactone carbonyl frequency (1780 cm^{-1}) and although the NMR spectra of **14a** (Tables I and II) showed features similar to those found in **12a**, a significant difference was that the coupling constant J(3a7a) = 13.3

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Table I. Selected ^{1}H NMR Spectral Data for the IMDA Products[a] (δ in ppm from TMS, J in Hz, (m) Multiplicity)

compd[b]	H(1α) J(1α1β) J(1α7a)	H(1β) J(1β7a)	H(3a) J(3a7a)	H(4) J(3a4)	H(5) J(45)	H(6) J(56) J(67a)	H(7) J(67)	H(7a) J(77a)
12a[2]	4.12 (dd)	4.48 (dd)	3.66 (dd)	3.30 (dd)	5.80 (m)	6.14 (ddd)	5.99 (dd)	3.38 (m)
	9.2 1.88	6.7	8.5	4.8	4.0	5.6	9.9	2.9
12b[3]	4.11 (dd)	4.42 (dd)	3.62 (dd)	3.30 (dd)	5.55 (m)	5.99 (m)	5.94 (m)	3.28 (m)
	9.6 1.2	7.2	8.4	4.8	4.8	5.6	10.4	3.0
12c[3]	4.19 (dd)	4.49 (dd)	3.69 (dd)	3.42 (dd)	5.92 (d)		5.74 (dd)	3.38 (m)
	8.8 1.0	6.7	8.2	4.7	3.9			2.8
12d[3]	4.08 (dd)	4.37 (dd)	3.51 (dd)	3.32 (dd)	5.33 (m)	5.95 (m)	5.94 (m)	3.27 (m)
	9.0 1.5	7.2	8.8	5.1	4.2	4.5	10.5	3.0
14a[1]	4.55 (dd)	4.06 (dd)	3.00 (dd)	3.14 (dd)	5.94 (dddd)	6.08 (ddd)	6.17 (ddd)	2.95 (m)
	8.1 6.5	11.1	13.3	11.7	5.5	3.8 2.6	9.8	1.5
14b[1]	4.55 (dd)	4.05 (dd)	2.95 (d)	3.68 (dd)	5.86 (dddd)	5.99 (ddd)	6.15 (ddd)	2.86 (m)
	8.1 6.2	11.1	13.2	11.7	5.5	4.0 2.5	10.0	1.5
14c[1]	4.54 (dd)	4.05 (dd)	2.98 (dd)	3.13 (dd)	5.91 (dd)	6.06 (ddd)	6.17 (d)	2.9 (m)
	8.1 6.3	10.9	13.3	11.4	5.2	3.6 2.7	9.8	
26[1]	4.68 (dd)	4.0 (dd)			6.08[c]	6.08[c]	6.53 (dd)	3.72 (ddd)
	8.2 8.2	10.6				10.7	1.6	10.7
27a[1]	4.18 (dd)	4.45 (dd)	3.67 (dd)	3.17 (dd)	5.92 (m)	6.25 (ddd)	5.90 (d)	3.30 (m)
	9.1 1.6	7.1	8.7	4.8	4.3	5.5 2.0	9.9	
28a[1]	4.18 (dd)	4.45 (dd)	3.58 (dd)	3.17 (dd)	5.9 (m)	6.24 (ddd)	5.9 (m)	3.30 (m)
	9.2 1.8	7.1	8.6	4.8	4.1	5.4 2.0	10.0	
29a[1]	4.18 (dd)	4.45 (dd)	3.68 (dd)	3.14 (dd)	5.92 (m)	6.23 (ddd)	5.90 (dd)	3.32 (m)
	9.1 1.6	6.8	8.5	4.7	4.1	5.4 2.1	9.9	2.8
30a[1]	4.14 (dd)	4.45 (dd)	3.62 (dd)	3.14 (dd)	5.78 (dd)	6.20 (ddd)	5.90 (dd)	3.33 (m)
	9.1 1.9	7.3	8.5	5.0	4.7	5.4 2.0	10.0	3.1
31[1]	4.47 (dd)	4.29 (dd)	3.55 (dd)	3.46 (dd)	5.76 (dd)	4.68 (dd)	4.98 (dd)	3.15 (m)
	8.6 6.4	10.0	12.0	11.9	3.1	2.5	4.8	2.1
32[1]	4.51 (m)	4.51 (m)	3.47 (m)	3.71 (dd)	5.76 (dd)	4.95 (dd)	4.55 (dd)	3.47 (m)
				6.5	3.6	3.8	5.7	

[a] Refer to structure **12** for numbers. [b] Solvents (1) $CDCl_3$, (2) CD_3CN, (3) DMSO-d_6. [c] H(5) and H(6) are parts of a tightly coupled AB system.

Table II. Selected ^{13}C NMR Spectral Data for the IMDA Products[a] (δ in ppm from TMS)

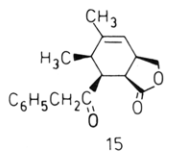
compd	C(1)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)
12a	70.1	35.9	40.2	63.4	125.4	132.7	35.9
12b	69.8	36.0	40.8	63.4	125.8	134.0	36.0
12c	69.7	36.3	42.2	70.5	125.8	134.0	36.3
12d	69.6	36.6	39.4	63.5	125.1	132.8	36.6
14a	69.6	40.8	44.9	67.3	128.1	133.5	40.0
14b	69.7	40.7	44.8	66.7	128.1	134.1	39.9
14c	69.5	40.5	44.5	67.1	127.9	133.3	39.9
26	68.5	123.4	133.0	68.4	120.1	145.4	39.4
27a	70.2	36.4	41.3	63.5	127.0	131.3	36.1
28a	70.2	36.5	41.4	63.5	127.1	131.2	36.2
29a	70.2	36.5	41.6	63.5	127.2	131.3	36.3
30a	70.2	36.4	41.5	63.1	127.1	131.1	36.0
31	69.8	39.4	41.7	72.4	45.9	47.3	35.4
32	69.6	38.7	40.4	70.5	47.0	49.1	37.2

[a] Refer to structure **12** for numbers.

Hz now was of a size clearly consonant with a trans-fused ring system,[11,12] arising via the anti transition state of **13a**. In addition the coupling constant J(3a4) = 11.7 Hz showed that H(3a) and H(4) were situated axial–axial, whereas H(4) and H(5) were situated at the same side of the ring system (J(45) = 5.5 Hz). **14a** was the sole Diels–Alder product obtained, as an examination of the mother liquor showed no presence of the cis-fused isomer. A molecular model clearly indicated that the trans-fused ring system **14a** was more strained than the cis-fused arrangement **12a**.

Final proof of the stereostructure was obtained by an X-ray crystallographic analysis of the trans-fused cycloadduct **14a**. A corresponding cis-fused cycloadduct (**15**) (Figure 1) had previously been X-ray crystallographically analyzed by Jones.[14]

15 contained the same condensed ring system as **14a**. However, the two ring systems were stereochemically



15

Figure 1. Cis-fused adduct that has been X-ray crystallographically analyzed by Jones.[14]

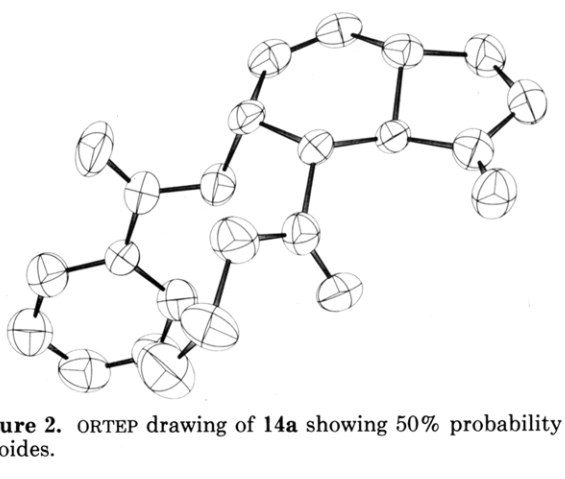


Figure 2. ORTEP drawing of **14a** showing 50% probability ellipsoides.

different as the five- and six-membered rings were fused with a trans configuration in **14a** (Figure 2) and a cis configuration in **15** (Figure 3).

The bond distances in **14a** and **15** have been compared. Significant differences (Δ > 0.026 Å) occurred for C(1)–O(2) and C(5)–C(6) (Figure 4). C(1)–O(1) = (**15**: 1.439 (4), **14a**: 1.470 (8) Å), C(5)–C(6) = (**15**: 1.534 (5), **14a**: 1.565 (8) Å). The longer C(1)–O(1) distance in **14a** may be a result of more strain in this molecule. The rather long C(5)–C(6) distance in **14a** was probably caused by the electron-withdrawing groups –OC(O)C_6H_5 and –$COOC_2H_5$. This point of view was supported by the long >CHCH<

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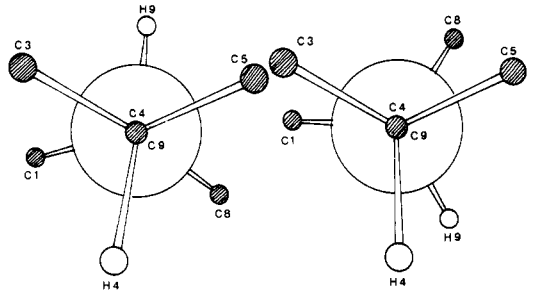


14a 15

Figure 3. Newman projection of the C(4)–C(9) bond and surrounding atoms in the compounds **14a** and **15**. The trans configuration for **14a** and cis configuration for **15** are clearly recognized.

Table III. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters for 14a

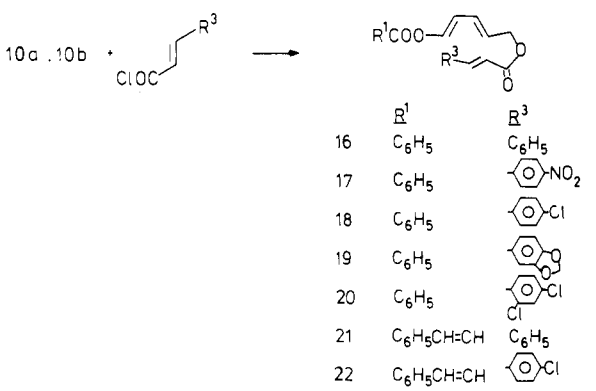
atom	x	y	z	B_{eq}
O(2)	0.6931 (3)	0.1131 (5)	0.1686 (3)	4.8 (4)
O(3)	0.5854 (3)	−0.0956 (5)	0.1740 (3)	4.9 (4)
O(10)	0.3725 (3)	−0.0620 (5)	0.0454 (3)	5.3 (4)
O(11)	0.2720 (3)	0.0196 (6)	0.1329 (3)	5.2 (4)
O(14)	0.2968 (3)	0.3848 (5)	0.0188 (2)	4.0 (3)
O(15)	0.1656 (3)	0.4501 (7)	0.0566 (3)	6.9 (5)
C(1)	0.6861 (4)	0.2941 (8)	0.1478 (5)	4.9 (6)
C(3)	0.5977 (4)	0.0486 (8)	0.1559 (4)	3.9 (5)
C(4)	0.5214 (4)	0.1855 (7)	0.1200 (4)	3.1 (4)
C(5)	0.4180 (4)	0.1815 (6)	0.1404 (3)	3.1 (4)
C(6)	0.3610 (4)	0.3509 (7)	0.1097 (3)	3.7 (5)
C(7)	0.4276 (5)	0.5002 (7)	0.1058 (4)	4.4 (5)
C(8)	0.5285 (5)	0.4955 (7)	0.1287 (4)	4.1 (5)
C(9)	0.5821 (4)	0.3381 (7)	0.1636 (4)	3.6 (5)
C(10)	0.3546 (4)	0.0337 (7)	0.1006 (4)	3.7 (5)
C(12)	0.2016 (5)	−0.1202 (9)	0.1003 (5)	5.8 (7)
C(13)	0.1351 (6)	−0.0818 (11)	0.0105 (6)	7.4 (8)
C(15)	0.2010 (4)	0.3810 (8)	0.0015 (4)	4.0 (5)
C(16)	0.1439 (4)	0.3532 (7)	−0.0925 (4)	3.5 (5)
C(17)	0.1907 (4)	0.2825 (8)	−0.1555 (4)	4.6 (5)
C(18)	0.1356 (6)	0.2612 (10)	−0.2436 (4)	5.9 (7)
C(19)	0.0332 (6)	0.3060 (10)	0.2686 (5)	6.1 (7)
C(20)	−0.0130 (5)	0.3726 (9)	−0.2066 (5)	6.2 (7)
C(21)	0.0421 (5)	0.3953 (9)	−0.1176 (4)	5.3 (6)

distances found in other molecules with the fragment –(RCOO)CHCH(COOR')–. >CH–CH< = (1.553 (6),[15] 1.56 (2),[16] 1.558 (11)[17] Å). A list of fractional coordinates for **14a** is given in Table III.

The parallel sequence with acylation of pentadienol **10b** by fumaric acid ethyl ester monochloride (Scheme VI) gave the triene ester **13b**, which could only be isolated as a yellow oil. Exposure of this material to refluxing xylene for 24 h resulted in a moderate yield of the trans-fused adduct **14b**, indicating that **13b** preferred to cyclize via the anti transition state. In the same way the triene ester **13c** arising from **10c** and fumaric acid methyl ester monochloride[13] upon cycloaddition gave the trans-fused ring system **14c**.

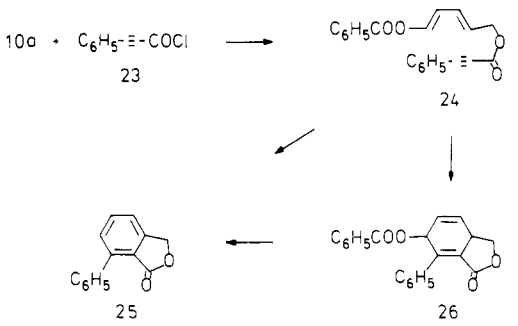
For further investigation of the IMDA reaction the triene esters **16–22** (Scheme VII) were prepared by acylation of the alcohols **10a** or **10b** by cinnamoyl chloride, *p*-nitrocinnamoyl chloride,[18] *p*-chlorocinnamoyl chloride,[19]

Scheme VII



	R^1	R^3
16	C_6H_5	C_6H_5
17	C_6H_5	NO_2
18	C_6H_5	Cl
19	C_6H_5	O
20	C_6H_5	Cl, Cl
21	$C_6H_5CH{=}CH$	C_6H_5
22	$C_6H_5CH{=}CH$	Cl

Scheme VIII



3,4-(methylenedioxy)cinnamoyl chloride,[20] and 2,4-dichlorocinnamoyl chloride,[19] respectively.

The triene esters **13a** and **13c** together with **16–22** were characterized by their NMR spectra (Tables IV and V). The assignments of the proton NMR spectra were based on ^1H–^1H correlation spectra and the assignment of the ^{13}C NMR spectra were based on ^1H–^{13}C correlation spectra.

Unfortunately, the triene esters **16–22** all failed to undergo internal cycloaddition even at 240 °C. In some cases TLC showed traces of products in the reaction mixture, but it was not possible to isolate any cyclization products.

It is known that an acetylene dienophile is more reactive in the IMDA reaction than the corresponding olefinic dienophile. It was therefore decided to investigate the acetylene system **24** (Scheme VIII) to determine whether this system was more willing to undergo cyclization than its olefinic counterpart **16**.

The relatively unstable phenylpropioloyl chloride (**23**) was prepared in three steps. The first step was the bromination of ethyl cinnamate[21] followed by dehydrohalogenation by KOH to the potassium salt[22] of phenylpropiolic acid. The last step was treatment of this potassium salt with oxalyl chloride, which was found to be more effective than the reported[22] conversion to the phenylpropiolic acid followed by treatment with thionyl chloride.[23] The acid chloride was used without purification, as it underwent polymerization during distillation.

Exposure of **24** to refluxing xylene for 30 h did not give the expected product **26** but instead the new biphenyl-γ-lactone **25**, due to elimination of benzoic acid. Under milder conditions (refluxing chloroform for 12 days), intermediate **26** was obtained in high yield. Heating of **26**

(15) Nakamura, H.; Iitaka, Y.; Kumada, Y.; Takeuchi, T.; Umezawa, H. *Acta Crystallogr., Sect. B* **1977**, *33*, 1260.
(16) Shen, M.; Ruble, J. R.; Hite, G. *Acta Crystallogr., Sect. B* **1975**, *31B*, 2706.
(17) Gabe, E. J.; Barnes, W. H. *Acta Crystallogr., Sect. B.* **1963**, *16B*, 796.
(18) White, W. N.; Fife, W. K. *J. Am. Chem. Soc.* **1961**, *83*, 3846.
(19) Andrews, E. R.; Van Campen, M. G.; Schumann, E. L. *J. Am. Chem. Soc.* **1953**, *75*, 4003.
(20) Freudenberg, K.; Fischer, E. *Chem. Ber.* **1956**, *89*, 1233. It was found that treatment of the acid with $SOCl_2$ in refluxing methylene chloride for 1 h was more effective.
(21) Abbott, T. W.; Althousen, D. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 270.
(22) Abbott, T. W. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 515.
(23) Johnston, K. M.; Shotter, R. G. *J. Chem. Soc. C* **1967**, 2476.

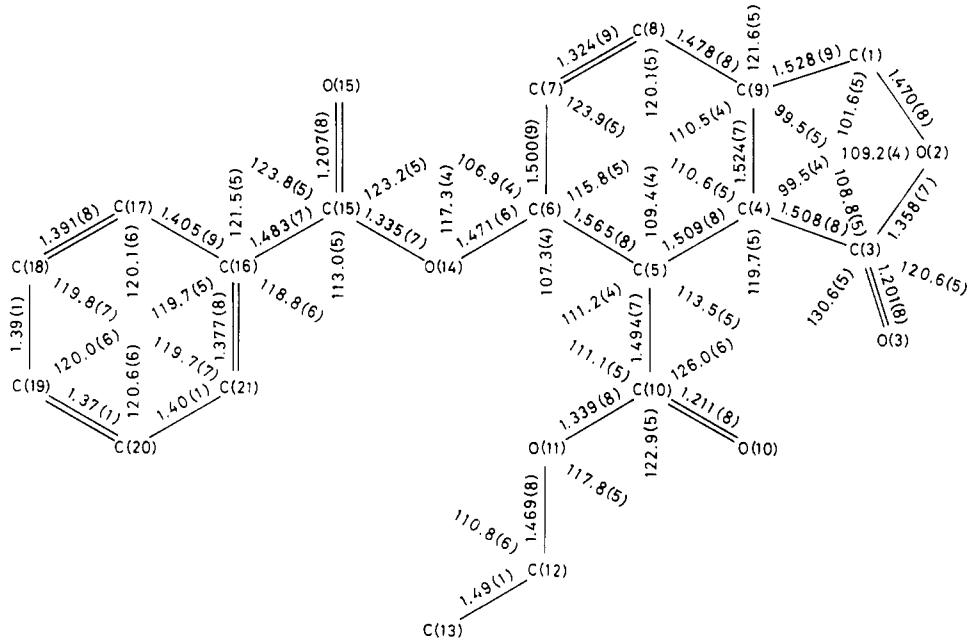


Figure 4. Bond distances (Å) angles (deg) and the atom numbering scheme for **14a**. Estimated standard deviations are given in parentheses.

Table IV. Selected ^{1}H NMR Spectral Data for the Trienes[a] (δ in ppm from TMS, J in Hz, (m) Multiplicity, Solvent $CDCl_3$)

compd	H(1) J(12)	H(2) J(23)	H(3) J(34)	H(4) J(45)	H(5)	H(6) J(67)	H(7)
13a	8.08 (d)	6.62 (dd)	6.75 (dd)	6.22 (dt)	5.15 (d)	7.27 (s)	7.27 (s)
	12.0	11.2	14.9	6.4			
13c	7.69 (d)	6.23 (dd)	6.36 (dd)	5.83 (dt)	4.75 (d)	6.76 (s)	6.76 (s)
	11.7	11.5	14.5	6.5			
16	7.70 (d)	6.25 (dd)	6.38 (dd)	5.89 (dt)	4.77 (dd)	6.47 (d)	7.73 (d)
	12.0	11.2	14.9	6.3		16.0	
17	7.70 (d)	6.25 (dd)	6.39 (dd)	5.88 (dt)	4.80 (d)	6.59 (d)	7.74 (d)
	12.0	11.4	14.9	6.5		16.1	
18	7.67 (d)	5.96 (dd)	6.07 (dd)	5.59 (dt)	4.48 (dd)	6.15 (d)	7.38 (d)
	11.9	11.1	14.9	6.4		16.0	
19	7.68 (d)	6.24 (dd)	6.36 (dd)	5.87 (dt)	4.75 (d)	6.28 (d)	7.62 (d)
	12.0	11.4	14.8	6.4		15.9	
20	7.69 (d)	6.24 (dd)	6.38 (dd)	5.75 (dt)	4.78 (d)	6.44 (d)	7.53 (d)
	11.8	11.2	14.6	6.5		16.0	
21	7.31 (d)	5.87 (dd)	5.92 (dd)	5.58 (dt)	4.47 (d)	6.17 (d)	7.43 (d)
	12.2	11.2	15.0	6.4		16.1	
22	7.60 (d)	6.15 (dd)	6.34 (dd)	5.85 (dt)	4.75 (d)	6.46 (d)	7.80 (d)
	12.0	11.3	15.1	6.4		16.0	
24	7.71 (d)	6.24 (dd)	6.40 (dd)	5.86 (dt)	4.79 (d)		
	11.9	11.4	14.9	6.6			

[a] Refer to structure **13** for numbers.

Table V. Selected ^{13}C NMR Spectral Data for the Trienes[a] (δ in ppm from TMS)

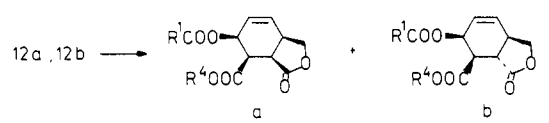
compd	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)
13a	139.8	114.6	129.8	125.7	65.4	134.0	133.7
13c	139.8	114.6	129.9	125.7	65.3	133.4	133.6
16	139.5	114.8	129.1	126.6	64.6	117.7	145.0
17	139.7	114.6	128.5	126.1	65.0	122.1	142.0
18	139.3	114.8	129.5	126.5	64.7	118.3	143.3
19	139.4	114.8	128.4	126.7	64.4	115.6	144.6
20	139.8	114.7	129.3	126.4	64.8	120.9	139.6
21	139.4	114.4	129.2	126.4	64.5	117.7	144.9
22	139.6	114.5	129.4	129.4	64.8	118.5	143.6
24	140.0	114.7	130.4	125.4	66.1	119.5	86.6

[a] Refer to structure **13** for numbers.

in refluxing xylene for 20 h caused elimination of benzoic acid, resulting in a quantitative yield of the lactone **25**.

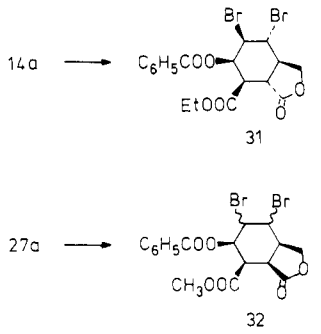
In an attempt to open the lactone ring of the IMDA products the cis-fused product **12a** was treated with refluxing methanol and 1 equiv of aqueous hydrochloric acid. This treatment did not result in opening of the lactone ring but instead led to esterification of the acid group, affording **27a** in high yield (Table VI). Analogous reactions were carried out with ethanol and 2-propanol; the former case gave, in addition to the expected **28a**, a minor portion of the trans-fused isomer **28b** (**28b** = **14a**). The isomers were not separated and the ratio **a**:**b** was deduced by integration of the ^{1}H NMR spectrum. Treatment with 2-propanol afforded a mixture of the cis-fused compound **29a** and the

Table VI



	R^1	R^4	a : b
27	C_6H_5	Me	100 : 0
28	C_6H_5	Et	9 : 1
29	C_6H_5	i-Pr	2 : 1
30	$C_6H_5CH{=}CH$	Me	100 : 0

Scheme IX



trans-fused isomer **29b** in the ratio 2:1, while treatment of **12b** with methanol only yielded the cis-fused product **30a**. This indicates a ring opening–ring closure sequence during the esterification reaction.

The esterification products **27–30** were characterized by their NMR spectra (Table I and II). The assignment of the ^1H NMR spectra was based on the ^1H–^1H correlation spectra while the ^{13}C NMR spectra were based on the ^1H–^{13}C correlation spectra.

For further elaboration of Diels–Alder adducts, introduction of extra functionality is often needed. Mellor[24] presents a strategy using the dienophilic unit dichloromaleic anhydride to incorporate extra functionality into the Diels–Alder products. In our example the additional functionality is introduced via the diene; thus cyclohexadiene **14a** was brominated, affording **31** in high yield (Scheme IX). According to the ^1H NMR spectrum the stereochemistry of the ring system was preserved (Table I), as the coupling constant $J(3a7a) = 12$ Hz was consistent with a trans-fused product. The Karplus relation showed that a coupling constant $J(77a) = 2.1$ Hz corresponded to a dihedral angle between H(7) and H(7a) of approximately 80–95°.

Treatment of the cis-fused IMDA product **27a** with bromine afforded **32**. Second-order effects in the 500-MHz ^1H NMR spectrum made the complete assignment of the stereostructure of **32** impossible.

As previously reported,[7] the pentadienol **10a** with the hydroxy group protected by an acetate ester was able to take part in the intermolecular Diels–Alder reaction with maleic anhydride as the dienophile. The pentadienals (Scheme IV) only given low yields of Diels–Alder products as the diene system in this case in a push–pull diene system. Schmidt[25] has shown that other dienes derived from glutaconaldehyde participate in the intermolecular version.

In order to examine the intermolecular Diels–Alder reaction of our diene system the alcohol **10a** was protected; thus **10a** was acylated with benzoyl chloride to give **33a** (Scheme X), while treatment of **10a** with phenyl isocyanate afforded the urethan **33b**. The stable dienes **33a** and **33b** both underwent cycloaddition with various dienophiles; in general it was found that diene **33b** required higher temperature in this reaction. Working at 110 °C diene **33b** yielded phthalate **37b** via elimination of benzoic acid.

Discussion

The intramolecular [4 + 2] cycloadditions of the trienes examined in this study proceeded with a consistent propensity for the cis-fused adduct when the dienophiles were terminally substituted with an acid group and for the trans-fused adduct when the substituent was an ester group. These results are in qualitative accord with the work of White[11,12] and Mellor.[24]

Nonsynchronous (but conserted) bond formation explains why the triene esters **13a–c** prefer to cyclize via the anti transition state. Frontier molecular orbital theory predicts more advanced bond formation between those termini of the diene and the dienophile that have the largest coefficients in HOMO and LUMO, respectively.[26] As the dienophiles in **13a–c** are C-1 (terminally) substituted with an electron-withdrawing substituent, the C-2 LUMO coefficient is larger than the C-1 LUMO coefficient and as the HOMO coefficients of the diene are comparable in size because the electron-donating substituent here only produces a minor influence, the development of the five-membered ring is more advanced, and in this situation the anti transition state is energetically favored.

The triene acids **11a–d** cyclize via the syn transition state. White[11] suggests that cyclizations giving cis-fused lactones proceed by thermodynamic control. Internal protonation of the lactone carbonyl might facilitate the reverse Diels–Alder reaction and hence lead to the more thermodynamically stable cis-fused lactones.

The trienes **16–22** all have an electron-donating substituent at the diene and an ester function in the chain. Regarding cyclization, the former fact is somewhat positive, while the latter is negative. The reduced reactivity of esters has been attributed to preference for the transoid form or loss of ester resonance in the transition state.[27]

The failure to obtain any cyclized product from the triene **16** led us to an investigation of a series of related trienes **17–22**, having both electron-donating or electron-withdrawing groups in the phenyl ring, but also in these cases with negative results. However, the more reactive acetylene dienophile **24** gave the **25** in high yield.

The main feature of our diene is the presence of a protected hydroxy function at the 2-position relative to the double bond in the resulting cyclohexene ring. The dienes **33a** and **33b** were able to participate in the intermolecular Diels–Alder reactions. As expected, the reaction took place under the mildest conditions with the most powerful dienophiles (PTAD > TCNE > *N*-phenylmaleimide). In **36b** the cyclohexane ring is seen to contain two differently protected hydroxy functions.

The reactions reported above clearly demonstrate the synthetic potential of the diene system **10**, and it can be concluded that **10** is a reactive diene, which via the intramolecular or intermolecular Diels–Alder reaction leads to highly functionalized products.

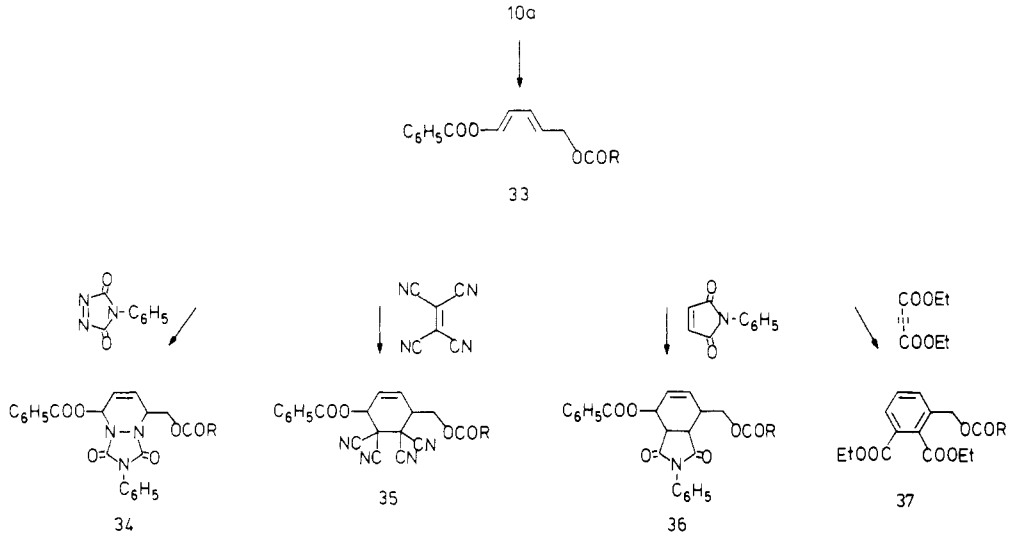
Further use of these and related Diels–Alder reactions is currently under investigation.

Experimental Section

Mass spectra were obtained on a Varian MAT 311A spectrometer. Data are reported in the form m/z (intensity relative to base 100). Infrared spectra (IR) were recorded on a Perkin-Elmer 580 spectrophotometer. ^1H and ^{13}C nuclear magnetic resonance spectra NMR) were recorded on either a Bruker AC 250 FT NMR spectrometer or a corresponding 300-MHz or 500-MHz apparatus in deuteriochloroform unless otherwise stated. Chemical shifts are reported in parts per million (δ) with tetramethylsilane as the internal standard. Coupling constants (J) are given in hertz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. NMR spectra are reported in this section unless they are presented in tables. Phenyl groups in the products showed satisfactory spectroscopic data,

(24) Batchelor, M. J.; Mellor, J. M. *Tetrahedron Lett.* **1985**, *26*, 5109.
(25) Schmidt, R. R.; Wagner, A. *Synthesis* **1982**, 958.
(26) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.
(27) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789.

Scheme X



a: R = C_6H_5
b: R = NHC_6H_5

which are not reported. Elemental combustion analyses were performed by NOVO A/S, Copenhagen. Melting points were determined on a Büchi apparatus and are uncorrected. Solvents were purified by standard procedures. Analytical TLC was performed on Merck silica gel plates; visualization was accomplished with UV light. Preparative layer chromatography (PLC) was performed on Merck silica gel plates and unless otherwise stated the eluent was methylene chloride and the extraction solvent was ethyl acetate.

X-ray crystallographic data of compound 14a: $C_{18}H_{18}O_6$, mol wt = 330.34. A crystal with the dimensions 0.1 × 0.3 × 0.3 mm was selected for intensity measurements. $F(000)$ = 696, monoclinic $P2_1/c$; a = 13.541 (3), b = 7.943 (4), and c = 15.455 (3) Å; β = 104.39 (2)°. The unit cell volume is 1610.13 Å^{-3}, Z = 4. The measured and the calculated density is d_M = 1.36 and d_C = 1.363 mg·mm^{-3}, respectively. The X-ray intensity data were collected on an Enraf-Nonius CAD-4F diffractometer using graphite-monochromatized Mo Kα radiation ($\lambda_{Mo K\alpha 1}$ = = 0.71073 Å), T = 295 K. Lattice parameters were determined from 22 diffractometer setting angles (8.40 < θ < 12.01°). The data collection range was (2 < θ < 22°), (h 0 → 14, k 0 → 8, l −16 → 15). Three reflections were used for orientation control every 100 reflections; intensity check every 10 800 s of exposure time, with one reflection. A reduction of the standard intensity of 10% during the data collection was observed, and correction for decay was therefore applied. A total of 1982 reflections were measured in the ω–2θ mode with scan angle = (1.20 + 0.35 tan θ)°. A total of 1157 reflections were considered as observed ($I > 2.5\sigma(I)$). Lorentz and polarization correction were applied; no absorption correction was made; μ = 0.096 mm^{-1}.

The structure was solved by direct methods: anisotropic full-matrix least-squares refinement of non-H atoms; positional H parameters from a difference density map; refinements of H (x,y,z) with sin θ/λ < 0.40 Å^{-1}; fixed isotropic H temperature factor. $\Sigma w(|F_o| - |F_c|)^2$ minimized; final R = 0.052 and wR = 0.053; w = 1 when F_o < 80, otherwise $w = (80/F_o)^2$. S = 1.79. $(\Delta/\sigma)_{max}$ = 0.02. Minimum and maximum in final $\Delta\rho$ map = −0.23 and 0.20 e Å^{-3}. Scattering factors from International Tables for X-ray Crystallography (1974).[28] Computer programs from XRAY 76.[29]

(3aα,4β,5β,7aα)-5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic Acid (12a). To a magnetically stirred solution of 1-(benzoyloxy)-5-hydroxy-1(*E*),3(*E*)-pentadiene (**10a**) (3.00 g, 14.7 mmol) in 25 mL of chloroform was added maleic anhydride (1.44 g, 14.7 mmol), and the mixture was refluxed for 4 h. On cooling white crystals of **12a** precipitated to yield 3.20 g (72%) (cyclohexane): mp 186–188 °C; IR (KBr) 1770, 1710, 1630 cm^{-1}; mass spectrum 302 (2), 102 (100). Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.58; H, 4.64. Found: C, 63.44; H, 4.68.

(3aα,4β,5β,7aα)-5-(Cinnamoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic Acid (12b). To a magnetically stirred solution of 1-(cinnamoyloxy)-5-hydroxy-1(*E*),3(*E*)-pentadiene (**10b**) (1.50 g, 6.5 mmol) in 25 mL of toluene was added maleic anhydride (0.64 g, 6.5 mmol), and the mixture was refluxed for 12 h. On cooling white crystals of **12b** precipitated to yield 1.70 g (80%) (cyclohexane): mp 190–191 °C; IR (KBr) 1770, 1700, 1645 cm^{-1}; mass spectrum 328 (10), 131 (100). Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.68; H, 4.89. Found: C, 65.85; H, 4.88.

(3aα,4β,5β,7aα)-5-(Benzoyloxy)-6-methyl-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic Acid (12c). To a magnetically stirred solution of 1-(benzoyloxy)-2-methyl-5-hydroxy-1(*E*),3(*E*)-pentadiene (**10c**) (4.00 g, 18.3 mmol) in 60 mL of toluene was added maleic anhydride (1.80 g, 18.3 mmol), and the mixture was refluxed for 10 h. On cooling white crystals of **12c** precipitated to yield 4.40 g (76%) (cyclohexane): mp 198–200 °C; IR (KBr) 1770, 1710, 1645 cm^{-1}; mass spectrum 316 (2), 105 (100). Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.27; H, 5.01.

(3aα,4β,5β,7aα)-5-[(Ethoxycarbonyl)oxy]-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic Acid (12d). To a magnetically stirred solution of 1-[(ethoxycarbonyl)oxy]-5-hydroxy-1(*E*),3(*E*)-pentadiene (**10d**) (1.50 g, 8.7 mmol) in 30 mL of chloroform was added maleic anhydride (0.85 g, 8.7 mmol), and the mixture was refluxed for 12 h. On cooling white crystals of **12d** precipitated to yield 1.80 g (77%) (cyclohexane): mp 145–146 °C; IR (KBr) 1765, 1710, 1645 cm^{-1}; mass spectrum 270 (0.1), 91 (100). Anal. Calcd for $C_{12}H_{14}O_7$: C, 53.33; H, 5.22. Found: C, 53.36; H, 5.34.

1-(Benzoyloxy)-5-[(ethoxyfumaroyl)oxy]-1(*E*),3(*E*)-pentadiene (13a). To a magnetically stirred cold (0 °C) solution of **10a** (4.00 g, 19.6 mmol) and Et_3N (2.75 ml, 19.6 mmol) in 40 mL of dry chloroform was added fumaric acid ethyl ester monochloride[13] (3.30 g, 20 mmol) during 1/2 h. The mixture was warmed to room temperature, stirred for an additional 3 h, and then washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. After the mixture was dried over Na_2SO_4, the solvent was evaporated in vacuo to give a solid material of **13a** in a yield of 5.15 g (80%) (ligroin 65–70 °C): mp 67–68 °C; IR (KBr) 1730, 1720, 1630 cm^{-1}; mass spectrum 330 (3), 127 (3), 105 (100). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.31; H, 5.49.

1-(Benzoyloxy)-5-[(methoxyfumaroyl)oxy]-1(*E*),3(*E*)-pentadiene (13c). To a magnetically stirred cold (0 °C) solution of **10a** (5.1 g, 25.0 mmol) and Et_3N (3.50 mL, 25.0 mmol) in 50 mL of dry benzene was added fumaric acid methyl ester mono-

(28) International Tables for X-ray Crystallography; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 99, 149.
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chloride[13] (3.71 g, 25.0 mmol) during 40 min. The mixture was warmed to room temperature, stirred for an additional 3 h, and then washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. After the mixture was dried over $MgSO_4$, the solvent was evaporated in vacuo to give a solid dark brown material of **13c**. PLC yielded 4.2 g (53%) (cyclohexane): mp 92–94 °C; IR (KBr) 1725, 1720, 1665 cm^{-1}; mass spectrum 316 (2), 203 (2), 105 (100). Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.31; H, 5.08.

(3aα,4α,5α,7aβ)-5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic Acid Ethyl Ester (14a). The triene ester **13a** (0.5 g, 1.5 mmol) and 20 mg of 2,6-di-*tert*-butyl-*p*-cresol were dissolved in 70 mL of dry xylene and the solution was refluxed for 18 h under a nitrogen atmosphere. On cooling white crystals of **14a** precipitated to yield 0.37 g (74%) (toluene): mp 172–173 °C; IR (KBr) 1780, 1745, 1715 cm^{-1}; mass spectrum 330 (3), 105 (100). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.16; H, 5.43.

(3aα,4α,5α,7aβ)-5-(Cinnamoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic Acid Ethyl Ester (14b). To a magnetically stirred cold (5–10 °C) solution of **10b** (4.0 g, 17.4 mmol) and triethylamine (2.03 g, 20.0 mmol) in 40 mL of dry chloroform was added during 45 min fumaric acid ethyl ester monochloride[13] (2.7 g, 17.4 mmol). The mixture was allowed to warm to room temperature, stirring was continued for 3 h, and the the mixture was washed with saturated $NaHCO_3$ solution. After being dried over Na_2SO_4, the solvent was evaporated in vacuo to afford a yellow oil of **13b** in a yield of 4.5 g (73%). This oil was dissolved in 30 mL of dry xylene and 20 mg of 2,6-di-*tert*-butyl-*p*-cresol was added. The mixture was refluxed for 24 h under an atmosphere of nitrogen. On cooling crystals of **14b** precipitated to yield 0.8 g (13%) (toluene): mp 186–187 °C; IR (KBr) 1785, 1745, 1710 cm^{-1}; mass spectrum 356 (6), 131 (100). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.42; H, 5.77.

(3aα,4α,5α,7aβ)-5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic Acid Methyl Ester (14c). The triene ester **13c** (0.4 g, 1.27 mmol) and 20 mg of 2,6-di-*tert*-butyl-*p*-cresol were dissolved in 60 mL of dry xylene and the solution was refluxed for 20 h under a nitrogen atmosphere. Evaporation of the solvent gave **14c** in a yield of 0.35 g (88%) (methanol): mp 170–171 °C; IR (KBr) 1775, 1745, 1705 cm^{-1}; mass spectrum 316 (8), 105 (100). Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.61; H, 5.15.

1-(Benzoyloxy)-5-((*E*)-cinnamoyloxy)-1(*E*),3(*E*)-pentadiene (16). To a magnetically stirred solution of **10a** (5.0 g, 24.5 mmol) and pyridine (1.98 ml, 24.5 mmol) in 50 mL of dry chloroform was added at 0 °C during 1/2 h cinnamoyl chloride (4.2 g, 25.0 mmol) in 10 mL of dry $CHCl_3$. After being warmed to room temperature, stirring was continued for an additional 3 h. The mixture was diluted with ether and washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. After being dried over $MgSO_4$, the solvent was evaporated in vacuo to afford light brown semicrystalline **16**. PLC of this material yielded 6.85 g (84%) (cyclohexane): mp 85–86 °C; IR (KBr) 1740, 1730, 1640 cm^{-1}; mass spectrum 334 (2), 131 (19), 105 (100); UV ($CHCl_3$) λ_{max} (log ϵ) 277 nm (3.33). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.18; H, 5.43.

1-(Benzoyloxy)-5-[(*p*-nitro-(*E*)-cinnamoyl)oxy]-1(*E*),3-(*E*)-pentadiene (17). To a magnetically stirred cold (0 °C) solution of **10a** (5.0 g, 24.5 mmol) and pyridine (1.98 ml, 24.5 mmol) in 50 mL of dry chloroform was added during 30 min *p*-nitrocinnamoyl chloride[15] (5.2 g, 24.5 mmol) in 20 mL of dry chloroform. After being warmed to room temperature and stirred for 4 h, the reaction mixture was diluted with ether, and the ethereal layer was washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. After being dried over $MgSO_4$, the ethereal extract was filtered and the solvent was evaporated in vacuo to afford a light brown oil of f **17**. PLC yielded 6.0 g (65%) (cyclohexane): mp 137–139 °C. IR (KBr) 1730, 1715, 1640, 1520, 1345 cm^{-1}; mass spectrum 379 (2), 176 (4), 105 (100). Anal. Calcd for $C_{21}H_{17}NO_6$: C, 66.49; H, 4.52; N, 3.69. Found: C, 66.59; H, 4.53; N, 3.64.

1-(Benzoyloxy)-5-[(*p*-chloro-(*E*)-cinnamoyl)oxy]-1(*E*),3-(*E*)-pentadiene (18). To a magnetically stirred solution of **10a** (2.03 g, 9.95 mmol) and pyridine (0.8 mL, 9.95 mmol) in 20 mL of dry chloroform was added at 0 °C during 20 min *p*-chlorocinnamoyl chloride[16] (2.00 g, 9.95 mmol) in 10 mL of dry chloroform. After being warmed to room temperature and stirred for 5 h, the mixture was diluted with ether and washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. After being dried over $MgSO_4$, the solvent was evaporated in vacuo to afford a light yellow oil of **18**. PLC of this oil provided 2.4 g (66%) (cyclohexane): mp 109–111 °C; IR (KBr) 1730, 1710, 1640 cm^{-1}; mass spectrum 368 (2), 165 (10), 105 (100). Anal. Calcd for $C_{21}H_{17}ClO_4$: C, 68.39; H, 4.65. Found: C, 68.38; H, 4.69.

1-(Benzoyloxy)-5-[((*E*)-piperonylacryloyl)oxy]-1(*E*),3-(*E*)-pentadiene (19). To a magnetically stirred cold (0 °C) solution of **10a** (3.0 g, 14.7 mmol) and pyridine (1.2 ml, 14.7 mmol) in 30 mL of dry chloroform was added during 30 min piperonylacryloyl chloride[17] (3.1 g, 14.7 mmol) in 15 mL of dry CH cl_3. After being warmed to room temperature and stirred for 4 h, the mixture was diluted with ether and washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. After being dried over $MgSO_4$, the solvent was evaporated in vacuo to afford a yellow solid of **19** in a yield of 3.1 g (56%) (cyclohexane): mp 135–136 °C; IR (KBr) 1730, 1700, 1630 cm^{-1}; mass spectrum 378 (2), 175 (11), 105 (100). Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.84; H, 4.79. Found: C, 69.75; H, 4.79.

1-(Benzoyloxy)-5-[((*E*)-2,4-dichlorocinnamoyl)oxy]-1-(*E*),3(*E*)-pentadiene (20). To a magnetically stirred cold (0 °C) solution of **10a** (1.9 g, 9.3 mmol) and pyridine (0.75 mL, 9.3 mmol) in 30 mL of dry chloroform was added during 20 min 2,4-dichlorocinnamoyl chloride[16] (2.20 g, 9.3 mmol) in 5 mL of dry DMF. After being warmed to room temperature and stirred for 5 h, the mixture was diluted with ether and washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo to afford a yellow oil of **20**. PLC of this oil yielded 0.75 g (20%) (cyclohexane): mp 103–105 °C; IR (KBr) 1740, 1720, 1630 cm^{-1}; mass spectrum 402 (1), 105 (100). Anal. Calcd for $C_{21}H_{16}Cl_2O_4$: C, 62.55; H, 4.00. Found: C, 62.33; H, 4.04.

1-(Cinnamoyloxy)-5-((*E*)-cinnamoyloxy)-1(*E*),3(*E*)-pentadiene (21). To a magnetically stirred cold (0 °C) solution of **10b** (2.8 g, 12.2 mmol) and pyridine (0.98 mL, 12.2 mmol) in 30 mL of dry chloroform was added during 20 min cinnamoyl chloride (2.03 g, 12.2 mmol) in 5 mL of dry chloroform. After being warmed to room temperature and stirred for 3 h, the mixture was diluted with ether and washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo to give a yellow oil of **21**. PLC of this oil afforded 2.4 g (55%) (cyclohexane): mp 85–87 °C; IR (KBr) 1720, 1710, 1630 cm^{-1}; mass spectrum 360 (1), 131 (100); UV ($CHCl_3$) λ_{max} (log ϵ) 287 nm (3.59). Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.32; H, 5.66.

1-(Cinnamoyloxy)-5-[(*p*-chloro-(*E*)-cinnamoyl)oxy]-1-(*E*),3(*E*)-pentadiene (22). To a magnetically stirred cold (0 °C) solution of **10b** (3.0 g, 13.0 mmol) and pyridine (1.04 ml, 13.0 mmol) in 30 mL of dry chloroform was added during 25 min *p*-chlorocinnamoyl chloride[16] (2.61 g, 13.0 mmol) in 10 mL of dry chloroform. After being warmed to room temperature and stirred for 4 h, the mixture was diluted with ether andd washed sequentially with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. After being dried over $MgSO_4$, the solvent was evaporated in vacuo to afford a yellow oil of **35**. PLC of this oil yielded 3.3 g (65%) (cyclohexane): mp 127–130 °C; IR (KBr) 1730, 1710, 1640, 1630 cm^{-1}; mass spectrum 394 (1), 165 (6), 131 (100). Anal. Calcd for $C_{23}H_{19}ClO_4$: C, 69.96; H, 4.85. Found: C, 70.11; H, 4.98.

1-(Benzoyloxy)-5-[(phenylpropioloyl)oxy]-1(*E*),3(*E*)-pentadiene (24). To a magnetically stirred solution of **10a** (3.2 g, 15.7 mmol) and pyridine (1.6 mL, 20 mmol) in 20 mL of dry benzene was added at 0 °C unpurified phenylpropioloyl chloride (**23**) (3.0 g, approximately 18 mmol) during 20 min. After being stirred at room temperature for 4 h, the mixture was diluted with ether and the ethereal layer was washed with saturated $CuSO_4$ solution, water, and saturated NaCl solution. The ethereal extracts were dried over $MgSO_4$, filtered, and evaporated to give a light yellow solid of **37** in a yield of 3.8 g (72%) (ligroin 65–70 °C): mp

91–93 °C; IR (KBr) 2220, 1740, 1720, 1630 cm^{-1}; mass spectrum 332 (1), 129 (8), 105 (100). Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 76.01; H, 4.83.

1,3-Dihydro-3-oxo-4-phenylisobenzofuran (25). A magnetically stirred solution of **24** (0.8 g, 2.4 mmol) and 20 mg of 2,6-*di-tert*-butyl-*p*-cresol in 50 mL of dry xylene was refluxed under an argon atmosphere for 30 h. The solvent was evaporated in vacuo to afford a brown oil. PLC of this oil provided 0.39 g (77%) of **25**. Recrystallization from ligroin (80–100 °C) gave white crystals: mp 155–157 °C; IR (KBr) 1750 cm^{-1}; ^1H NMR δ 7.42–7.95 (8 H, m), 4.34 (2 H, s); ^{13}C NMR δ 120–147.76 (phenyl), 169.7 (C=O) 68.3 (CH_2); mass spectrum 210 (87), 181 (100). Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.80. Found: C, 79.54; H, 4.81.

5-(Benzoyloxy)-1,3,5,7-tetrahydro-4-phenylisobenzofuran (26). A magnetically stirred solution of **24** (0.35 g, 1.05 mmol) and 10 mg of 2,6-di-*tert*-butyl-*p*-cresol in 25 mL of dry $CHCl_3$ was refluxed under an N_2 atmosphere for 12 days. The solvent was evaporated in vacuo to afford a light yellow solid material of **26** in a yield of 0.30 g (86%): mp 118–123 °C; IR (KBr) 1765, 1720, 1630 cm^{-1}; mass spectrum 332 (8), 210 (10), 105 (100). Peak matching calcd for 332.10486, found 332.1046.

General Procedure for Preparation of Esterified IMDA Products 27–30. To a solution of the appropriate (3aα,4β,5β,7aα)-5-(acyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofuran, **12a** or **12b** (1.0 equiv), in the appropriate alcohol was added under magnetic stirring 4 M HCl (1.0 equiv). The mixture was refluxed for 1–2 h. On cooling white crystals precipitated.

(3aα,4β,5β,7aα)-5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic acid methyl ester (27a): yield 0.5 g (78%); mp 159–160 °C; IR (KBr) 1780, 1735, 1710 cm^{-1}; mass spectrum 316 (3), 105 (100). Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.39; H, 5.09.

5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic acid ethyl ester (28): yield 0.45 g (69%) of **28a** and 0.05 g (8%) of **28b** (= **14a**) (according to the integral in the ^1H NMR spectrum; the mixture was not separated): mp 160–162 °C; IR (KBr) 1780, 1730, 1720 cm^{-1}; mass spectrum 330 (3), 105 (100). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 64.95; H, 5.51.

5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic acid isopropyl ester (29): yield 0.13 g (23%) of **29a** and 0.07 g (12%) of **29b** (according to the integral in the ^1H NMR spectrum; the mixture was not separated): mp 97–99 °C; IR (KBr) 1780, 1730, 1720 cm^{-1}; mass spectrum 344 (4), 105 (100). Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.35; H, 5.90.

(3aα,4β,5β,7aα)-5-(Cinnamoyloxy)-1,3,3a,4,5,7a-hexahydro-3-oxo-4-isobenzofurancarboxylic acid methyl ester (30a): yield 0.4 g (64%): mp 170–172 °C; IR (KBr) 1775, 1740, 1710, 1635 cm^{-1}; mass spectrum 342 (12), 131 (100). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.26; H, 5.40.

5-(Benzoyloxy)-1,3,3a,4,5,6,7,7a-octahydro-3-oxo-6,7-dibromo-4-isobenzofurancarboxylic Acid Ethyl Ester (31). To a magnetically stirred solution of **14a** (0.42 g, 1.27 mmol) in 10 mL of CH_2Cl_2 was added Br_2 at room temperature (0.2 mL, 3.90 mmol). The solution was stirred for 30 h and then poured into a dish, allowing the solvent and unused bromine to evaporate, affording a yellow oil which crystallized on standing for 2 days in a yield of 0.61 g (98%) (ethanol 96%): mp 202–204 °C; IR (KBr) 1780, 1740, 1720 cm^{-1}; mass spectrum 490 (0.5), 105 (100). Anal. Calcd for $C_{18}H_{18}Br_2O_6$: C, 44.11; H, 3.70. Found: C, 44.41; H, 3.74.

5-(Benzoyloxy)-1,3,3a,4,5,6,7,7a-octahydro-3-oxo-6,7-dibromo-4-isobenzofurancarboxylic Acid Methyl Ester (32). To a magnetically stirred solution of **27a** (1.0 g, 3.16 mmol) in 15 mL of CH_2Cl_2 was added Br_2 at room temperature (0.51 mL, 10.0 mmol). The solution was stirred for 24 h and then poured into a dish, allowing the solvent and unused bromine to evaporate, affording a light brown oil. After 3 weeks this oil had become crystalline in a yield of 1.5 g (99.7%) (ethanol 96%): mp 174–176 °C; IR (KBr) 1775, 1730, 1720 cm^{-1}; mass spectrum 476 (0.3), 105 (100). Anal. Calcd for $C_{17}H_{16}Br_2O_6$: C, 42.89; H, 3.39. Found: C, 42.97; H, 3.46.

1,5-Bis(benzoyloxy)-1(*E*),3(*E*)-pentadiene (33a). To a stirred cold (0 °C) solution of **10a** (1.0 g, 4.90 mmol) in 10 mL of dry pyridine was added during 30 min benzoyl chloride (0.7 mL, 6.03 mmol). After an additional 1 h of stirring, the mixture was poured on ice water and the resulting precipitate was filtered and dried to afford **33a** in a yield of 1.37 g (90%) (EtOH/H_2O): mp 79–80 °C; IR (KBr) 1725, 1710, 1660 cm^{-1}; mass spectrum 308 (3), 105 (100); ^1H NMR δ 7.69 (1 H, d, J = 12.1 Hz), 6.38 (1 H, dd, J = 13.5 Hz, J = 12.1 Hz), 6.24 (1 H, dd, J = 12.1 Hz, J = 12.1 Hz), 5.92 (1 H, dt, J = 13.5 Hz, J = 6.5 Hz), 4.88 (2 H, d, J = 6.4 Hz). Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.19; H, 5.31.

1-(Benzoyloxy)-5-(carbaniloyloxy)-1(*E*),3(*E*)-pentadiene (33b). To a stirred solution of **10a** (1.0 g, 4.90 mmol) in 20 mL of dry toluene was added phenyl isocyanate (0.53 ml, 4.90 mmol), and the mixture was heated at reflux for 1.5 h. Evaporation of the solvent gave a solid material of **33b** in a yield of 1.52 g (96%). PLC of this material afforded 0.82 g (52%) of orange needles and recrystallization from cyclohexane yielded 0.66 g (42%) of pale yellow needles of **33b**: mp 119–120 °C; IR (KBr) 3305, 1730, 1690, 1660 cm^{-1}; mass spectrum 323 (2), 105 (100); ^1H NMR δ 7.68 (1 H, d, J = 11.3 Hz), 6.83 (1 H, s), 6.32 (1 H, dd, J = 13.5 Hz, J = 11.3 Hz) 6.22 (1 H, dd, J = 11.3 Hz, J = 11.3 Hz), 5.85 (1 H, dt, J = 13.5 Hz, J = 6.5 Hz), 4.71 (2 H, d, J = 6.6 Hz). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.70; H, 5.35; N, 4.20.

2-Phenyl-5-(benzoyloxy)-8-[(benzoyloxy)methyl]-4,5,8,9-tetrahydro-2*H*-triazolo[1,2-*a*]pyridazine-1,3-dione (34a). To a magnetically stirred solution of **33a** (0.5 g, 1.62 mmol) in 10 mL of dry methylene chloride was added 4-phenyl-1,2,4-triazoline-3,5-dione (0.28 g, 1.62 mmol). The mixture was kept at room temperature for 1/2 h. Evaporation of the solvent yielded 0.57 g (73%) of solid material **34a**. Recrystallization from ethanol/ethyl acetate (1:1) gave 0.50 g (64%): mp 168–170 °C; IR (KBr) 1720–1780 cm^{-1}; mass spectrum 483 (6), 361 (12), 256 (8), 105 (100). ^1H NMR δ 7.04–7.14 (1 H, m), 6.41 (1 H, ddd, J = 10.3 Hz, J = 4.8 Hz, J = 2.2 Hz), 6.22 (1 H, dd, J = 10.3 Hz, J = 2.3 Hz), 5.95 (1 H, dd, J = 11.7 Hz, J = 4.1 Hz), 5.21 (1 H, dd, J = 11.7 Hz, J = 3.0 Hz), 4.80–4.90 (1 H, m). Anal. Calcd for $C_{27}H_{21}N_3O_6$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.00; H, 4.38; N, 8.68.

3-[(Benzoyloxy)methyl]-4,4,5,5-tetracyano-6-(benzoyloxy)cyclohex-1-ene (35a). To a stirred solution of **33a** (0.5 g, 1.62 mmol) and 10 mg of 2,6-di-*tert*-butyl-*p*-cresol in 10 mL of dry methylene chloride was added tetracyanoethylene (0.21 g, 1.62 mmol). The mixture was heated at reflux under a nitrogen atmosphere for 2 days. Evaporation of the solvent yielded 0.6 g (85%) of solid material **35a**. Recrystallization from ethanol/ethyl acetate (1:1) gave 0.45 g (64%): mp 165–166 °C; IR (KBr) 22550, 1725, 1630 cm^{-1}; mass spectrum 436 (6), 314 (10), 105 (100); ^1H NMR δ 6.22–6.32 (2 H, m), 6.10 (1 H, dd, J = 10.1 Hz, $J \simeq$ 1.7 Hz), 4.92 (1 H, dd, J = 12.6 Hz, J = 5.1 Hz), 4.69 (1 H, dd, J = 12.3 Hz, J = 8.4 Hz, 3.73 (1 H, dd, J = 8.4 Hz, J = 5.1 Hz). Anal. Calcd for $C_{25}H_{16}N_4O_4$: C, 68.80; H, 3.70; N, 12.84. Found: C, 68.92; H, 3.73; N, 12.72.

4-[(Benzoyloxy)methyl]-7-(benzoyloxy)-3a,4,7,7a-tetrahydro-2-phenyl-1,3-isoindoledione (36a). To a stirred solution of **33a** (0.5 g, 1.62 mmol) and 10 mg of 2,6-di-*tert*-butyl-*p*-cresol in 10 mL of dry chloroform was added *N*-phenylmaleimide (0.28 g, 1.62 mmol), and the mixture was refluxed under a nitrogen atmosphere for 3 days. Evaporation of the solvent gave yellow oil **36a**. PLC of this oil afforded 0.46 g (59%). Recrystallization from ethanol/ethyl acetate (1:1) gave 0.38 g (49%): mp 141–143 °C; IR (KBr) 1710, 1700 cm^{-1}; mass spectrum 481 (0.1), 359 (2), 237 (14), 122 (52), 105 (100); ^1H NMR δ 6.21 (1 H, ddd, J = 9.7 Hz, $J \simeq$ 2.8 Hz, $J \simeq$ 2.8 Hz), 6.11 (1 H, ddd, J = 9.7 Hz, $J \simeq$ 2.8 Hz, $J \simeq$ 2.8 Hz), 5.70 (1 H, ddd, J = 7.9 Hz, J = 4.3 Hz, $J \simeq$ 2.5 Hz), 5.05 (1 H, dd, J = 11.2 Hz, J = 7.1 Hz), 4.83 (1 H, dd, J = 11.2 Hz, J = 8.2 Hz), 3.93 (1 H, dd, $J \simeq$ 8.3 Hz, $J \simeq$ 8.3 Hz), 3.55 (1 H, dd, J = 9.0 Hz, J = 6.0 Hz), 2.96–3.04 (1 H, m). Anal. Calcd for $C_{29}H_{23}NO_6$: C, 72.34; H, 4.81; N, 2.91. Found: C, 72.49; H, 4.85; N, 2.85.

4-[(Carbaniloyloxy)methyl]-7-(benzoyloxy)-3a,4,7,7a-tetrahydro-2-phenyl-1,3-isoindoledione (36b). To a stirred solution of **33b** (0.5 g, 1.55 mmol) and 10 mg of 2,6-di-*tert*-butyl-*p*-cresol in 10 mL of dry chloroform was added *N*-phenylmaleimide (0.27 g, 1.55 mmol), and the mixture was refluxed under a nitrogen atmosphere for 5 days. Evaporation of the solvent gave a solid material of **36b** in a yield of 0.76 g (99%). Recrystallization from ethanol/ethyl acetate (1:1) afforded 0.54 g (70%) of white

crystals: mp 173–174 °C; IR (KBr) 1680–1740 cm^{-1}; mass spectrum 496 (0.4), 105 (100); ^1H NMR δ 6.92 (1 H, s), 6.15 (1 H, ddd, J = 9.5 Hz, $J \simeq$ 2.4 Hz, $J \simeq$ 2.4 Hz), 6.01 (1 H, ddd, J = 9.5 Hz, $J \simeq$ 3.2 Hz, $J \simeq$ 3.2 Hz), 5.65 (1 H, ddd, J = 7.9 Hz, J = 5.6 Hz, J = 2.4 Hz), 4.79 (1 H, dd, J = 11.1 Hz, J = 7.1 Hz), 4.67 (1 H, dd, J = 11.1 Hz, J = 7.9 Hz), 3.86 (1 H, dd, $J \simeq$ 8.7 Hz, $J \simeq$ 8.7 Hz), 3.46 (1 H, dd, J = 9.0 Hz, J = 6.0 Hz), 2.8–2.9 (1 H, m). Anal. Calcd for $C_{29}H_{24}N_2O_6$: C, 70.15; H, 4.87; N, 5.64. Found: C, 70.40. H, 4.89; N, 5.57.

Diethyl 3-[(Carbaniloyloxy)methyl]phthalate (37b). To a stirred solution of **33b** (0.5 g, 1.55 mmol) and 10 mg of 2,6-di-*tert*-bytyl-*p*-cresol in 10 mg of dry toluene was added diethyl acetylenedicarboxylate (0.26 g, 1.55 mmol), and the mixture was refluxed under a nitrogen atmosphere for 4 days. Evaporation of the solvent gave a yellow oil. PLC of this oil afforded 0.35 g (61%) of **37b**. Recrystallization from ethanol/ethyl acetate (1:1) yielded 0.29 g (50%) of light yellow crystals: mp 105–107 °C; IR (KBr) 3420, 1720 cm^{-1}; mass spectrum 371 (20), 161 (100); ^1H NMR δ 6.94 (1 H, s), 5.25 (2 H, s), 4.41 (2 H, q, J = 7.5 Hz), 3.34 (2 H, q, J = 7.5 Hz), 1.36 (3 H, t, J = 7.5 Hz), 1.34 (3 H, t, J = 7.5 Hz). Peak matching calcd for 371.13688, found 371.13735.

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A Stereospecific Total Synthesis of (3*R**,5*S**,9*S**)-Gephyrotoxin 223AB

Yumi Nakagawa* and Robert V. Stevens†

University of California, Los Angeles, Los Angeles, California 90024

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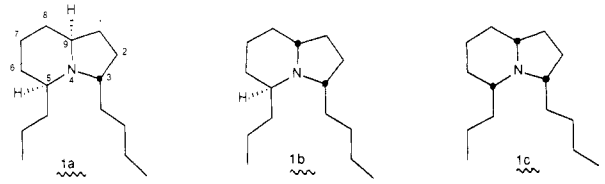
The title compound was synthesized stereospecifically by the nucleophilic addition of hydride ($NaCNBH_3$) to the conformationally rigid tetrahydropyridinium ion **6**. This key intermediate was obtained in six steps from the ethylene ketal of 1-chloro-4-heptanone. Biological evaluation of **1c** is also reported.

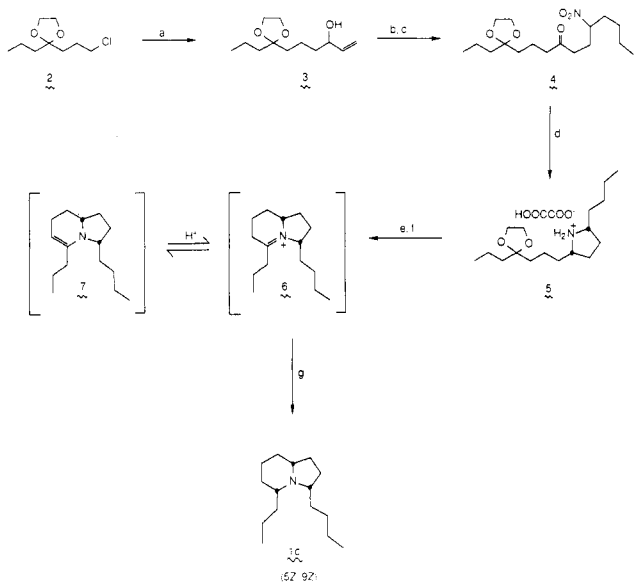
Indolizidine alkaloids isolated from the skin secretions of neotropical poison-dart frogs (family Dendrobatidae) have been the target of many synthetic efforts which have demonstrated the importance of stereoelectronic control in the design of a total synthesis.[1] In particular, gephyrotoxin 223AB (GTX 223AB) has been of interest since the relative stereochemistry of this compound remained a mystery for several years following the structure determination. The correct relative stereochemistry of GTX 223AB as structure **1a** was established in 1981,[2] and several syntheses of this natural product have since appeared.[3]



One of the unnatural isomers, **1b**, has also been prepared by total synthesis utilizing the stereospecific addition of a nucleophile to a conformationally rigid tetrahydropyridinium ion.[4] We now report a variation of this approach which leads stereospecifically to the the all-cis 3*R**,5*S**,9*S** isomer of GTX 223AB, **1c**.

The Grignard reagent from the ethylene ketal of 1-chloro-4-heptanone[5] was treated with a solution of freshly distilled acrolein to give allylic alcohol **3** (Scheme I), which was oxidized with pyridinium dichromate[6] to the corresponding α,β-unsaturated ketone. Tetramethylguanidine-catalyzed Michael addition[7] of 1-nitropentane to the enone was followed by hydrogenation of the resultant nitro ketone **4** over palladium in the presence of anhydrous sodium sulfate. This procedure afforded the 2,5-disubstituted pyrrolidine, which was isolated from ether as its oxalate salt **5**. The ^{13}C NMR spectrum of the free base exhibited 16 peaks, indicating the presence of a single

Scheme I[a]



[a] (a) i, Mg/THF; ii, acrolein (30%); (b) PDC (77%); (c) 1-nitropentane, tetramethylguanidine/CH_2Cl_2 (57%); (d) i, H_2/Pd/C; MeOH, Na_2SO_4; ii, HOOCCOOH/Et_2O (59%); (e) 2 N HCl/THF; (f) 10% aqueous KOH; (g) $NaCNBH_3$/MeOH/THF; bromocresol green (62% from **5**).

* Address all correspondence to Dr. Yumi Nakagawa, Ortho Research Center, Chevron Chemical Company, 15049 San Pablo Avenue, Richmond, CA 94804-0010.

† Deceased March 9, 1984.

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