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DIELS-ALDER CYCLOADDITIONS OF CHIRAL BUTENOLIDES WITH CYCLOPENTADIENE: endo/exo SELECTIVITY

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Abstract.- Chiral butenolides are revealed to be good dienophiles in Diels-Alder reactions with cyclopentadiene, affording endo and exo adducts, whose fully characterization is provided. Selectivity of these cycloaddition reactions has been shown to be temperature dependent not as a result of a thermodynamic equilibrium between the isomers, but due to a kinetically controlled process.

INTRODUCTION

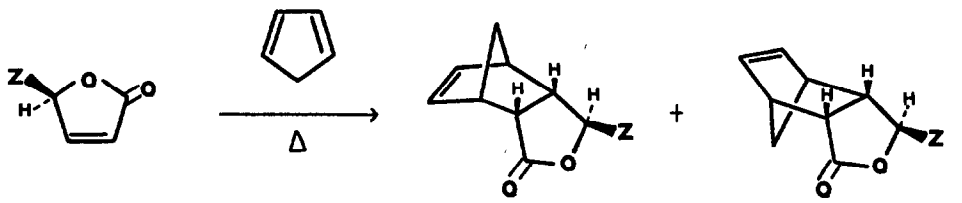
Diels-Alder reactions of cyclopentadiene and open-chain α-carbonyl dienophiles has been extensively studied and there are many data in the literature about the reactivity and selectivity of acrylic and crotonic acids and derivatives.[1,2] However, results related to pentagonal cyclic dienophiles are scarce. Therefore, following our research program on the behaviour of chiral α,β-butenolides in Diels-Alder cycloadditions, we decide to study the reactions of such lactones with cyclopentadiene, devoting our attention to the endo/exo selectivity and the synthetic applications of the adducts. Thus, we have reported in a previous communication[3] that chiral butenolides (2(5H)-furanones) react smoothly with cyclopentadiene giving enantiomerically pure endo and exo adducts in good yields, the observed selectivity being temperature dependent. These compounds are potent chiral building blocks, since all of them have unequivocally controlled five asymmetric centers in addition to a versatile functionalization. In effect, these kind of adducts have already been used in the preparation of some natural products such as santalene,[4] and 3-alkyl-5-methyl-2(5H)-furanones. These last compounds have been synthesized in our laboratory through a sequence that involves cycloaddition-alkylation-cycloreversion.[5]

We report in this article that the observed increase of the relative amounts of exo adducts with the increasing temperature does not result from an equilibrium process to give the thermodynamically more stable isomers, but selectivity is determined by the energy gap between the TS's leading to the endo and exo isomers respectively, through a kinetically controlled process.

RESULTS AND DISCUSSION

1. Endo and exo adducts: their formation and structural assignment.

Cycloadditions of butenolides 1,[6] 2, 3 and 4[7] with a large excess of cyclopentadiene, at 100° C for 20 hours, lead to tricyclic endo (5, 7, 9, 11) and exo (6, 8, 10, 12) adducts in about 80% overall yield (Scheme 1). All these compounds (5-12) could be isolated by column chromatography and characterized by the usual spectroscopic methods. Specific proton assignment, endo/exo, and facial diastereoisomerism were elucidated in 7 through a 400 MHz 2-D COSY pmr spectrum, that allowed the assignment of all signals and couplings (Fig. 1 and Table 1). Since an excellent correlation was found for the chemical shifts of all the protons attached to the tricyclic skeleton in the endo and in the exo series, as shown on Table 2, the structure of all adducts was thus veri-



	Z	endo	exo
1	CH_3	5	6
2	CH_2OCH_2Ph	7	8
3	CH_2OCH_3	9	10
4	CH_2OH	11	12

Scheme 1

Table 1. Analysis of the 400 MHz pmr spectrum of adduct 7 in $CDCl_3$.

Proton	δ	Signals and J's(Hz)
H_1	3.28	m
H_2	3.25	m
H_5	4.02	dd, J = 7.3; 3.8
H_6	2.94	ddd, J = 7.3; 4.2; 2.1
H_7	3.08	m
H_8	6.22	dd, J = 5.0; 2.7
H_9	6.28	dd, J = 5.0; 2.7
H_{10a}	1.41	d, J = 8.2
H_{10b}	1.60	d, J = 8.2
H_{11a}	3.52	dd, J = 9.3; 3.8
H_{11b}	3.58	dd, J = 9.3; 3.8
H_{12a}	4.50	d, J = 11.1
H_{12b}	4.56	d, J = 11.1
Ph	7.24-7.36	complex absorption

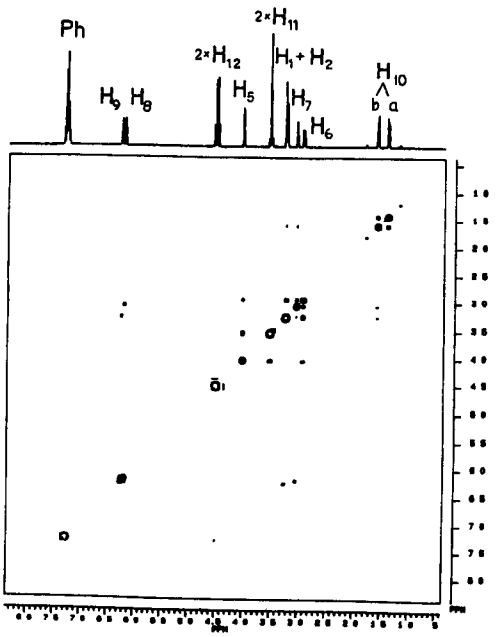


Fig 1. 400 MHz 2-D COSY spectrum of adduct 7

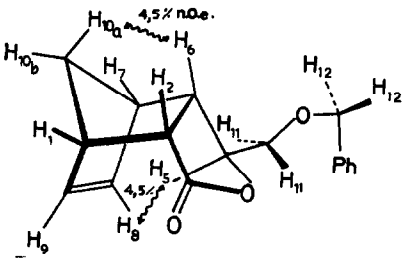


Fig 2. n.O.e. between H_6/H_{10} and H_5/H_8 in adduct 7

Table 2. pmr Chemical shifts (δ scale) in adducts 5-12.

Z	endo isomers				exo isomers			
	CH_3	CH_2OBn	CH_2OCH_3	CH_2OH	CH_3	CH_2OBn	CH_2OCH_3	CH_2OH
Adduct / Proton(s)	5	7	9	11	6	8	10	1
H_1	3.3	3.3	2.7-3.3	3.2	3.3	3.2-3.3	3.2	3.2
H_2	3.4	3.2	2.7-3.3	3.2	2.7	3.2-3.3	2.6	2.3
H_5	4.1	4.0	4.0	4.0	4.3	4.2	4.2	4.2
H_6	2.6	2.9	2.7-3.3	3.1	2.1	2.2-2.9	2.3	2.3
H_7	3.1	3.1	2.7-3.3	3.1	2.9	2.2-3.0	2.9	2.8
H_8, H_9	6.2	6.2	6.2	6.3	6.2	6.1	6.1	6.2
H_{10a}, H_{10b}	1.5	1.5	1.5	1.6	1.5	1.5	1.5	1.3
$\underline{CH}_3$	1.4				1.4			
$\underline{CH}_2OCH_2Ph$		3.5				3.6		
$CH_2O\underline{CH}_2Ph$		4.5				4.5		
$\underline{CH}_2OCH_3$			3.5				3.5	
$CH_2O\underline{CH}_3$			3.4				3.4	
$\underline{CH}_2OH$				3.3				3.7

fied. Moreover differential n.O.e. experiments performed on these products gave complementary confirmation of the endo or exo stereochemistry. Thus, a 4.5% n.O.e. was observed on H_5 from H_8, and on H_{10a} from H_6 in adducts identified as endo isomers, while this effect did not exist in exo stereoisomers. (Fig. 2).

The optical purity of these products was established using the chiral shift reagent tris-|3-heptafluorobutiryl-d-camphorato|europium(III): only one set of pmr signals was visible for each adduct in the presence of 0.6 eq. of lanthanide, while the spectra of racemic mixtures, obtained from racemic butenolides,[8,9] exhibited duplication of some signals in the same conditions.

2. *Endo/exo selectivity.*

Reaction of butenolides 1-4 with cyclopentadiene were performed at different temperatures in order to study the variation of the endo/exo ratio of adducts.

Hydroxymethylbutenolide 4 was revealed not to be a good model to study the selectivity of the process since the distribution of endo and exo isomers became misleading due to a pyrolytic elimination of water from 4 in the reaction conditions leading to byproducts.[10]

Cycloaddition reactions were very slow at low temperatures. E.g. a 3.5:1 mixture of compounds 9 and 10 was obtained in only 30% yield when butenolide 3 was reacted with cyclopentadiene at 30° C for 4 days. The ratio of endo/exo isomers prepared from lactones 1-3 resulted to be temperature dependent, the proportion of the obtained exo isomers increasing at high reaction temperatures. Thus, mixtures of (3-2.5):1 endo/exo adducts were formed in a temperature range from 80° C to 120° C.

In general, exo Diels-Alder adducts are the thermodynamically more stable isomers. The increase of the relative amount of such compounds at high temperatures has been justified in many occassions as the result of an equilibrium from the kinetically more favored endo isomers probably via a retro-cycloaddition assuming the reversibility of the reaction.[11] In our case, when endo adduct 7 was heated at 155° C for 21 hours neither butenolide 2 nor exo 8 were detected. Furthermore, we have found that similar adducts, bearing an alkyl substituent at the α-carbonyl position C-2, need temperatures higher than 225° C to undergo retro-Diels-Alder reaction.[5] Then, having thermodynamic equilibrium being precluded, it seemed that kinetic control of the reaction in the studied range of temperatures could govern the attack of the diene, either to an endo or to an exo orientation.

Table 3. Endo/exo ratio and activation parameters in the Diels-Alder reaction of butenolide 3 with cyclopentadiene.

N/X					E_N-E_X	$\Delta H_N^{\neq}-\Delta H_X^{\neq}$	$\Delta S_N^{\neq}-\Delta S_X^{\neq}$
30°	55°	73°	92°	135°C	(kcal mol)$^{-1}$	(kcal mol^{-1})	(eu)
3.54	3.17	2.85	2.70	2.33	-0.99±0.01	-0.98±0.04	-0.72±0.1

Therefore, a kinetic study of the reaction at different temperatures between cyclopentadiene and the methoxymethylbutenolide 3, chosen as a representative model, was realized using a large excess of diene (about forty times the amount of dienophile in moles). First it was confirmed that the isomer proportions remained constant throughout the course of each reaction. This result indicates that neither of the isomeric tricycles suffers endo-exo isomerization during the process and that neither isomer adduct was consumed by preferential reaction with excess cyclopentadiene.

Measurements of the relative yields of the product isomers were made at different temperatures. The results are summarized in Table 3. Accepting a kinetic control of the product mixtures in this reaction, the product ratio endo/exo, N/X, was considered to be equal to the ratio of the specific rate coefficients k_N/k_X. The differences in the activation parameters for the two reaction courses were evaluated from the plots of ln(N/X) against 1/T. The results are shown on Table 3 and give an energy gap of about 1 kcal mol^{-1}. This value is in good accordance with literature data concerning kinetic parameters in the reactions of open-chain acrylic and crotonic acid derivatives with cyclopentadiene.[1,2] (Table 4).

Table 4. Kinetic parameters for the Diels-Alder reaction of cyclopentadiene with the butenolide 3 and some acrylic acid derivatives.

Dienophile	Endo/exo ratio[a]	$E_{a(N)} - E_{a(X)}$ (kcal mol^{-1})	$\Delta H_N^{\neq} - \Delta H_X^{\neq}$[b] (kcal mol^{-1})	$\Delta S_N^{\neq} - \Delta S_X^{\neq}$[b] (eu)
Butenolide 3	3.54	-0.99±0.01	-0.98±0.04	-0.72±0.10
CH_2=CH-COOH	4.36	-0.9[c]	-0.65±0.01	-0.59±0.03
(Z)-CH_3CH=CHCN	3.87		-1.01±0.09	+0.69±0.27
(Z)-CH_3CH=CHCOOH	5.13		-1.01±0.03	+0.13±0.15

[a] At 25° C but for butenolide 3 at 30° C

[b] Data from ref. 2

[c] Ref. 1

In conclusion, kinetic control of the steric course of the cycloaddition reactions leading to isomeric endo/exo adducts has been confirmed. Moreover, we have found that the best range of reaction temperatures to obtain Diels-Alder adducts with a good selectivity and optimal yields is comprised between 100-120° C for butenolides 1-4.

The use of these tricycle compounds in enantio- and diastereoselective synthesis is currently under investigation in our laboratory.

EXPERIMENTAL SECTION

Melting points have been determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained from chloroform solutions on a Propol polarimeter, model Dr. Kernchen. Distillation of small amounts were effected on a rotational distillator Büchi, model KRV 65/30 (only external or oven temperature given). The 70 eV electron impact mass spectra were recorded on a Hew-

lett-Packard spectrometer model 5985B. The ir spectra were obtained on a Perkin-Elmer apparatus model 1310. The 80 MHz pmr and the 20 MHz cmr spectra were recorded on a Bruker spectrometer model WP 80 SY, and the 2D-COSY on a Bruker AM 400 WB apparatus, from chloroform-d solutions; chemical shifts are given in parts per million relative to TMS (δ scale). GC analyses were performed on a Perkin-Elmer apparatus model Sigma 1 using a 10% DEGS column of 1 m length. Microanalyses were performed at the Instituto de Química Bio-Orgánica, C.S.I.C., Barcelona.

General procedures: Reactions with lactones 1, 2 and 4 were carried out at temperatures of 25, 80, and 120° C. The kinetic study of the reaction between lactone 3 and cyclopentadiene was performed at temperatures (±0.5) shown on Table 3. These reactions were conducted in sealed tubes containing $4x10^{-3}$ mol of the dienophile and $162x10^{-3}$ mol of cyclopentadiene, obtained by cracking dicyclopentadiene at 170° C. The time necessary to achieve convenient yields of products varied from 0.5 hours to 2 days, depending upon the temperatures. The reaction products from cyclopentadiene and each butenolide 1 and 3 were subjected to gas chromatography analysis and the proportions of endo/exo isomers determined from the ratio of peak areas using 2,6-dimethylphenol as internal standard. The response factors of each adduct and the starting butenolide were obtained in front of the internal standard through calibration curves. The ratios of endo/exo isomers from butenolide 2 and cyclopentadiene were determined from the isolated products. All adducts 5-9 could be isolated by column chromatography and characterized by their physical and spectroscopic data:

(2R,5R,6S)-5-Methyl-4-oxa-endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 5.

Liquid, b. p. 106° C/0.2 torr; $[\alpha]_D$ -74.8° (c 2.9); ir (film) 1750, 1700 cm^{-1}; cmr 22.69, 45.28, 45.63, 47.96, 48.20, 51.35, 78.61, 134.53, 136.25, 177.17; ms, m/e 165 (M + 1, 2.2), 99 (15), 91 (76), 77 (32), 66 (100), 51 (28), 43 (26). Anal. for the isomeric mixture 5/6. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.36. Found: C, 73.68; H, 7.30.

(2R,5R,6S)-5-Methyl-4-oxa-exo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 6.

Crystals, m. p. 74-75° C; $[\alpha]_D$ -95.7° (c 1.0); ir ($CHCl_3$) 1750 cm^{-1}; cmr 23.19, 43.55, 43.68, 47.64, 48.88, 49.76, 80.50, 137.55, 137.63, 177.01; ms, m/e 165 (M + 1, 5), 99 (9), 91 (26), 66 (100), 43 (31).

(2R,5S,6S)-5-Benzyloxymethyl-4-oxa-endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 7.

Crystals, m. p. 82-83° C; $[\alpha]_D$ -46.6° (c 0.3); ir ($CHCl_3$) 1750, 1450 cm^{-1}; cmr 43.09, 45.39, 45.68, 48.24, 51.42, 71.87, 73.35, 80.69, 127.30, 127.48, 128.18, 134.27, 136.50, 137.67, 177.34; ms, m/e 271 (M + 1, 2.3), 205 (1), 121 (6), 91 (100), 83 (18), 66 (94). Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found. C, 75.47; H, 6.68.

(2R,5S,6S)-5-Benzyloxymethyl-4-oxa-exo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 8.

Liquid, b. p. 125° C/0.03 torr; $[\alpha]_D$ -28.8° (c 1.1); ir 1760 1450 cm^{-1}; cmr 43.36, 44.75, 46.30, 47.30, 48.59, 71.89, 73.44, 82.15, 127.38, 127.56, 128.24, 136.17, 137.23, 137.58, 177.02. Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.46; H, 6.45.

(2R,5S,6S)-5-Methoxymethyl-4-oxa-endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 9.

Crystals, m. p. 75-76° C; $[\alpha]_D$ -59.0 (c 0.4); ir ($CHCl_3$) 1755 cm^{-1}; cmr 43.11, 45.50, 45.80, 48.33, 51.57, 59.25, 74.40, 80.80, 134.45, 136.55, 177.50; ms, m/e 195 (M + 1), 129 (9), 85 (56), 83(100), 66(31), 49 (16), 47 (48), 45 (20). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.95; H, 7.34.

(2R,5S,6S)-5-Methoxymethyl-4-oxa-endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 10.

Liquid, b. p. 142° C/0.05 torr; $[\alpha]_D$ -76.1 (c 0.4); ir (chloroform) 1760 cm^{-1}; cmr 43.5, 44.82, 46.42, 47.60, 48.66, 59.41, 74.48, 82.19, 137.42, 137.42, 137.67, 177.12; ms, m/e 195 (M + 1, 4), 120 (30), 97 (10), 91 (13), 83 (17), 66 (100), 65 (14), 55 (11), 45 (32). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.86; H, 7.34.

(2R,5S,6S)-5-Hydroxymethyl-4-oxa-endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 11.

Crystals, m.p. 96-97° C; $[\alpha]_D$ -48.9 (c 1.1); (Lit.[4] m.p. 96-97° C; $[\alpha]_D$ -49.8° (c 1.0)); cmr 42.73, 45.54, 45.80, 48.71, 51.65, 64.57, 83.01, 134.71, 136.58, 178.25.

(2R,5S,6S)-5-Hydroxymethyl-4-oxa-exo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one, 12.

Crystals, m. p. 108-109° C; $[\alpha]_D$ -68.7 (c 0.6); cmr 43.55; 44.28, 46.47, 47.49, 48.92, 64.64, 84.24, 137.33, 137.65, 177.78.

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