Diels–Alder Trapping of 3-Methylene-2,4-chromandione. A New Entry to Substituted Pyrano[3,2-c]coumarins[1]

Giovanni Appendino,*,† Giancarlo Cravotto,† Lucio Toma,‡ Rita Annunziata,§ and Giovanni Palmisano*,§,||

Dipartimento di Scienza e Tecnologia del Farmaco, via Giuria 9, 10125 Torino, Italy, Dipartimento di Chimica Organica, Viale Taramelli 10, 27100 Pavia, Italy, Dipartimento di Chimica Organica e Industriale, via Venezian 21, 20133 Milano, Italy, and Centro Studio delle Sostanze Organiche Naturali, CNR, via Venezian 21, 20133 Milano, Italy

Received April 5, 1994[⊗]

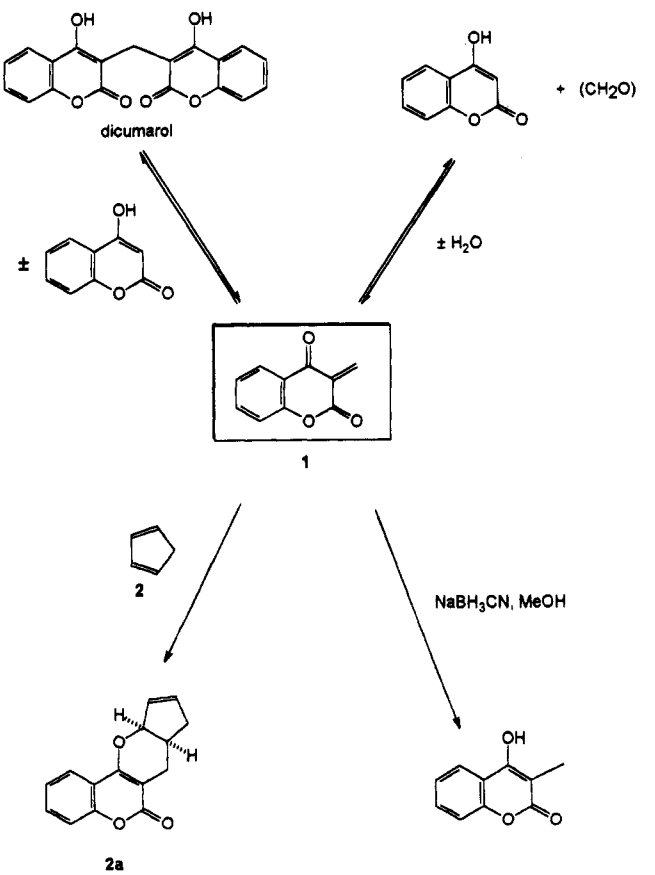
3-Methylene-2,4-chromandione (**1**) can be generated from dicumarol or from paraformaldehyde and 4-hydroxycoumarin. **1** is a versatile substrate for cycloaddition reactions. Depending on the reaction partner, **1** can behave as an ambident heterodiene or as a dienophile. The reaction was investigated with a series of olefins and dienes, including several isoprenoids. Some generalizations could be drawn and rationalized in terms of HOMO–LUMO interactions. The reaction of **1** and certain asymmetrically substituted olefins gives pyrano[3,2-*c*]coumarins in a highly regio- and chemoselective way. As an application of this reaction to natural products chemistry, a concise (three steps) synthesis of the prenylated coumarin (±)-isoferprenin (**35a**) is reported.

Introduction

The dimeric coumarin dicumarol is the hemorrhagic principle of fermented sweet clover[2] and was once widely prescribed as an oral anticoagulant.[3] We recently reported that dicumarol can be reductively cleaved by $NaBH_3CN$ to 3-alkyl-4-hydroxycoumarin and 4-hydroxycoumarin (Scheme 1).[4] This surprising fragmentation is general for dimeric 4-hydroxycoumarins and was rationalized assuming the presence of an alkylidenebis(4-hydroxycoumarin) ⇄ alkylidenechromandione retro-Michael equilibration (Scheme 1).[4,5] Support for this mechanism came from nucleophilic and Diels–Alder trapping of the alkylidene chromandione form.[4] The detection of electrophilic behavior in 4-hydroxycoumarin derivatives is intriguing, since the molecular basis for their anticoagulant activity might be the reaction with a nucleophilic center of the enzyme vitamin K epoxide reductase.[6] However, no reaction where 3-alkyl-4-hydroxycoumarins behave as electrophiles was known.

In the course of these studies, we noticed that the Diels–Alder trapping of 3-methylene-2,4-chromandione (**1**) (an ambident heterodiene as well as a dienophile) with cyclopentadiene (**2**) (an asymmetrically substituted dienophile as well as a diene) occurred with remarkable chemo- and regioselectivity, affording exclusively one of the six possible Diels–Alder adducts (**2a**, Scheme 1).[4] A similar result had been observed with a related methylenechromandione.[7] Intrigued by these results, we undertook a detailed study on the Diels-Alder reactivity of **1**.

Scheme 1



Generation of 1 and Experimental Protocol for Its Diels–Alder Trapping. 3-Methylene-2,4-chroman-

† Dipartimento di Scienza e Tecnologia de Farmaco.
‡ Dipartimento di Chimica Organica.
§ Dipartimento di Chimica Organica e Industriale.
|| Centro Studio delle Sostanze Organiche Naturali.
⊗ Abstract published in *Advance ACS Abstracts,* August 15, 1994.

(1) The Chemistry of Coumarin Derivatives. VI. Part V: Appendino, G.; Cravotto, G.; Nano, G. M.; Palmisano, G.; Annunziata, R. *Helv. Chim. Acta* **1993**, *76*, 1194.

(2) Stahmann, M. A.; Huebner, C. F.; Link, K. P. *J. Biol. Chem.* **1941**, *138*, 513.

(3) Levin, W. G. In *The Pharmacological Basis of Therapeutics*; 4th ed.; Goodman, L. S., Gilman, A., Eds.; New York: Macmillan, 1970; pp 1445–1463.

(4) Appendino, G.; Cravotto, G.; Tagliapietra, S.; Ferraro, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta* **1991**, *74*, 1451.

(5) For a review on alkylidenechromandiones, see: Lockhart, I. M. In *The Chemistry of Heterocyclic Compounds*; Ellis, G. P. Ed.; New York: Wiley, 1977; Vol. 31, pp 429–453.

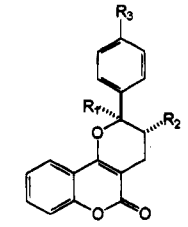
(6) (a) Silverman, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 5421. (b) Silverman, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 3910. (c) Silverman, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 5939.

(7) Wolfrum, C.; Bohlmann, F. *Liebigs Ann. Chem.* **1989**, 295.

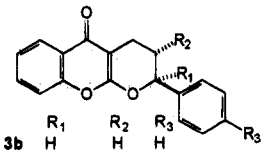
0022-3263/94/1959-5556$04.50/0

dione (**1**) can be generated from dicumarol or alternatively from paraformaldehyde and 4-hydroxycoumarin, whose condensation gives dicumarol *via* **1** (Scheme 1).[2] In both cases the choice of the solvent is critical to allow a certain solubility of dicumarol and thus the establishment of the retro-Michael equilibration. The best results were obtained in refluxing dioxane, but C-1′-substituted alkylidenechromandiones could be generated also in other solvents (THF, acetone, methanol) and at lower temperature, since their corresponding dimeric coumarins are more soluble.[4] In practice, the chromandione precursor(s) (dicumarol or 4-hydroxycoumarin and paraformaldehyde) was suspended in a dioxane solution of the Diels–Alder partner and the mixture was refluxed, monitoring the disappearance of 4-hydroxycoumarin by TLC. In a test reaction with cyclopentadiene (**2**), the yield of the Diels–Alder adduct **2a** was higher starting from 4-hydroxycoumarin and paraformaldehyde than from dicumarol (73% *vs* 35%).[4] The former procedure was thus employed throughout. Under this experimental protocol, the reaction is a domino Knoevenagel condensation–(hetero) Diels–Alder cycloaddition.[8] This sequential transformation has been investigated with several 1,3-dicarbonyl compounds,[8] but not yet with 4-hydroxycoumarin, formally the enol form of 2,4-chromandione.[9]

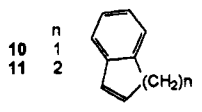
Diels–Alder Reactions of 1. The olefins tested as Diels–Alder partners of **1** are listed in Table 1 and can be divided into four groups:



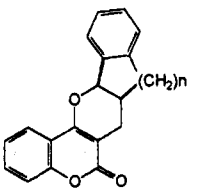
	R_1	R_2	R_3
3a	H	H	H
4a	Me	H	H
5a	H	Me	H
6a	H	H	Ph
7a	double bond		H



	R_1	R_2	R_3
3b	H	H	H
4b	Me	H	H
5b	H	Me	H
6b	H	H	Ph
7b	double bond		H



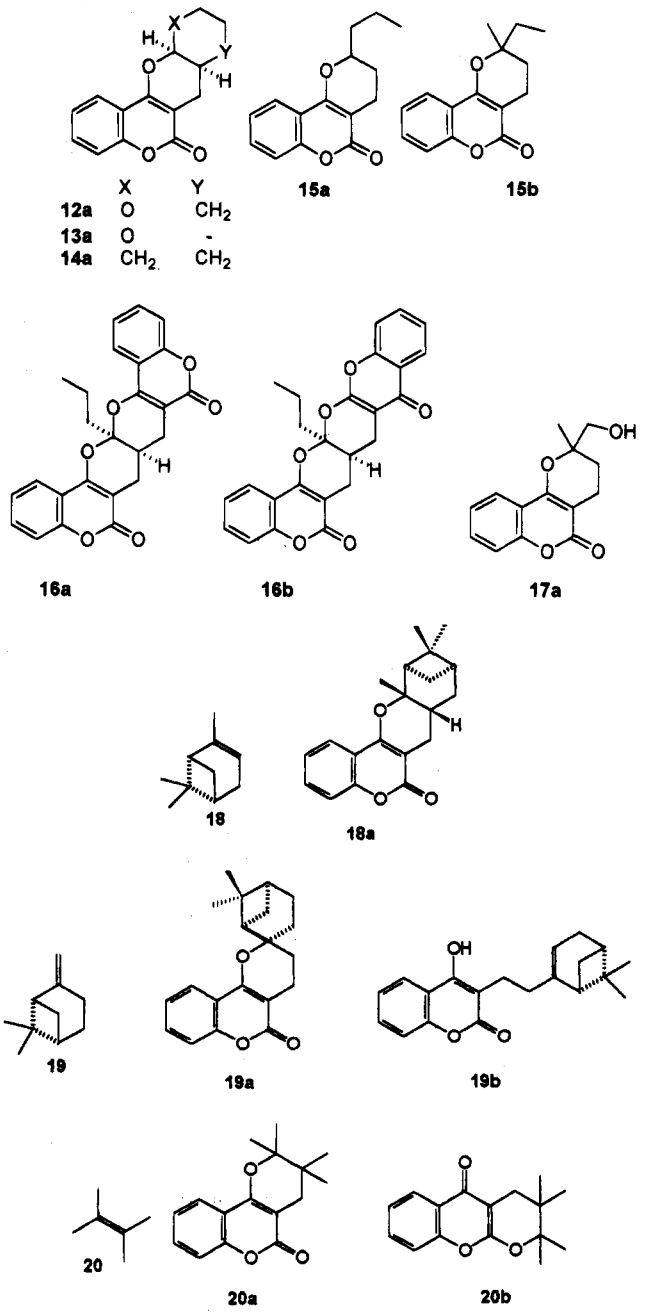
	n
10	1
11	2



	n
10a	1
11a	2

1. Aromatic Olefins and Acetylenes (Table 1, entries 1–7). With styrene (**3**), α-and β-methylstyrene (**4**, **5**) and 4-phenylstyrene (**6**), a hetero Diels–Alder reaction took place, giving a mixture of angular (**3a**–**6a**) and linear (**3b**–**6b**) adducts.[10] The same behavior was observed with phenylacetylene (**7**), that gave the adducts **7a** and **7b**, whereas no reaction took place with *trans*-stilbene (**8**) and diphenylacetylene (**9**). With indene (**10**) and 1,2-dihydronaphthalene (**11**), embodying an endocyclic double bond, only 2-phenyl-substituted angular adducts were obtained (**10a** and **11a**).

2. Aliphatic Olefins (Table 1, entries 8–16). With 3,4-dihydro-2*H*-pyran (**12**) and ethyl vinyl ether (**13**) the reaction gave angular adducts with the heteroatom-bearing carbon bound to the pyran oxygen (**12a**, **13a**). The reaction was not synthetically useful with mono- and 1,2-dialkyl-substituted olefins and acetylenes. The yield was poor (*e.g.* cyclohexene, **14**), and mixtures of products were formed as a result of competitive skeletal rearrangement of the starting olefin in the acidic reaction medium.[11] Further reaction of the primary adduct took place with 1-pentyne (**16**), that gave in very low yield (6%)



(8) Tietze, L. F.; Beifuss, U. *Ang. Chem. Int. Ed. Engl.* **1993**, *32*, 131.

(9) For recent studies on the 4-hydroxycoumarin–2,4-chromandione tautomerism, see: (a) Obaseki, A. O.; Porter, W. R.; Trager, W. F. *J. Heterocycl. Chem.* **1982**, *19*, 385. (b) Porter, W. R.; Trager, W. F. *J. Heterocycl. Chem.* **1982**, *19*, 475.

(10) The spectroscopical differentiation of linear and angular adducts is detailed in the Experimental Section.

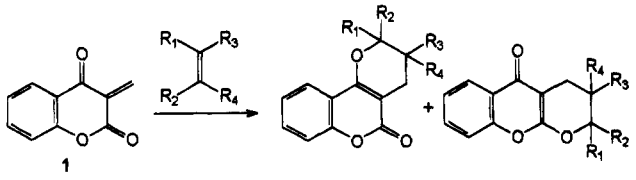
(11) The reaction of **1** and long-chain olefins such as 1-decene gave in poor yield (7%) a complex mixture of adducts, which could not be characterized; the formation of **15b** from the reaction of 1-pentene and **1** might be due to an impurity of 2-methyl-1-butene present in the starting olefin. We thank one of the referees for this suggestion.

Table 1. Diels–Alder Trapping of 1

entry	olefin (diene)(acetylene)	reaction time (h)	product(s) (% yields)[a]
1	styrene (**3**)	5	**3a** (48), **3b** (20)
2	α-methylstyrene (**4**)	6	**4a** (66), **4b** (22)
3	β-methylstyrene (**5**)	10	**5a** (29), **5b** (11)
4	4-phenylstyrene (**6**)	6	**6a** (49), **6b** (12)
5	phenylacetylene (**7**)	4	**7a** (12), **7b** (12)
6	indene (**10**)	6	**10a** (62)
7	dihydronaphthalene (**11**)	24	**11a** (18)
8	dihydropyran (**12**)	5	**12a** (56)
9	ethyl vinyl ether (**13**)	5	**13a** (35)
10	cyclohexene (**14**)	24	**14a** (6)
11	1-pentene (**15**)	24	**15a** (2), **15b** (2)
12	1-pentyne (**16**)	24	**16a** (2), **16b** (4)
13	β-methallyl alcohol (**17**)	24	**17a** (29)
14	(1*S*)-(−)-α-pinene (**18**)	2	**18a** (38)
15	(1*S*)-(−)-β-pinene (**19**)	1	**19a** (48), **19b** (5)
16	2,3-dimethyl-2-butene (**20**)	24	**20a** (40), **20b** (7)
17	norbornene (**24**)	6	**24a** (21), **24b** (8)
18	norbornadiene (**25**)	8	**25a** (26), **15b** (12)
19	(−)-β-caryophyllene (**26**)	3	**26a** (54), **26b** (38)
20	cyclohexadiene (**27**)	8	**27a** (26), **27b** (2)
21	isoprene (**28**)	24	**28a** (66)
22	α-terpinene (**29**)	4	**29a,b** (70)
23	(*R*)-(−)-phellandrene (**30**)	5	**30a** (32), **30b** (22), **30c** (26)

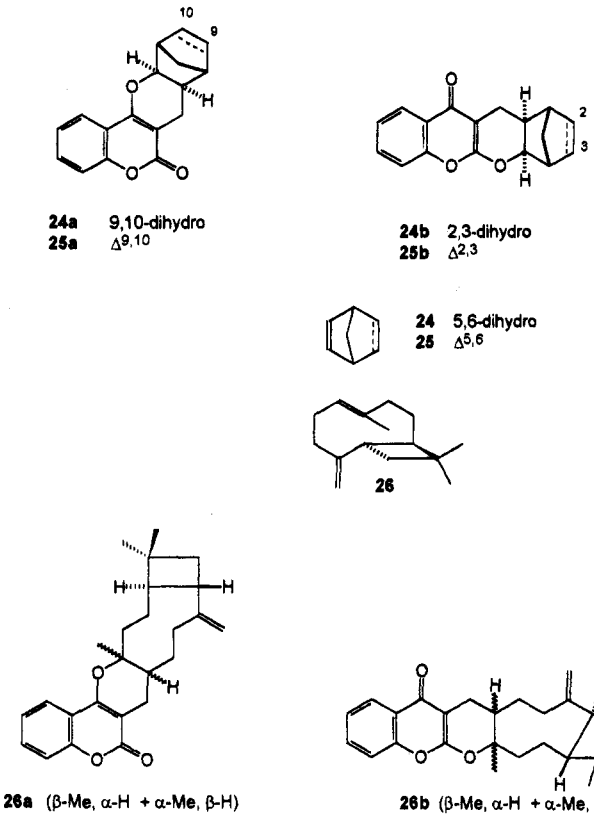
[a] Isolated yield.

Scheme 2



the bis-adducts **16a,b**.[12] However, asymmetrically substituted olefins gave angular adducts in synthetically more useful yields. Thus β-methallyl alcohol (= 2-methyl-2-propen-1-ol, **17**) gave the adduct **17a**, and (−)-α- and (−)-β-pinene (**18**, **19**) the adducts **18a** and **19a**.[13] In all these cases exclusively angular adducts were formed, but the symmetrically substituted olefin 2,3-dimethyl-2-butene (**20**) gave a mixture of angular and linear adducts (**20a,b**). The Diels–Alder trapping of **1** with β-methallyl alcohol was not plagued by competing Michael addition of the hydroxyl, a surprising observation on account of the highly polarized double bond of **1** and the efficiency by which cyclic β-dicarbonyl compounds can stabilize anions.[14] The cycloaddition of **1** and the pinenes was stereoselective. Indeed, only products derived from approach of the heterodiene from the dienophilic π-face *trans* to the *gem*-dimethyl bridge were isolated.[15] Furthermore, β-pinene is a reactive ene component,[16] and thus the isolation of only traces of the ene-adduct **19b** is also noteworthy. No reaction was observed with electron poor olefins (*N*-ethylmaleimide (**21**), *p*-benzoquinone (**22**), vinylene carbonate (**23**)).

3. Strained Olefins (Table 1, entries 17–19). Norbornene (**24**) and norbornadiene (**25**) gave a mixture of angular and linear adducts (**24a,b** and **25a,b**,respectively); the structure of the linear adduct **24b** and of the angular adducts **25a** was confirmed by X-ray diffraction analysis.[17,18] The same behavior was observed with β-caryophillene (**26**), that gave the adducts **26a,b**. Only the strained endocyclic *E*-double bond of β-caryophillene reacted,[19] and the reaction was regioselective as regards the 2π component. However, each adduct was a mixture of two stereoisomers, corresponding to the two conformations of the nine-membered ring.[20]



4. Conjugated Dienes (Table 1, entries 20–23). The reaction of **1** and 1,3-dienes is a peculiar Diels–Alder cycloaddition, where each partner can behave as a 2π or a 4π component. Cyclohexadiene (**27**) and some isoprenoid substrates (isoprene (**28**), α-terpinene (**29**) and (*R*)-α-phellandrene (**30**)) were tested. Cyclohexadiene gave the hetero Diels–Alder adduct **27a** (26%). The regioselectivity of the reaction was the same observed with cyclopentadiene,[4] since the olefinic double bond of the adduct was adjacent to the oxygenated pyranyl carbon. However, the yield was lower, and small amounts (2%) of the Diels–Alder adduct **27b** were also obtained. In sharp contrast to the behavior of cyclopentadiene and cyclohexadiene, isoprene gave a normal Diels–Alder reaction, and the spiro-adduct **28a** was isolated in 66% yield. α-Terpinene gave the hetero Diels–Alder adduct **29a,b** (ca. 3:1 mixture), whereas with (*R*)-α-phellandrene both normal (**30a**) (32%) and inverse electron demand (**30b**) (22%) Diels–Alder adducts were isolated, along with the ene-adduct **30c** (26%).

(12) The failure to obtain bis-adducts from phenylacetylene is presumably due to steric factors.

(13) The structure elucidation of stereochemically complex adducts such as those formed from terpenoids is detailed in the Experimental Section. Diagnostic NOE effects are reported under each heading.

(14) The pK_a of 4-hydroxycoumarin is 4.1 (Yakatan, G. J.; Juneav, R. J.; Schulman, E. *J. Phar. Sci.* **1972**, *61*, 749).

(15) The same behavior was observed in a related hetero Diels–Alder reaction of β-pinene (Koser, S.; Hoffmann, H. M. R.; Williams, D. J. *J. Org. Chem.* **1993**, *58*, 6163).

(16) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

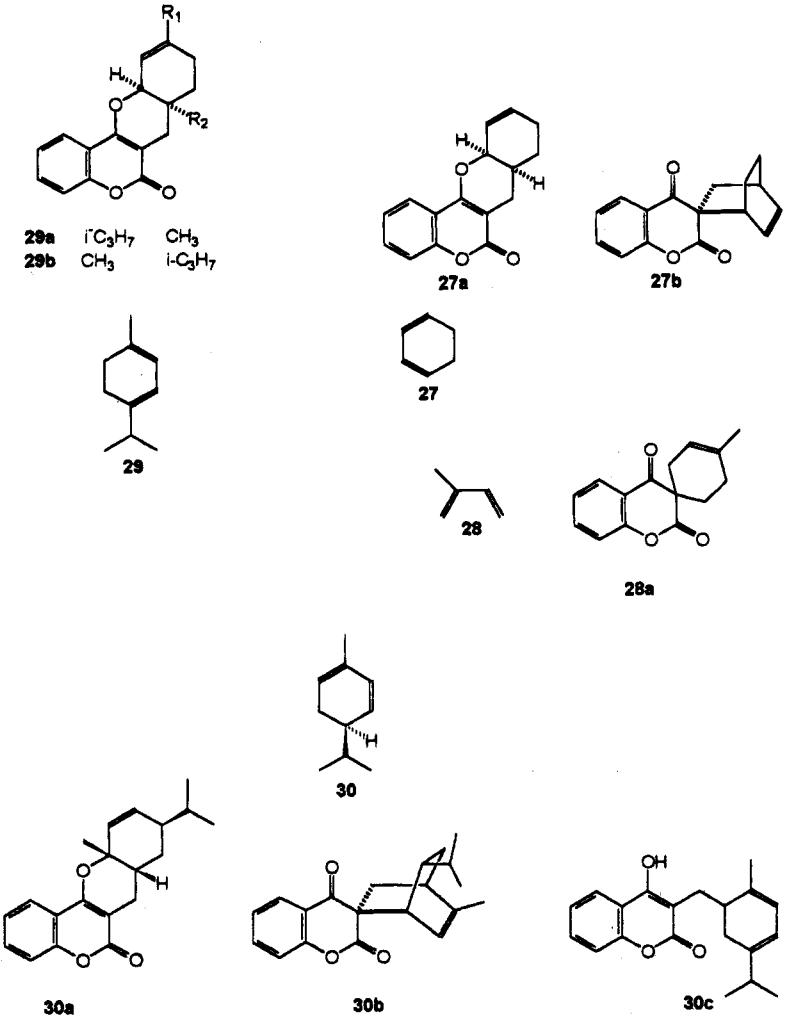
(17) Pilati, T., Centro C.N.R. per lo Studio delle Relazioni fra Struttura e Reattività Chimica, Milano, private communication.

(18) Traces (<5%) of bis-adducts were also formed in the condensation of **1** and **25**. These compounds were not further characterized.

(19) (a) Barton, D. H. R., de Mayo, P. *Quart. Rev. (London)* **1957**, *11*, 197. (b) Halsall, T. G. *Quart. Rev. (London)* **1962**, *16*, 100.

(20) Ramana Rao, V. V.; Devaprabhakara, D. *Tetrahedron* **1978**, *34*, 2223.

Chart 1



Discussion

3-Methylene-2,4-chromandione (**1**) is a versatile substrate for Diels–Alder reactions. Depending on the reaction partner, it can act as a 2π or as a 4π component, resulting in Diels–Alder and hetero-Diels–Alder adducts respectively. The hetero-Diels–Alder cycloadditions of **1** are stereospecific; the geometry of the dienophiles was maintained in the course of the reaction, as expected for a concerted mechanism.[21] Furthermore, the reaction was regioselective; in all adducts the allylic-, benzylic-, more substituted, or heteroatom-substituted carbon of the dienophile was bound to the heterodiene oxygen. This is not surprising, since hetero-Diels–Alder reactions are known to proceed *via* a concerted but not synchronous mechanism, where carbon–carbon bond formation is more advanced than carbon–oxygen bond formation.[22] The presence of an electron-withdrawing carbon on C(3) of the 1-oxabutadiene moiety further enhances this tendency,[21] and thus the regioselectivity of the reaction is mainly governed by the relative capability of the dienophilic carbons to accommodate a positive charge. On the other hand, the methylene group of **1** is adjacent to two carbonyls, and both the ketone and the lactone carbonyl can take part in the reaction, as evidenced by the formation of isomeric linear and angular adducts in the reaction with several olefins (Scheme 1 and Table 1, entries 1–5, 12, and 16–19). These chemoselectivity problems are surprising, since α,β-unsaturated ketones are much better heterodienes than α,β-unsaturated esters,[23] and control of chemoselectivity in hetero-Diels–Alder reactions of alkylidene 1,3-dicarbonyl compounds is generally excellent.[21]

To rationalize the unforeseen ambident behavior of **1** and the regioselectivity observed in its reaction with olefins, molecular mechanics calculations were carried out. From a theoretical standpoint, the cycloaddition of quinone methide **1** and dienophiles can be studied in the frame of perturbation theory[24] by considering the relative position and the coefficients of the frontier orbitals of the reagents. Figure 1 and Table 2 report the data calculated at semiempirical level (AM1 program[25]) for **1** and some olefins investigated in this work. Inspection of the energies of the HOMO and the LUMO orbitals of the heterodiene **1** and the dienophiles **3–7**, **9**, **10**, **17**, **19**, and **23** leads to the conclusion that the dominant interaction takes place between the LUMO of the diene and the

(21) Boger, D. L.; Weinreb, S. M. *Hetero Diel-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. For the use of terpenoids in hetero Diels-Alder reactions, see: Koser, S.; Hoffmann, H. M. R. *Heterocycles* **1994**, *37*, 661.

(22) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.

(23) (a) Yamauchi, M.; Katayama, S.; Baba, O.; Watanabe, T. *J. Chem. Soc., Chem. Commun.* **1983**, 281. (b) Yamauchi, M.; Katayama, S.; Baba, O.; Watanabe, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3041 (c) Tietze, L. F.; Meier, H.; Nutt H. *Liebigs Ann. Chem.* **1990**, 253.

(24) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.

(25) Dewar, M. I. J. S.; Zoebish, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

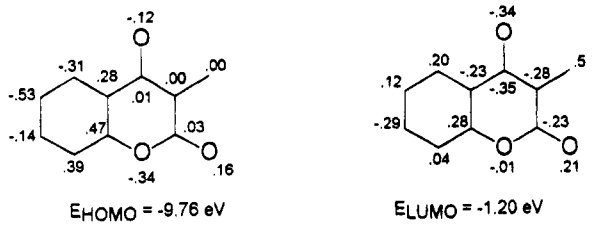


Figure 1. P_z coefficients of the HOMO and the LUMO of 1 (ΔH_f = −53.90 kcal/mol).

Table 2. Energy and p_z Coefficients of the HOMO and LUMO of compounds 3–7, 9, 10, 17, 19, and 23[a]

	ΔH_f (kcal/mol)	E_{HOMO} (eV)	HOMO		E_{LUMO} (eV)	LUMO	
			c_1	c_1		c_1	c_2
3	38.55	−9.00	0.33	0.47	0.02	−0.30	0.45
4	33.00	−8.93	0.35	0.51	0.04	−0.33	0.45
5	29.00	−8.78	0.38	0.50	0.01	−0.31	0.46
6	65.96	−8.54	0.20	0.33	−0.47	−0.18	0.32
7	76.35	−9.29	0.25	0.41	0.00	−0.21	0.36
9	97.78	−9.23	0.27	0.41	−0.05	−0.23	0.37
10	45.58	−8.84	0.35	0.48	0.05	0.31	0.46
17	−43.07	−9.64	0.55	0.66	1.16	−0.67	0.68
19	−17.58	−9.43	0.54	0.65	1.30	−0.66	0.68
23	−86.48	−10.34	0.56	0.56	0.02	−0.68	0.68

[a] In all cases, C(1) is the more substituted or the phenyl-substituted carbon.

HOMO of the dienophile. Thus, we are dealing with an inverse Diels–Alder reaction.[21] On this basis, the low energy (−10.34 eV) of the HOMO of vinylene carbonate (**23**) explains its absence of reactivity. Analogous considerations hold for the electron-poor olefins **21** and **22**.

In order to explain the chemo- and regioselectivity observed in these reactions, the coefficients of the LUMO of **1** and the HOMO of the dienophiles must be taken into account. The major factor affecting the chemoselectivity is the LUMO coefficient at the two carbonyl oxygens of **1** (0.21 for O(2) and −0.34 for O(4), see Figure 1), whereas regioselectivity depends on the relative size of the dienophile HOMO coefficients. From the data presented in Figure 1 and Table 2, it is clear that the preferred reaction path involves the interaction of the least substituted or non-phenyl-substituted carbon of the dienophile (C(2) in Table 2) and the carbon terminus of the heterodiene (C(1′) in Figure 1), since these atoms have the larger p_z coefficients of the HOMO and LUMO, respectively. These theoretical results are in agreement with the experimental data, that show the cycloaddition is fully regioselective and partially (**3**–**6**) or completely (**10**, **17**, **19**) chemoselective, the preferred addition being on the C(1′)–C(3)–C(4)–O(4) system. The behavior of the alkynes **7** and **9** cannot be explained by these calculations; the lack of reactivity of diphenylacetylene (**9**) might be due to steric reasons, and similar considerations presumably apply also to *trans*-stilbene (**8**). As to phenylacetylene (**7**), the lack of chemoselectivity might be due to differences in the π-system and/or additional factors not taken into account by the perturbation-theory analysis.

A second approach to these reactions is the determination of the transition states for the addition of ethylene to the model ambident substrate **31**. Table 3 and Figure 2 present the results of the optimized RHF transition states for the two possible sites of attack. Once again the attack to the C(1′)–C(3)–C(4)–O(4) system (transition state **32**) is predicted to be favored over the attack

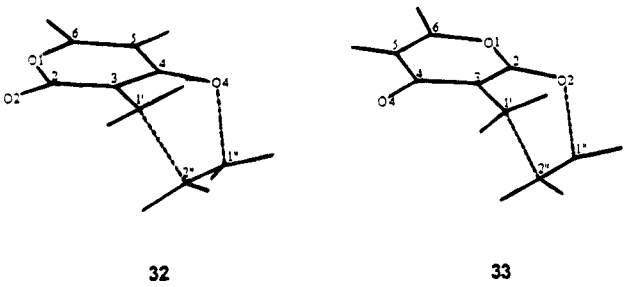
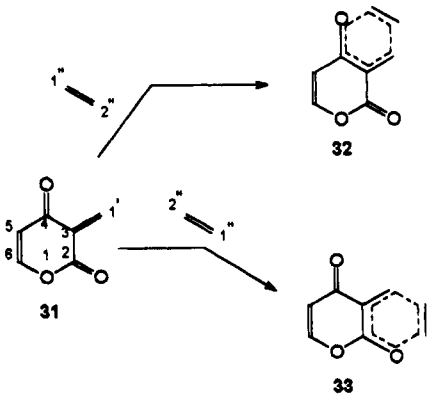


Figure 2. Optimized geometry of the transition states 32 and 33.

Table 3. Lengths of the Two Forming Bonds at the Transition States and Activation Enthalpy for the Addition of Ethylene to 31



	$d_{1'-2'}$ (Å)	$d_{O4-1''}$ (Å)	$d_{O2-1''}$ (Å)	$\Delta H_{f(kcal/mol)}$	$\Delta H^{\ddagger}_{(kcal/mol)}$
32	2.00	1.83	5.04	−28.76	23.27
33	1.98	5.00	1.91	−24.66	27.37

Table 4. Heat of Formation of 2a,b, 27a,b, and 28a,b (AM1 program)

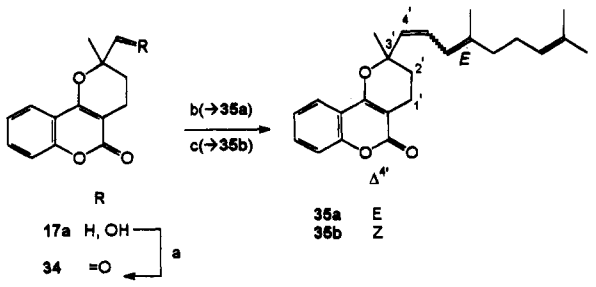
	ΔH_f (kcal/mol)		ΔH_f(kcal/mol)	$\Delta\Delta H_{f(a,b)}$
2a	−50.24	**2b**	−31.53	−18.71
27a	−64.12	**27b**	−58.78	−5.34
28a	−73.62	**28b**	−61.36	−12.26

to the C(1′)–C(3)–C(2)–O(2) system (transition state **33**), and the difference in the activation enthalpies is large enough to predict the presence of only one isomer, as observed for the addition with several olefins. In cases where the reaction occurred with partial (**3**–**6**, **20**) or complete (**7**) lack of chemoselectivity, secondary interactions might play a non negligible role in lowering the energy differences between the two transition states.

The cycloaddition of **1** and dienes **2**, **27**, and **28** was then considered, calculating the heats of formation of the corresponding Diels–Alder and hetero Diels–Alder adducts. The program AM1[25] was employed. Table 4 shows that the hetero Diels–Alder adduct **2a** is more stable than the Diels–Alder adduct **2b** by 18.71 kcal, thus explaining the exclusive formation of the former in the reaction of **1** and **2**. With cyclohexadiene, the energy difference between the normal and hetero Diels–Alder adducts is not so marked (5.34 kcal), thus making possible their interconversion *via* a 3,3-sigmatropic rearrangement.[26] Indeed, when the Diels–Alder adduct **27a** was heated in refluxing dioxane for 48 h, a ca. 10:1 (^{1}H-NMR analysis) mixture of **27a** and **27b** was formed, along

(26) Brugnolotti, M.; Corsico Coda, A.; Desimoni, G.; Faita, G.; Gamba Invernizzi, A.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1988**, *44*, 5229.

Scheme 3[a]



[a] (a) Dess–Martin reagent (90%); (b) geranyl-$PO(OEt)_2$, NaH, THF (25%); (c) geranyl-$PPh_3^+Br^-$, BuLi, THF (34%).

with degradation products that were not further investigated. As to isoprene (**28**), the calculations predict instead a major stability (ca. 12 kcal/mole) of the normal (**28a**) over the hetero Diels–Alder adduct (**28b**). This was verified experimentally, since only **28a** was obtained from the cycloaddition of **1** and **28**.

The reaction of the quinone methide **1** and terpenoids is an interesting mimic of reactions involved in the biogenesis of the polyketide meroterpenoids robustadials[27] and euglobals.[28,29] Furthermore, the reaction can be applied to the synthesis of natural products having a pyrano[3,2-*c*]coumarin structure. This is typified by a two-step conversion of the hetero Diels–Alder adduct **17a** to (±)-isoferprenin (**35a**),[30] a compound isolated from a toxic population of the Mediterranean plant *Ferula communis* L.[31] The synthesis depicted in Scheme 3 constitutes an expeditious entry into the natural product and its 4'-olefinic isomer, obtainable by modification of the final Wittig reaction.

Conclusions. A study of the reaction of **1** and olefins or acetylenes evidenced several reaction modes, since **1** can behave as a heterodiene, a dienophile, or an enophile. An experimental protocol for the uncatalyzed domino Knoevenagel–hetero Diels–Alder reaction of 4-hydroxycoumarin, paraformaldehyde, and olefins was developed. The range of applicability of this reaction is fairly wide, including some simple nonactivated olefins, a class of compounds rarely used in intermolecular hetero Diels–Alder reactions.[21] Pyrano[3,2-*c*]coumarinic adducts could be obtained in synthetically useful yields from *gem*-di-, tri-, and tetrasubstituted olefins, although chemoselectivity control was poor with tetrasubstituted olefins and when one of the substituents was a phenyl. The reaction has great potential for the synthesis of natural products, as shown by a concise synthesis of the prenylated coumarin (±)-isoferprenin.

Experimental Section

General Methods. Anhydrous conditions were achieved (when indicated) by flame-drying flasks and equipment. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized with 5% H_2SO_4 in EtOH and heating. Merck silica gel (70–230 mesh) was used for open-column chromatography. A Waters microPorasil column (0.8 × 30 cm) was used for semipreparative HPLC, with detection by a Waters differential refractometer 340. Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Bruker AC-300 spectrometer at 25 °C.

Materials. Commercially available reagents and solvents were used without further purification, unless otherwise noted. CH_2Cl_2 was dried by distillation from P_4O_{10}, THF by distillation from Na–benzophenone, and DMF by distillation from CaH_2.

Structure Elucidation. Linear and angular adducts could be distinguished on the basis of the chemical shift of H-5 (coumarin numbering). In linear adducts this proton is deshielded by the magnetic anisotropy of the chromone carbonyl and resonates at δ 8.10–8.20, whereas values of δ 7.70–8.00 were found in angular adducts.[32] Differences between the UV and IR spectra of linear and angular adducts could also contribute to the disinction. Thus, the stretching of the δ-lactone carbonyl of angular adducts is found at ca. 1700 cm^{-1}, whereas the same vibration of the chromone ketone carbonyl occurs at lower frequencies (1650–1600 cm^{-1}).[9] The UV spectra of linear adducts showed only one band at 260–280 nm (log ε 4–4.3), with shoulder(s) at 290–315 nm, whereas angular adducts displayed at least three distinct maxima between 260 and 320 nm (log ε > 4).[9,32] ^{13}C-NMR spectra were run only for structurally challenging adducts, and the spectra were fully assigned using two-dimensional techniques (^2J and ^3J (HMBC) ^{1}H–^{13}C correlations). Interprotonic NOE correlations were derived from the NOESY spectra; only correlation crucial for structural elucidation are reported. Systematic numbering was used for the assignments, making reference to the Ring System Handbook.[33] For the natural product isoferprenin (**35a**), the conventional biogenetic numbering of pyranocoumarins was instead employed.

Methods of Calculation. The calculations were performed with the AM1[25] method, implemented in the MOPAC program.[34] Full geometry optimization was carried out at the RHF level. Transition states were located through the SADDLE procedure. Stationary points of the potential energy surfaces were characterized through the calculation of the energy second derivative (force constant matrix).

General Procedure for the Generation and the Diels–Alder Trapping of 3-Methylene-2,4-chromandione. Paraformaldehyde (8 mol equiv) was added to a mixture of 4-hydroxycoumarin (1 mol equiv) and the olefinic (or acetylenic) substrate (4 mol equiv) in dioxane (ca. 15 mL/g of 4-hydroxycoumarin).[35] The mixture was refluxed until TLC (hexane–EtOAc 1:9 or toluene-ether 1:1 saturated with aqueous 1% HOAc) showed the complete disappearance or no further consumption of 4-hydroxycoumarin. After cooling and removal of the solvent, the residue was taken up in $CHCl_3$, washed with saturated Na_2CO_3 and brine, and dried ($MgSO_4$). Removal of the solvent left a residue that was purified by column chromatography. The column was packed with hexane and eluted with this solvent until the excess of olefin had been removed. The adducts were then obtained using the following mixtures of hexane–EtOAc as eluant (when necessary, HPLC was used to further separate the adducts): **3a**, **3b**: 8:2; **4a**, **4b**: 9:1, **5a**, **5b**: 9:1 **6a**, **6b**: 8.2; **7a**, **7b**: 9:1; **10a**: 8:2; **12a**: 7:3; **13a**: 8:2; **14a**: 9:1; (**15a** + **15b**): 9:1; **16a**, **16b**: 9:1; **17a**:

(27) Isolation: Xu, R.-S.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734. Revised structure: (a) Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1311. (b) Cheng, Q.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 4562. (c) Reference 15 (footnote 24).

(28) Kozuka, M.; Sawada, T.; Kasahara, F.; Mizuta, E.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1952.

(29) A similar reaction is also conceivable for the biogenesis of the humulene–methylene tropone adduct pycnidione (Harris, G. H.; Hoogsteen, K.; Silverman, K. C.; Raghoobar, S. L.; Billis, G. F.; Lingham, R. B.; Smith, J. K.; Dougherty, H. W.; Cascales, C.; Peláez, F. *Tetrahedron* **1993**, *49*, 2139) and of the humulene–*o*-quinone methide adduct lucidene (Weenen, H.; Nkunya, M. H. H.; El-Fadl, A. A.; Harkema, S.; Zweanenburg, B. *J. Org. Chem.* **1990**, *55*, 5107).

(30) Lamnaouer, D.; Fraigui, O.; Martin, M.-T.; Gallard, J. F.; Bodo, B. *J. Nat. Prod.* **1991**, *54*, 576.

(31) For studies on the toxins of this plant, see: Appendino, G.; Tagliapietra, S.; Gariboldi, P.; Nano; G. M.; Picci, V. *Phytochemistry* **1988**, *27*, 3619 and references therein.

(32) Ellis, G. P. In *The Chemistry of Heterocyclic Compounds*; Ellis, G. P., Ed.; Wiley: New York, 1977; Vol. 31, pp 481–494.

(33) *The Ring System Handbook*; American Chemical Society: Washington, D.C., 1993.

(34) Dewar, M. J. S.; Stewart, J. J. P. *QCPE Bull.* **1986**, *6*, 24; QCPE Program 506.

(35) Volatile compounds (1-pentene, 1-pentyne, ethyl vinyl ether) were used in a larger excess (ca. 10 mol equiv).

y:3, **18a**: 9:1; **19a**, **19b**: 9:1; **20a**, **20b**: 9:1; (**24a** + **24b**): 8:2 and then HPLC with the same eluant; (**25a** + **25b**): 9:1 and then HPLC with the same eluant; **26a**, **26b**: 95:5; **27a**, **27b**: 8:2; **28a**: 8:2; (29a + **29b**): 95:5; **30a**, **30b**: 95:5 and then 8:2 to elute **30c**.

(2*R*,*S*)-3,4-Dihydro-2-phenyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one (3a): mp 88–89 °C (ether); IR (KBr) 1700, 1620, 1410, 1310, 1180, 1110, 820 cm^{-1}; UV (EtOH) λ_{max} 315, 304, 281 nm; ^{1}H-NMR ($CDCl_3$) δ 7.81 (br d, J = 7.8 Hz, 1H, H-10), 7.52 (br t, J = 7.8 Hz, 1H, H-8), ca. 7.41 (m, 5H, 2-Ph), 7.31 (d, J = 7.8 Hz, 1H, H-7), 7.27 (br t, J = 7.8 Hz, 1H, H-9), 5.27 (dd, J = 9.9, 2.6 Hz, 1H, H-2), ca. 2.71 (m, 2H, H-4-a,b), ca. 2.37 (m, 1H, H-3-a), ca. 2.13 (m, 1H, H-3-b); MS (70 eV) 278 (100) [M$^+$]. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.82; H, 5.14.

(2*R*,*S*)-3,4-Dihydro-2-phenyl-2*H*,5*H*-pyrano[2,3-b][1]benzopyran-5-one (3b): mp 80 °C (ether); IR (KBr) 1630, 1580, 1480, 1410, 1270, 1150, 930 cm^{-1}; UV (EtOH) λ_{max} 290-(sh), 275 nm; ^{1}H-NMR ($CDCl_3$) δ 8.20 (brd, J = 8.2 Hz, 1H, H-6), 7.59 (br t, J = 8.2 Hz, 1H, H-8), ca. 7.43 (m, 5H, 2-Ph), ca. 7.35 (m, 2H, H-7 + H-9), 5.33 (dd, J = 10.6, 2.56 Hz, 1H, H-2), 2.84 (ddd, J = 16.8, 5.5, 3.0 Hz, 1H, H-4-a), 2.66 (ddd, J = 16.8, 11.0, 5.9 Hz, 1H, H-4-b), ca. 2.31 (m, 1H, H-3-a), ca. 2.11 (m, 1H, H-3-b); MS (70 eV) 278 (100) [M$^+$]. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.50; H, 5.10.

(2*R*,*S*)-3,4-Dihydro-2-propyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one (15a) (ca. 1:1 mixture with **15b**): ^{1}H-NMR ($CDCl_3$) δ 7.75 (br d, J = 7.8 Hz, 1H, H-10), 7.46 (br t, J = 7.8 Hz, 1H, H-8), 7.26 (br t, J = 7.8 Hz, H-9), 7.22 (br d, J = 7.8 Hz, 1H, H-7), 4.20 (m, 1H, H-2), 2.65 (m, 1H, H-4-a), 2.46 (m, 1H, H-4-b), 2.07 (m, 1H, H-3-a), 1.83 (m, 1H, H-1′-a), 1.78 (m, 1H, H-3-b), 1.66 (m, 1H, H-1′-b), 1.66 (m, 1H, H-2′-a), 1.50 (m, 1H, H-2′-b), 1.01 (t, J = 6.8 Hz, 3H, H-3′); ^{13}C-NMR ($CDCl_3$) δ 77.8 (s, C-2), 26.2 (t, C-3), 19.1 (t, C-4), 99.8 (s, C-4a), 163.2 (s, C-5), 152.3 (s, C-6a), 116.5 (d, C-7), 131.2 (d, C-8), 123.6 (d, C-9), 122.3 (d, C-10), 115.9 (s, C-10a), 159.1 (s, C-10b), 36.8 (t, C-1′), 18.6 (t, C-2′), 13.9 (q, C-3′).

(2*R*,*S*)-3,4-Dihydro-2-methyl-2-propyl-2*H*,5*H*-pyrano-[3,2-*c*][1]benzopyran-5-one (15b) (ca. 1:1 mixture with **15a**): ^{1}H-NMR ($CDCl_3$) δ 7.73 (br d, J = 7.8 Hz, 1H, H-10), 7.46 (br t, J = 7.8 Hz, 1H, H-8), 7.26 (br d, J = 7.8 Hz, 1H, H-7), 7.22 (br t, J = 7.8 Hz, 1H, H-9), 2.56 (m, 2H, H-4a + H-4-b), 1.76 (m, 2H, H-1′-a + H-1′b), 1.38 (s, 3H, H-1″), 1.01 (t, J = 6.8 Hz, 3H, H-2″); ^{13}C-NMR ($CDCl_3$): δ 80.0 (s, C-2), 29.8 (t, C-3), 17.0 (t, C-4), 100.8 (s, C-4a), 163.1 (s, C-5), 152.4 (s, C-6a), 116.4 (d, C-7), 131.2 (d, C-8), 123.6 (d, C-9), 122.3 (d, C-10), 159.9 (s, C-10a), 116.2 (s, C-10b), 23.0 (t, C-1), 7.7 (q, C-2′), 23.0 (q, C-1″).

***meso*-7,7a-Dihydro-15-propyl-6*H*,8*H*,9*H*,15a*H*[1]benzopyrano[3″,4″:5′,6′]pyrano[3′,2′-5,6]pyrano[3,2-*c*][1]-benzopyran-6,9-dione (16a)**: mp 225 °C (ether); IR (KBr) 1710, 1650, 1630, 1610, 1390, 1150, 1040, 940, 750 cm^{-1}; UV (EtOH) λ_{max} 304, 280 nm; ^{1}H-NMR ($CDCl_3$) δ 7.80 (br d, J = 8.0 Hz, 2H, H-1(14)), 7.53 (br t, J = 8.0 Hz, 2H, H-2(13)), 7.34 (br d, J = 8.0 Hz, 2H, H-4(11)), 7.30 (br t, J = 8.0 Hz, 2H, H-3(12)), 2.86 (dd, J = 16.2, 4.4 Hz, 2H, H-7-a(8-a)), 2.63 (m, 1H, H-7a), 2.53 (m, 2H, H-7-b(8-b)), 2.07 (m, 2H, H-1′-a + H-1′-b), 1.75 (m, 2H, H-2′-a + H-2′-b), 1.03 (t, J = 6.8 Hz, 3H, H-3′); ^{13}C-NMR ($CDCl_3$) δ 122.4 (d, C-1(14)), 124.1 (d, C-2(13)), 132.1 (d, C-3(12), 116.9 (d, C-4(11)), 152.8 (s, C-4A (10A)), 162.2 (s, C-6(9)), 100.2 (s, C-6a(8a)), 23.2 (t, C-7(8)), 29.3 (d, C-7a), 103.7 (s, C-15a), 156.4 (s, C-16a(14b)), 114.9 (s, C-16b(14a)), 37.6 (t, C-1′), 15.7 (t, C-2′), 14.2 (q, C-3′); MS (70 eV) 434 (100) [M + NH_4]$^+$. Anal. Calcd for $C_{25}H_{20}O_6$: C, 72.11, H, 4.84. Found: C, 72.25; H, 4.89.

(7a*RS*,15a*SR*)-7,7a-Dihydro-15a-propyl-6*H*,8*H*,9*H*,15a*H*-[1]benzopyrano[3″,2″:5′,6′]pyrano[3′,2′:5,6]pyrano[3,2-*c*]-[1]benzopyran-6,9-dione (16b): oil; IR (film): 1700, 1660, 1640, 1580, 1450, 1360, 1290, 110, 870 cm^{-1}; UV (EtOH) λ_{max} 280 nm; ^{1}H-NMR ($CDCl_3$) δ 8.17 (br d, J = 8.1 Hz, 1H, H-10), 7.79 (br d, J = 8.0 Hz, 1H, H-1), 7.63 (br t, J = 8.1 Hz, 1H, H-12), 7.54 (br t, J = 8.0 Hz, 1H, H-3), 7.41 (br t, J = 8.1 Hz, 1H, H-10), 7.39 (br d, J = 8.1 Hz, 1H, H-13), 7.33 (br d, J = 8.0 Hz, 1H, H-4), 7.30 (br t, J = 8.0 Hz, 1H, H-2), 2.86 (m, 1H, H-7-a), 2.83 (m, 1H, H-8-a), ca. 2.16 (m, 3H, H-7-b + H-8-b + H-7a), 2.06 (m, 2H, H-1′-a + H-1′-b), 1.74 (m, 2H, H-2′-a,b), 1.00 (t, J = 6.9 Hz, H-3′); ^{13}C-NMR ($CDCl_3$) δ 122.3 (d, C-1), 124.1 (d, C-2), 132.0 (d, C-3), 116.7 (d, C-4), 152.6 (s, C-4a), 162.0 (s, C-6), 100.0 (s, C-6a), 22.7 (t, C-7 or C-8), 29.3 (d, C-7a), 21.15 (t, C-8 or C-7), 94.7 (s, C-8a), 177.7 (s, C-9), 122.5 (s, C-9a), 125.8 (d, C-10), 125.3 (d, C-11), 133.2 (d, C-12), 117.3 (d, C-13), 153.3 (s, C-13a), 162.9 (s, C-14a), 105.5 (s, C-15a), 156.0 (s, C16a), 114.6 (s, C-16b), 37.5 (t, C-1′), 15.5 (t, C-2′), 14.0 (q, C-3′); MS (70 eV) 434 (100) [M + NH_4]$^+$. Anal. Calcd for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84. Found: C, 72.00; H, 4.90.

(2*R*,*S*)-3,4-Dihydro-2-(hydroxymethyl)-2-methyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one (17a): mp 165 °C (ether); IR (KBr) 3360, 1750, 1625, 1605, 1400, 1165, 1075, 1055 cm^{-1}; UV (EtOH) λ_{max} 317, 304, 280, 270 nm; ^{1}H-NMR ($CDCl_3$) δ 7.77 (br d, J = 7.8 Hz, 1H, H-10), 7.50 (br t, J = 7.8 Hz, 1H, H-8), ca. 7.30 (m, 2H, H-7 + H-9), 3.81 (br d, J= 11.7 Hz, 1H, H-1-a), 3.72 (br d, J = 11.7 Hz, 1H, H-1′-b), 2.69 (m, 1H, H-4-a), 2.57 (m, 1H, H-4-b), 2.10 (m, 1H, H-3-a), 1.89 (br s, 1H, OH), 1.85 (m, 1H, H-3-b), 1.39 (s, 3H, 2-Me); MS (70 eV) 246 (20) [M$^+$], 92 (100). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.44; H, 5.80.

(7a*R*,9*S*,11*S*,11a*S*)-10,10,11a-Trimethyl-9,11-methano-7,7a,8,9,10,11-hexahydro-6*H*,11a*H*-[1]benzopyrano[4,3-*b*]-[1]benzopyran-6-one (18a): oil; IR (film) 1690, 1625, 1400, 1350, 1185, 1085, 1010, 910 cm^{-1}; UV (EtOH) λ_{max} 310, 304, 280 nm; ^{1}H-NMR ($CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H, H-1), 7.47 (d, J = 8.0 Hz, 1H, H-3), 7.27 (d, J = 8.0 Hz, 1H, H-4), 7.22 (d, J = 8.0 Hz, 1H, H-2), 7.27 (m, 1H, H-7a), 2.59 (br s, 2H, H-7-a,b), 2.30 (t, J = 6.0 Hz, 1H, H-11), 2.17 (m, 1H, H-8-a), 2.11 (m, 1H, H-1′-a), 1.89 (m, 1H, H-9), 1.48 (s, 3H, 11a-Me), 1.35 (m, 1H, H-8-b), 1.30 (s, 3H, 10-Me-a), 1.10 (s, 10-Me-b), 0.70 (d, J = 10.4 Hz, 1H, H-1′-b); diagnostic NOE H-7a, 10-Me(b); H-7a, 11a-Me; ^{13}C-NMR ($CDCl_3$) δ 122.2 (d, C-1), 123.6 (d, C-2), 131.6 (d, C-3), 116.5 (d, C-4), 152.6 (s, C-4a), 163.6 (s, C-6), 99.0 (s, C-6a), 21.2 (t, C-7), 31.7 (d, C-7a), 34.6 (t, C-8), 40.9 (d, C-9), 40.0 (s, C-10), 54.7 (d, C-11), 86.8 (s, C-11a), 160.7 (s, C-12a), 115.7 (s, C-12b), 26.8 (t, C-1′), 28.5 (q, 10-Me), 22.6 (q, 10-Me), 28.7 (q, 11a-Me); MS (70 eV) 310 (15) [M$^+$], 189 (100). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.50; H, 7.10.

(2*R*,1′*S*,5′*S*)-3,4-Dihydro-6,6′-dimethylspiro[2*H*,5H-pyrano[3,2-*c*][1]benzopyran-2,2′-bicyclo[3.1.1]heptane]-5-one (19a): oil, IR (film) 1710, 1630, 1400, 1180, 1105, 1055, 740 cm^{-1}; UV (EtOH) λ_{max} 317, 281, 170 nm; ^{1}H-NMR ($CDCl_3$) δ 7.72 (br d, J = 8.1 Hz, 1H, H-10), 7.45 (br t, J = 8.1 Hz, 1H, H-8), 7.26 (br d, J = 8.1 Hz, 1H, H-7), 7.22 (br t, J = 8.1 Hz, 1H, H-9), 2.55 (br t, J = 7.7 Hz, 2H, H-4-a,b), 2.27 (m, 1H, H-7′-a), 2.17 (t, J = 5.0 Hz, H-1′), 2.03 (m, 1H, H-3-a), ca. 2.00 (m, 5H, H-3′-a,b + H-4′-a,b + H-5′), 1.84 (m, 1H, H-3′-b), 1.76 (d, J = 10 Hz, 1H, H-7′-b), 1.31 (s, 3H, 6′-Me-a), 1.10 (s, 3H, 6′-Me-b); Diagnostical NOE: 6′Me(b), H-3-b; ^{13}C-NMR ($CDCl_3$) δ 85.2 (s, C-2), 32.1 and 17.0 (2 × t, C-3 and C-4), 100.2 (s, C-4a), 163.1 (s, C-5), 152.5 (s, C-6a), 116.5 (d, C-7), 131.1 (d, C-8), 123.6 (d, C-9), 122.3 (d, C-10), 116.5 (s, C-10a), 159.2 (s, C-10b), 49.8 (d, C-1′), 28.5 (t, C-3′), 24.7 (t, C-4′), 40.6 (d, C-5′), 38.3 (s, C-6′), 26.5 (t, C-7′), 23.0 (6′-Me), 27.0 (6′-Me); MS (70 eV) 310 (48) [M$^+$], 189 (100). Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.20; H, 7.08.

(1″*S*,5″*S*)-3-(2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)-4-hydroxy-2*H*-1-benzopyran-2-one (19b): mp 58 °C (hexane–EtOAc); IR (KBr) 1680, 1610, 1570, 1500, 1220, 1180, 1150, 1075, 760 cm^{-1}; UV λ_{max} 318, 307, 280 nm; ^{1}H-NMR ($CDCl_3$) δ 7.92 (br, d, J = 8.0 Hz, 1H, H-5), 7.50 (br t, J = 8.0 Hz, 1H, H-7), 7.29 (br t, J = 8.0 Hz, 1H, H-6), 7.27 (br d, J = 8.0 Hz, 1H, H-8), 5.28 (br d, J = 1.0 Hz, 1H, H-2″), 2.70 (m, 2H, H-1′-a,b), 2.32 (m, 1H, H-7″-a), 2.22 (m, 2H, H-2′-a,b), 2.18 (m, 1H, H-3″-a), 2.17 (m, 1H, H-6″), 2.03 (m, 2H, H-3″-b + H-4″), 1.21 (s, 3H, 5″-Me), 1.07 (d, J = 10.0 Hz, 1H, H-7″-b), 0.77 (s, 3H, 5″-Me); ^{13}C-NMR ($CDCl_3$) δ 159.8 (s, C-2), 105.0 (s, C-3), 164.2 (s, C-4), 115.9 (s, C-4′), 123.0 (d, C-5), 123.8 (d, C-6), 131.4 (d, C-7), 116.5 (d, C-8), 152.2 (s, C-8a), 22.8, 34.9 (2 × t, C-1′ and C-2′), 40.7 (d, C-1″), 148.0 (s, C-2″), 116.8 (d, C-3″), 31.6 (t, C-4″), 45.8 (d, C-5″), 38.0 (s, C-6″), 31.2 (t, C-7″), 21.0 (q, 6″-Me), 26.2 (q, 6″-Me); MS (70 eV) 310 (32) [M$^+$], 135 (100). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.30; H, 7.21.

(7a*RS*,11a*SR*)-7a,8,9,10,11,11a-Hexahydro-8,11-methano-

6*H*,7*H*-[1]benzopyrano[4,3-*b*][1]benzopyran-6-one (24a): mp 172 °C (hexane); IR (KBr) 1697, 1637, 1611, 1493, 1410, 1322, 1273, 1180 cm^{-1}; UV (EtOH) λ_{max} 316, 305, 282, 260 nm; ^{1}H-NMR ($CDCl_3$) δ 7.82 (br d, J = 8.0 Hz, 1H, H-1), 7.54 (br t, J = 8.0 Hz, 1H, H-3), 7.24 (m, 2H, H-2 + H-4), 4.19 (d, J = 7.0 Hz, 1H, H-11a), 3.0 (dd, J = 16.0, 9.0 Hz, 1H, H-7-a), 2.65 (br s, 1H, H-8), 2.20 (br s, 1H, H-11), 2.20 (m, 1H, H-7a), 2.06 (dd, J = 16.0, 6.2 Hz, H-7-b), 1.70–1.20 (overlapped m, 6H, H-9-a,b + H-10-a,b + H-13-a,b); MS (70 eV) 268 (100) [M^+]. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.98; H, 6.10.

(4a*RS*,12a*SR*)-2,3,4,4a,12,12a-Hexahydro-1,4-methano-1*H*,11*H*-[1]benzopyrano[2,3-*b*][1]benzopyran-11-one (24b): mp 150 °C (ether); IR (KBr) 1645, 1565, 1465, 1430, 1250 cm^{-1}; UV (EtOH) λ_{max} 285 nm; ^{1}H-NMR ($CDCl_3$) δ 8.20 (br d, J = 8.0 Hz, 1H, H-10), 7.61 (br t, J = 8.0 Hz, 1H, H-8), 7.30 (m, 2H, H-7 + H-9), 4.40 (d, J = 7.0 Hz, 1H, H-4-a), 3.25 (dd, J = 16.0, 9.2 Hz, 1H, H-12-a), 2.64 (br s, 1H, H-4 or H-1), 2.20 (br s, 1H, H-1 or H-4), 2.15 (m, 1H, H-12a), 2.06 (dd, J = 16.0, 6.2 Hz, 1H, H-12-b) 1.80–1.20 (m, 6H, H-2-a,b + H-3-a,b, + H-13-a,b); MS (70 eV) 268 (100) [M^+]. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.32; H, 5.97.

(7a*SR*,11*S*,14*R*,16a*RS*)-7,7a,8,9,11,12,13,14,15,16-Decahydro-13,13,16a-trimethyl-10-methylene-6*H*,10*H*,16a*H*-bicyclo[7.2.0]undecano[5′,4′:5,6]pyrano[3,2-*c*][1]benzopyran-6-one (26a) (major:minor = ca. 2:1): mp 105 °C (ether); IR (KBr) 1700, 1630, 1490, 1400, 1275, 1110, 1040 cm^{-1}; UV (EtOH) (EtOH) λ_{max} 315, 300, 285, 270 nm; ^{1}H-NMR ($CDCl_3$) major isomer (minor isomer) δ 7.48 (br d, J = 8.1 Hz, 1H, H-1), 7.43 (br t, J = 8.1 Hz, 1H, H-3), 7.30 (br d, J = 8.1 Hz, 1H, H-4), 7.23 (br t, J = 8.1 Hz, 1H, H-2), 4.93 (4.90) (br s, 1H, H-18-a), 4.90 (4.78) (br s, 1H, H-18-b), 2.41 (2.60) (m, 1H, H-11), 2.55 (2.83) (dd, J = 16.0, 9.2 Hz, 1H, H-7-a), 2.13 (2.15) (m, 1H, H-7a), 2.01 (2.09) (dd, J = 16.0, 6.4 Hz, 1H, H-7-b), 1.21 (1.14) (s, 3H, 16a-Me), 0.98 (s, 3H, 13-Me), 0.94 (0.93) (s, 3H, 13-Me); ^{13}C-NMR ($CDCl_3$) major isomer (minor isomer) δ 122.3 (122.5) (d, C-1), 123.6 (127.6) (d, C-2), 131.1 (d, C-3), 116.5 (d, C-4), 152.5 (s, C-5), 162.9 (s, C-6), 99.8 (s, C-6a), 26.1 (25.3) (t, C-7), 33.9) (d, C-7a), 22.3 (22.8) (t, C-8 or C-16), 35.2 (36.5) (t, C-9), 151.9 (154.5) (s, C-10), 41.5 (42.5) (d, C-11), 36.5 (38.5) (t, C-12), 33.7 (33.8) (t, C-13), 53.5 (55.3) (d, C-14), 37.8 (38.9) (t, C-15), 33.4 (t, C-16 or C-8), 84.4 (s, C-16a), 21.0 (20.0) (q, 16a-Me), 30.2 (29.7) (q, 13-Me), 22.2 (22.6) (q, 13-Me), 158.8 (158.9) (s, C-17a), 116.1 (s, C-17b), 110.6 (110.1) (t, C-18); MS (70 eV) 378 (48) [M^+], 180 (100). Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.50; H, 8.03.

(6a*SR*,9*R*,12*S*,15a*RS*)-7,8,9,10,11,12,14,15,15a,16-Decahydro-6a*H*,13*H*,17*H*-bicyclo[7.2.0]undecano[5′,4′:5,6]pyrano-[2,3-*b*][1]benzopyran-17-one (26b) (major:minor = ca. 3:1): mp 121 °C (ether); IR (KBr) 1625, 1570, 1425, 1210, 1160, 1060, 880 cm^{-1}; UV (EtOH) λ_{max} 300 nm; ^{1}H NMR ($CDCl_3$) major isomer (minor isomer) δ 8.20 (br d, J = 8.0 Hz, 1H, H-1), 7.67 (br t, J = 8.0 Hz, 1H, H-3), 7.33 (br t, J = 8.0 Hz, 1H, H-2), 7.33 (br d, J = 8.0 Hz, 1H, H-4), 4.95 (4.87) (br s, 1H, H-18-a), 4.75 (4.73) (br s, 1H, H-18-b), 2.77 (3.00) (dd, J = 16.0, 9.0 Hz, 1H, H-16-a), 2.45 (m, 1H, H-14-a), 2.40 (2.60) (m, 1H, H-12), 2.13 (m, 1H, H-14-b), 2.15 (2.17) (dd, J = 16.0 6.0 Hz, 1H, H-16-b), 1.93 (1.57) (m, 1H, H-9), 1.27 (1.21) (s, 3H, 6a-Me), 0.99 (0.89) (s, 3H, 10-Me), 0.99 (0.90) (s, 3H, 10-Me); ^{13}C-NMR ($CDCl_3$) major isomer (minor isomer) δ 125.7 (d, C-1), 124.8 (d, C-2), 132.6 (d, C-3), 117.0 (d, C-4), 153.0 (152.4) (s, C-4a), 163.0 (163.1) (s, C-5a), 88.7 (s, C-6a), 33.0 (t, C-7), 37.8 (t, C-8), 53.5 (55.3) (d, C-9), 33.2 (34.0) (s, C-10), 36.4 (t, C-11), 41.7 (42.5) (d, C-12), 151.7 (154.4) (s, C-13), 35.1 (t, C-14), 22.3 (t, C-15), 34.3 (35.0) (d, C-15a), 24.8 (24.0) (t, C-16), 95.5 (s, C-16a), 177.5 (s, C-17), 122.5 (s, C-17a), 21.0 (20.0) (q, 6a-Me), 22.0 (22.5) (q, 10-Me), 30.0 (29.0) (q, 10-Me), 110.8 (110.1) (t, C-18); MS (70 eV) 378 (20) [M^+], 180 (100). Anal. Calcd for $C_{23}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.10; H, 7.90.

(7a*SR*,11a*RS*)-7,7a,8,9-Tetrahydro-6*H*,11*H*-[1]benzopyrano[4,3-*b*][1]benzopyran-6-one (27a): mp 135 °C (ether); IR(KBr) 1710, 1630, 1500, 1395, 1280, 915, 760 cm^{-1}; UV (EtOH) λ_{max} 315, 300, 280, 270 nm; ^{1}H-NMR ($CDCl_3$) δ 7.73 (br d, J = 7. Hz, 1H, H-1), 7.43 (br t, J = 7.8 Hz, 1H, H-3), 7.23 (br d, J = 7.8 Hz, 1H, H-4), 7.20 (br t, J = 7.8 Hz, 1H, H-2), 6.00 (m, 1H, H-10), 5.90 (m, 1H, H-11), 4.69 (br s, 1H, H-11a), 2.68 (dd, J = 17.6, 6.6 Hz, 1H, H-7-a), 2.44 (dd, J = 17.6, 4.2 Hz, 1H, H-7-b), 2.23 (m, 1H, H-7a), 2.20 (m, H-8-a,b + H-8-a,b + H-9-a,b); ^{13}C-NMR ($CDCl_3$) δ 122.4 (d, C-1), 123.7 (d, C-2), 131.2 (d, C-3), 116.4 (d, C-4), 152.0 (s, C-4a), 163.5 (s, C-6), 99.2 (s, C-6a), 24.5 (t, C-7), 29.4 (d, C-7a), 23.2 (t, C-8), 23.5 (d, C-9), 124.7 (d, C-10), 133.6 (d, C-11), 72.7 (s, C-11a), 158.0 (s, C-12a), 116.0 (s, C-12b); MS (70 eV) 254 (20) [M^+], 80 (100). Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.70; H, 5.59.

(3*RS*,1′*RS*,4′*RS*)-Spiro[2*H*,4*H*-[1]benzopyran-3,2′-bicyclo[2.2.2]oct-5′-ene]-2,4′-dione (27b): oil; IR (film) 1675, 1635, 1410, 1240, 1080, 1080, 860, 770 cm^{-1}; UV (EtOH) λ_{max} 310, 260 nm; ^{1}H-NMR ($CDCl_3$) δ 7.89 (br d, J = 8.1 Hz, 1H, H-5), 7.62 (br t, J = 8.1 Hz, 1H, H-7), 7.27 (br 1, J = 8.1 Hz, 1H, H-6), 7.18 (br d, J = 8.1 Hz, 1H, H-8), 6.50 (t, J = 7.2 Hz, 1H, H-5′), 6.07 (t, J = 7.2 Hz, 1H, H-6′), 2.87 (m, 1H, H-1′), 2.82 (m, 1H, H-4′), 2.47 (dd, J = 13.0, 2.5 Hz, 1H, H-3′-a), 2.05 (dt, J = 13.0, 3.0, 3.0 Hz, 1H, H-3′-b), 1.67 (m, 1H, H-8′-a), 1.50 (m, 1H, H-7′-a), 1.20 (m, 1H, H-8′-b), 1.07 (m, 1H, H-7′-b); Relevant NOE: H-8, H-6′; H-8, H-1′; ^{13}C-NMR ($CDCl_3$) δ 169.5 (s, C-2), 63.0 (s, C-3), 193.0 (s, C-4), 119.0 (s, C-4a), 127.3 (d, C-5), 124.7 (d, C-6), 136.4 (d, C-7), 117.0 (d, C-8), 154.5 (s, C-8a), 40.1 (d, C-1′), 27.8 (t, C-3′), 29.4 (d, C-4′), 137.5 (d, C-5′), 128.1 (d, C-6′), 21.4 (t, C-7′), 22.3 (t, C-8′); MS (70 eV) 254 (20) [M^+], 119 (100). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57, H, 5.55. Found: C, 75.60; H, 5.59.

(3*RS*)-4′-Methylspiro[2*H*,4*H*-[1]benzopyran-3,1′-cyclohex-3′-ene]-2,4-dione (28a): mp 70 °C (ether); IR (KBr) 3060, 1770, 1680, 1450, 1300, 1220, 1100, 1050 cm^{-1}; UV (EtOH) λ_{max} 310, 256 nm; ^{1}H-NMR ($CDCl_3$) δ 7.90 (br d, J = 7.8 Hz, 1H, H-5), 7.64 (br t, J = 7.8 Hz, 1H, H-7), 7.28 (br t, J = 7.8 Hz, 1H, H-6), 7.19 (br d, J = 7.8 Hz, H-8), 5.50 (br s, H-3′), 2.78 (br d, J = 18.0 Hz, H-2′-a), 2.58 (br d, J = 18.0 Hz, 1H, H-2′-b), ca. 2.06 (m, 4H, H-5′-a,b + H-6′-a,b), 1.71 (br s, 3H, H-4′); MS (70 eV) 242 (20) [M^+], 121 (100). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.45; H, 5.88.

(7a*SR*,11a*SR*)-7a-Methyl-10-(1-methylethyl)-7,7a,8,9-tetrahydro-6*H*,11a*H*-[1]benzopyrano[4,3-*b*][1]benzopyran-6-one (29a) (3:1 mixture with **29b**): ^{1}H-NMR ($CDCl_3$) δ 7.78 (br, d, J = 8.0 Hz, 1H, H-1), 7.45 (br t J = 8.0 Hz, 1H, H-3), 7.26 (br d, J = 8.0 Hz, 1H, H-4), 7.23 (br t, J = 8.0 Hz, 1H, H-2), 5.41 (br s, 1H, H-11), 4.58 (br s, 1H, H-11a), 2.45 (d, J = 16.0 Hz, 1H, H-7-a), 2.13 (d, J = 16.0 Hz, 1H, H-7-b), 2.18 (m, 1H, H-1′), 1.03 (s, 3H, 7a-Me), 0.99 (d, J = 6.8 Hz, 3H, 1′-Me), 0.85 (d, J = 6.8 Hz, 3H, 1′-Me); ^{13}C-NMR (CDCl, δ 122.6 (d, C-1), 123.7 (d, C-2), 131.2 (d, C-3), 116.5 (d, C-4), 152.3 (s, C-4a), 163.7 (s, C-6), 99.45 (s, C-6a), 27.1 (t, C-7), 29.4 (d, C-7a), 31.5 (t, C-8), 23.2 (t, C-9), 148.6 (s, C-10), 118.1 (d, C-11), 80.35 (d, C-11a), 157.8 (s, C-12a) 115.9 (s, C-12b), 25.4 (7a-Me), 34.5 (d, C-1′), 21.4 (q, 1′-Me), 21.3 (q, 1′-Me); MS (70 eV) 310 (8) [M^+], 136 (100). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.50; H, 7.18.

(7a*SR*,11a*SR*)-10-Methyl-7a-(1-methylethyl)-7,7a,8,9-tetrahydro-6*H*,11a*H*-[1]benzopyrano[4,3-*b*][1]benzopyran-6-one (29b) (1:3 mixture with **29a**): ^{1}H-NMR ($CDCl_3$) δ 7.76 (br d, J = 8.0 Hz, 1H, H-1), 7.44 (br t, J = 8.0 Hz, 1H, H-3), 7.24 (br d, J = 8.0 Hz, 1H, H-4), 7.20 (br t, J = 8.0 Hz, 1H, H-2), 5.47 (br s, 1H, H-11), 4.72 (br s, 1H, H-11a), 2.42 (d, J = 16.0 Hz, 1H, H-7-a), 2.27 (d, J = 16.0 Hz, 1H, H-7-b), 1.81 (m, 1H, H-1′), 1.67 (br s, 10-Me), 0.99 (d, J = 6.8 Hz, 3H, 1′-Me), 0.92 (d, J = 6.8 Hz, 3H, 1′-Me); ^{13}C-NMR ($CDCl_3$) δ 122.6 (d, C-1), 123.7 (d, C-2), 131.2 (d, C-3), 116.4 (d, C-4), 152.3 (s, C-4a), 163.7 (s, C-6), 99.9 (s, C-6a), 27.4 (t, C-7), 34.2 (d, C-7a), 24.1 (t, C-8), 27.3 (t, C-9), 140.0 (s, C-10), 210.1 (d, C-11), 76.5 (d, C-11a), 158.2 (s, C-12a), 115.9 (s, C-12b), 23.0 (q, 10-Me), 29.5 (d, C-1′), 17.0 (q, 1′-Me), 16.8 (q, 1′-Me).

(7a*R*,9*R*,11a*S*)-11a-Methyl-9-(1-methylethyl)-7,7a,8,9-tetrahydro-6*H*,11a*H*-[1]benzopyrano[4,3-*b*][1]benzopyran-6-one (30a): mp 69 °C (hexane–EtOAc); IR (KBr) 1700, 1645, 1400, 1190, 1115, 1060, 1035, 750 cm^{-1}; UV (EtOH) λ_{max} 317, 303, 280, 270 nm; ^{1}H-NMR ($CDCl_3$) δ 7.72 (br d, J = 8.0 Hz, 1H, H-1), 7.43 (br d, J = 8.0 Hz, 1H, H-3), 7.23 (br d, J = 8.0 Hz, 1H, H-4), 7.20 (br d, J = 8.0 Hz, 1H, H-2), 5.72 (d, J = 10 Hz, 1H, H-11), 5.67 (d, J = 10 Hz, 1H, H-10), 2.62 (dd, J =

17.2, 6.3 Hz, 1H, H-7-a), 2.38 (dd, J = 17.2, 7.8 Hz, 1H, H-7-b), 2.10 (m, 2H, H-7A + H-9), 1.68 (m, 3H, H-1′ + H-8-a,b), 1.50 (s, 3H, 11a-Me), 0.89 (d, J = 7.0 Hz, 3H, 1′-Me), 0.88 (d, J = 7.0 Hz, 3H, 1′-Me); diagnostic NOE 11a-Me, H-7a; 11a-Me, H-1′; ^{13}C-NMR ($CDCl_3$) δ 122.4 (d, C-1), 123.5 (d, C-2), 131.1 (d, C-3), 116.4 (d, C-4), 152.3 (s, C-4a), 163.2 (s, C-6), 99.4 (s, C-6a), 22.1 (t, C-7), 33.5 (d, C-7a), 27.4 (t, C-8), 38.7 (d, C-9), 130.5 (d, C-10), 133.0 (d, C-11), 78.5 (s, C-11a), 158.0 (s, C-12a), 115.9 (s, C-12b), 31.7 (d, C-1′), 20.0 (q, 1′-Me),19.8 (q, 1′-Me), 27.3 (q, 11a-Me); MS (70 eV) 310 (13) [M$^+$], 93 (100). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.27; H, 7.09.

(3*R*,1′*S*,4′*R*,7′*R*)-5′-Methyl-7′-(1-methylethyl)-spiro-[2*H*,4*H*-[1]benzopyran-3,2′-bicyclo[2.2.2]oct-5′-ene]-2,4-dione (30b): mp 102 °C (hexane–ether); IR (KBr) 1670, 1630, 1390, 1180, 1110, 1080, 845, 750 cm^{-1}; UV (EtOH) λ_{max} 310, 256 nm; ^{1}H-NMR ($CDCl_3$) δ 7.85 (br d, J = 7.9 Hz, 1H, H-5), 7.61 (br t, J = 7.9 Hz, 1H, H-7), 7.25 (br t, J = 7.9 Hz, 1H, H-6), 7.17 (br d, J = 7.9 Hz, 1H, H-8), 5.46 (br d, J = 6.5 Hz, 1H, H-6′), 2.83 (dd, J = 6.5, 2.0 Hz, 1H, H-1′), 2.56 (m, 1H, H-5′), 2.40 (dd, J = 13.1, 2.5 Hz, 1H, H-3′-a), 2.23 (dt, J = 13.1, 2.8, 2.8 Hz, 1H, H-3′-b), 1.80 (s, 3H, 5′-Me), 1.77 (ddd,J = 13.0, 7.0, 2.6, 1H, H-8′-a), 1.13 (m, 1H, H-7′), 0.96 (m, 1H, H-1″), 0.83 (m, 1H, H-8′Hb), 0.66 (d, J = 6.4 Hz, 3H, 1″-Me-a), 0.48 (d, J = 6.4 Hz, 3H, 1″-Me-b); diagnostic NOE H-5, 1″-Me-a; ^{13}C-NMR ($CDCl_3$) δ 169.5 (s, C-2), 193.2 (s, C-4), 119.3 (s, C-4a), 127.0 (d, C-5), 124.6 (d, C-6), 136.2 (d, C-7), 116.8 (d, C-8), 15.4 (s, C-8a) 64.7 (s, C-2′), 44.1 (d, C-1′), 117.5 (d, C-6′), 147.0 (s, C-5′), 36.2 (d, C-4′), 25.0 (t, C-3′), 40.7 (d, C-7′), 30.0 (t, C-8′), 20.0 (q, 5′-Me), 32.5 (d, C-1″), 20.05 (q, 1″-Me), 20.65 (q, 1″-Me); MS (70 eV) 310 (5) [M$^+$], 176 (100). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39, H, 7.14. Found: 77.51; H, 7.16.

(1″*RS*)-4-Hydroxy-3-[(2-methyl-5-(1-methylethyl)-2,4-cyclohexadienyl)methyl]-2*H*-[1]benzopyran-2-one (30c): mp 138 °C (ether); IR (KBr) 1780, 1690, 1615, 1465, 1310, 1225, 1065, 1035 cm^{-1}; UV (EtOH) λ_{max} 315, 303, 280, 260 nm; ^{1}H-NMR ($CDCl_3$) δ 5.82 (br d, J = 8.2 Hz, 1H, H-5), 7.53 (br t, J = 8.2 Hz, 1H, H-7), 7.33 (br d, J = 8.2 Hz, 1H, H-8), 7.30 (br t, J = 8.2 Hz, 1H, H-6), 6.80 (br s, -OH), 5.78 (br d, J = 7.0 Hz, 1H, H-3″), 5.72 (br d, J = 7.0 Hz, 1H, H-4″), 2.89 (dd, J = 13.4, 8.2 Hz, 1H, H-1′-a), 2.47 (m, 2H, H-1″ + H-6′-a), 2.47 (dd, J = 13.4, 7.0 Hz, 1H, H-1′-b), 2.33 (m, 1H, iPr), 2.03 (d, J = 15.9 Hz, 1H, H-6-b), 1.73 (br s, 3H, 2′-Me), 1.03 (d, J = 6.8 Hz, 3H, iPr), 1.05 (d, J = 6.8 Hz, 3H, iPr); ^{13}C-NMR ($CDCl_3$) δ 160.7 (s, C-2), 104.0 (s, C-3), 163.6 (s, C-4), 115.0 (s, C-4a) 123.2 (d, C-5), 124.0 (d, C-6), 131.9 (d, C-7), 116.6 (d, C-8), 152.6 (s, C-8a), 26.5 (t, C-1′), 36.0 (d, C-1″), 120.7 (d, C-3″), 115.9 (d, C-4″), 142.7 (s, C-5″), 31.7 (t, C-6″), 23.1 (q, 2″-Me), 34.6 (d, iPr), 21.2 (q, iPr), 20.5 (q, iPr). MS (70 eV) 310 (2) [M$^+$], 176 (100). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.33; H, 7.10.

Synthesis of (±)-Isoferprenin (36a). (a) Oxidation of Neopentyl Alcohol 17a. A solution of **17a** (500 mg, 2.06 mmol) in 10 mL of dry CH_2Cl_2 was added dropwise to a solution of Dess–Martin reagent[36] (3.5 g, 8.24 mmol, 4 mol equiv) in 60 mL of dry CH_2Cl_2. The mixture was stirred under nitrogen for 1 h, diluted with EtOAc, and treated with a saturated $NaHCO_3$ solution containing 2.75 g of $Na_2S_2O_3$. After stirring 20 min at room temperature, the organic phase was washed with brine and dried ($MgSO_4$). Removal of the solvent gave **34** as a colorless gum (450 mg, 90%), which could not be stored, and was directly used for the next step: IR (film) 1700, 1635, 1590, 1400, 1200, 1100, 930, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.63 (s, 1H, C*HO*), 7.85 (br d, J = 8.0 Hz, 1H, H-10), 7.53 (br t, J = 8.0 Hz, 1H, H-8), ca. 7.30 (m, 2H, H-7 + H-9), 2.61 (m, 1H, H-4-a), 2.42 (m, 1H, H-4-b), 2.32 (m, 1H, H-3-a), 1.91 (m, 1H, H-3-b), 1.57 (s, 3H, C(2)-Me); MS (70 eV) 244 (35) [M$^+$] [$C_{14}H_{12}O_4^+$], 121 (100).

(b) Reaction of Aldehyde 34 and Diethyl Geranylphosphonate. To a solution of diethyl geranylphosphonate[37] (620 mg, 1.1 mol equiv) in dry DMF (15 mL) was added of 236 mg (2.2 mol equiv) freshly prepared NaOMe. After stirring 5 min under nitrogen, a solution of aldehyde **34** (530 mg, 2.19 mmol) in 6 mL of dry DMF was added dropwise. The mixture was stirred overnight at room temperature, diluted with water and extracted with hexane–ether 3:1. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (hexane–EtOAc 9:1) to give 20 mg (2%) (±) *Z*-isoferprenin (R_f 0.25, hexane–EtOAc 7:3) and 195 mg (25%) (±) *E*-isoferprenin (R_f 0.20 hexane–EtOAc 7:3). **(b′) Reaction of Aldehyde 34 and Geranyltriphenylphosphonium Bromide.** To a solution of geranyltriphenylphosphonium bromide[38] (1.842 g, 3.84 mmol) in dry THF was added BuLi (1.6 M in hexanes, 2.4 mL, 3.84 mmol) dropwise. After stirring 2 h at room temperature, 423 mg of **34** (mmol) was added, and the mixture was refluxed for 3 h. Saturated NH_4Cl was then added, and the mixture was extracted with ether. After washing with brine, drying ($MgSO_4$), and removal of the solvent, the residue was purified by column chromatography (hexane–EtOAc 9:1) to give 348 mg of a mixture of **35a** and **35b** (ca. 1:9, ^{1}H-NMR analysis). Crystallization from hexane–ether gave 219 mg (34%) of **35b**. **(3′*RS*)-Isoferprenin (35a)**: oil; IR (film) 1715, 1700, 1640, 1615, 1400, 1330, 1100, 1050, 750 cm^{-1}; UV (EtOH) λ_{max} 315, 305, 280 nm; ^{1}H-NMR ($CDCl_3$) δ 7.83 (br d, J = 8.3 Hz, 1H, H-5), 7.49 (br t, J = 8.3 Hz, 1H, H-7), 7.27 (m, 2H, H-6 + H-8), 6.35 (dd, J = 15.0, 10.9 Hz, 1H, H-5′), 5.76 (br d, J = 10.9 Hz, 1H, H-6′), 5.58 (d, J = 15.0 Hz, 1H, H-4′), 5.06 (br t, J = 7.0 Hz, 1H, H-10′), 2.60 (m, 1H, H-1′a), 2.45 (m, H-1′b), 2.10–1.95 (m, 6H, H-2′-a,b + H-8′-a,b + H-9′-a,b), 1.65 (br s, 3H, H-12′), 1.62 (br s, 3H, H-14′), 1.56 (br s, 3H, H-15′), 1.54 (s, 3H, H-13′); ^{13}C-NMR ($CDCl_3$) δ 163.1 (s, C-2), 100.4 (s, C-3), 158.9 (s, CH4), 122.2 (d, C-5), 123.7 (d, C:6), 131.2 (d, C-7), 116.5 (d, C-8), 152.3 (s, C-9), 115.9 (s, C-10), 17.4 (t, C-1′), 31.4 (t, C-2′), 79.8 (s, C-3′), 132.0 (d, C-4′), 125.8 (d, C-5′), 123.3 (d, C-6′), 140.6 (s, C-7′), 39.8 (t, C-8′), 26.4 (t, C-9′), 123.7 (d, C-10′), 131.55 (s, C-11′), 25.6 (q, C-12′), 25.6 (q, C-13′), 16.7 (q, C-14′), 17.6 (q, C-15′); MS (70 eV) 364 (20) [M$^+$], 243 (100). Anal. Calcd for $C_{24}H_{28}O_3$: C 79.09; H, 7.74. Found: C, 79.28; H, 7.79. **(3′*RS*)-(4′*Z*)-Isoferprenin (35b)**: mp 96 °C (hexane); IR (KBr) 1700, 1630, 1605, 1490, 1390, 1110, 1070, 1050, 755 cm^{-1}; UV (EtOH) λ_{max} 315, 285 nm; ^{1}H-NMR ($CDCl_3$) δ 7.83 (br d, J = 8.1 Hz, 1H, H-5), 7.46 (br t, J = 8.1 Hz, 1H, H-7), 7.27 (br d, J = 8.1 Hz, 1H, H-8), 7.23 (br t, J = 8.1 Hz, 1H, H-6), 6.38 (d, J = 10.4 Hz, 1H, H-6′), 6.24 (dd, J = 10.4, 11.0 Hz, 1H, H-5′), 5.25 (d, J = 11.0 Hz, 1H, H-4′), 4.96 (br t, J = 7.0 Hz, 1H, H-10′), 2.62 (m, 1H, H-1′-a), 2.53 (m, 1H, H-1′-b), 2.05–1.90 (m, 6H, H-2′-a,b + H-8′-a,b + H-9′-a,b), 1.68 (br s, 3H, H-14′), 1.67 (s, 3H, H-13′), 1.64 (br s, 3H, H-12′), 1.54 (br s, 3H, H-15′); ^{13}C-NMR ($CDCl_3$) δ 163.1 (s, C-2), 100.8 (s, C-3), 158.9 (s, C-4), 122.4 (d, C-5), 123.6 (d, C-6), 131.1 (d, C-7), 116.6 (d, C-8), 152.5 (s, C-9), 116.1 (s, C-10), 17.5 (t, C-1′), 32.6 (t, C-2′), 80.6 (s, C-3′), 129.3 (d, C-4′), 127.4 (d, C-5′), 120.3 (d, C-6′), 142.4 (s, C-7′), 40.3 (t, C-8′), 26.5 (t, C-9′), 123.7 (d, C-10′), 131.7 (s, C-11′), 25.6 (q, C-12′), 17.1 (a, C-13′), 16.1 (q, C-14′), 17.7 (q, C-15′); MS (70 eV) 364 (30) [M$^+$], 243 (100). Anal. Calcd for $C_{24}H_{28}O_3$: C 79.09; H, 7.74. Found: C, 79.20; H, 7.67.

Acknowledgment. This research was supported by M.U.R.S.T. (Fondi 40 e 60%).

Supplementary Material Available: Characterization data for **4a**, **4b**, **5a**, **5b**, **6a**, **6b**, **7a**, **7b**, **10a**, **11a**, **12a**, **13a**, **14a**, **19b**, **20a**, **20b**, **25a**, and **25b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(36) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *46*, 4155. For a improved preparation procedure, see: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(37) Surmatis, J. D.; Thommen, R. *J. Org. Chem.* **1969**, *34*, 559.

(38) Surmatis, J. D.; Ofner, A. *J. Org. Chem.* **1963**, *28*, 2735.