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Investigación

A New Approach for the Synthesis of the Cyclohexene Core of Anthracyclines and Milbemycins

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Dedicated to the memory of Dr. Lydia Rodriguez-Hahn and Dr. Jacobo Gómez-Lara

Abstract. A new synthesis of the cyclohexene core of the anthracyclines and milbemycins antibiotics is described, using 3-*p*-nitrobenzoyloxy-3-buten-2-one (**9a**) as an efficient dienophile in Diels-Alder reactions with substituted dienes. Allylic functionalization and epimerization of the cycloadducts led, in moderate overall yields, to the corresponding related cyclohexene A-rings of aclacinomycin, α– and β-rhodomycins, and the cyclohexene moiety of milbemycins β_1 and E.

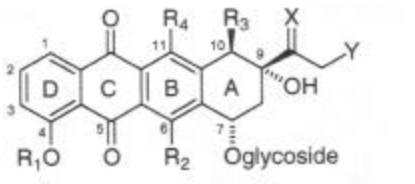
Key Words: Captodative olefin, Diels-Alder, cyclohexene core, anthracyclines, milbemycins

Resumen. Se describe una nueva ruta sintética para la preparación de la unidad ciclohexénica de algunos antibióticos de la familia de las antraciclinas y milbemicinas, empleando la 3-*p*-nitrobenzoiloxi-3-buten-2-ona (**9a**) como dienófilo en reacciones de Diels-Alder con dienos sustituidos. La funcionalización alílica y epimerización de los aductos condujo en rendimientos moderados a anillos ciclohexénicos análogos a los correspondientes de la aclacinomicina, de las rodomicinas alfa y beta, y también del fragmento ciclohexénico de las milbemicinas β_1 y E.

Palabras clave: Olefina captodativa, Diels-Alder, núcleo ciclohexénico, antraciclinas, milbemicinas.

Introduction

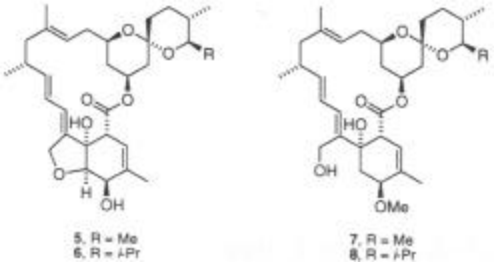
Anthracyclines are tetrahydronaphthacenequinone antibiotics isolated from numerous actinomycete species, and they are considered among the most active antineoplastic drugs [1]. Daunorubicin (**1**) and adriamycin (**2**) are clinically broad chemotherapeutic agents used for leukemia and cancer treatment [2]. Their structures are characterized by a tetracyclic aglycone to which an aminoglycoside is linked to the C-7 hydroxyl group. Aclacinomycin (**3**) is one of the most important member of the aklavinone antibiotics group [3]. Its major structural difference with respect to **1** and **2** is the methoxycarbonyl group at the C-10 position, and the absence of the carbonyl group at the C-9 side chain. Instead of this group on C-10, β-rhodomycin (**4**), a member of a large series of analogs, has a hydroxy group, and the ethyl substituent on C-9 is preserved [4]. Interestingly, a common structural feature in all these compounds is the quaternary carbon C-9 bearing an *alpha* hydroxy group.



1, R_1 = Me, R_2 = R_4 = OH, R_3 = Y = H, X = O
2, R_1 = Me, R_2 = R_4 = Y = OH, R_3 = H, X = O
3, R_1 = R_4 = Y = H, R_2 = OH, R_3 = CO_2Me, X = H_2
4, R_1 = Y = H, R_2 = R_3 = R_4 = OH, X = H_2

A further relevant class of antibiotics are avermectins and milbemycins, which are sixteen-membered ring macrolides isolated from *Streptomyces hygroscopicus* [5]. They have shown a potent and broad activity spectrum as anthelmintics, acaricides, and insecticides. Some of them have been commercialized for agricultural and veterinarian purposes, such as milbemycin α_1 (**5**) and D (**6**) [6]. In contrast, milbemycins β_1 (**7**) and E (**8**), among other natural analogs, do not have the tetrahydrofuran ring fused to the highly functionalized cyclohexene moiety [6b]. Consequently, an intense effort has been devoted to the synthesis of these important molecules [6, 7].

Previously, we have demonstrated that captodative olefins 3-aroyloxy-2-butenones **9** were highly regio- and stereo-selective in Diels-Alder cycloadditions towards unsymmetrical carbocyclic dienes [8], and they proved to be efficient synthons in the synthesis of natural terpenoids [9]. Considering that these olefins are able to introduce an *alpha*-ketol on a quaternary



carbon, like the cyclohexene moiety of anthracyclinones **1-2** and potentially of **3-4**, and milbemycins **7** and **8**, we have undertaken a study for the preparation of the cyclohexenic core of these molecules via a Diels-Alder addition of captodative olefin **9a** to the suitable dienes, followed by functionalization of the corresponding adducts (Fig. 1).

Results and Discussion

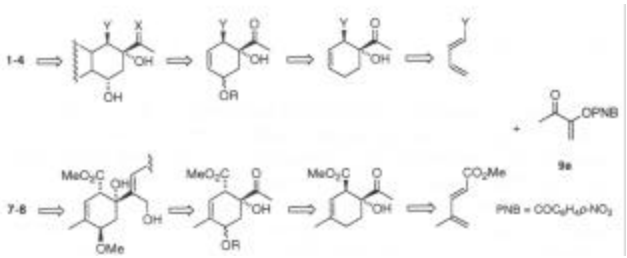


Figure 1.

Thermal reaction (xylene, 130 °C, 11 h) of 1-acetoxy-1,3-butadiene (**10a**) with olefin **9a** provided adduct **11a** as a single isomer (Fig. 2) [8a]. In contrast, the cycloaddition of **9a** with 1-(methoxycarbonyl)-1,3-butadiene (**10b**), under similar conditions, yielded a mixture of stereoisomers **11b** and **12b** (80:20) in good yield (81%). The major isomer was isolated from the reaction mixture as colorless needles by recrystallization (hexane/EtOAc, 8:2). No regioisomers **13** were detected by NMR in the crude mixtures [8a].

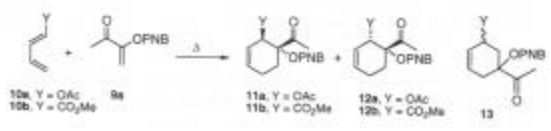
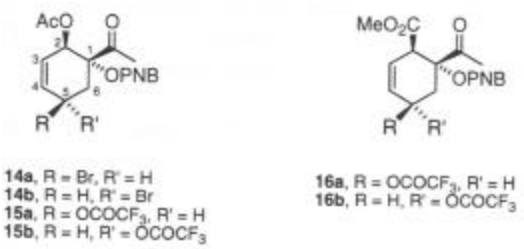


Figure 2.

Previously, allylic hydroxylation of cyclohexenes has been successfully attained by treatment with NBS in two phases (CCl_4/H_2O) [10]. This method was applied on adduct **11a** giving a complex mixture of products, including the aromatized acetophenone product. Other reagents for the allylic oxidation such as CrO_3 and SeO_2 were also used [11], yielding no conversion. The best results were found by non-aqueous bromination (NBS, CH_2Cl_2/CCl_4, 8:2, 50 °C, 30 min), and succesive trifluoroacetoxylation by adding silver trifluoroacetate in ether, furnishing a mixture of epimers **15a**/**15b** (60:40) in 29% yield [12]. It seems that the bromination step was more efficient, since we were able to isolate the bromocyclohexenes **14a**/**14b** in 60% yield as an unstable mixture, which undergoes elimination and aromatization. Analogous results were obtained with adduct **11b**. Thus, under the same conditions of allylic trifluoroacetoxylation, the expected products **16a**/**16b** (60:40) were isolated with a yield (30%) comparable to that observed for derivatives **15**. The isomeric ratios of **15** and **16** were calculated from the ^1H NMR spectra, but the configuration attributed to carbon C-5 was not unambiguously established.



Therefore, this methodology gives rise to diasteroisomers **15a** and **15b**, which are equivalent synthons of the A-rings of α- and β-rhodomycins, **17** and **4**, respectively (Fig. 3) [4]. Inasmuch as one wishes to separate isomers **15a** and **15b**, the major compound **15a** would be, for the best, obtained in 60% yield. On the other hand, in spite of the unfavorable ratio of **15b** for the synthesis of the A-ring of **4**, the epimerization of carbon C-5 under acidic conditions may afford the most stable *alpha* epimer **4** [13].

A more convergent synthesis of the A-ring of α-rhodomycin (**17**) may be designed by cycloaddition of olefin **9a** with the diene (*E*,*E*)-1,4-diacetoxy-1,3-butadiene (**18**), which is already bearing the oxygenated functionalities (Fig. 3). The thermal (xylene, 130 °C, 16 h) addition of these starting materials yielded a mixture of adducts **19a**/**19b** (9:1), as previously reported [8a].

We have explored the hydrolysis of **19a** with the aim to prepare a derivative structurally closer to the A-ring of **17**.

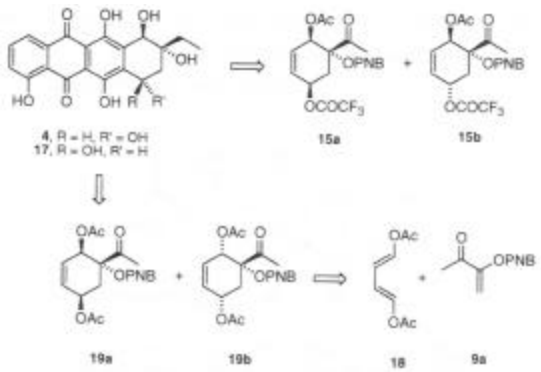


Figure 3.

When **19a** was treated with potassium carbonate in dry methanol at 25 °C for 2 h, a single product was obtained in high yield (92%). Double irradiation experiments in ^{1}H NMR and ^{13}C NMR spectra showed that the structure would be attributed to diol **20** (Fig. 4). Longer reaction times led to epimerization of carbon C-2, before the hydrolysis of the third acetate takes place. Further efficient conditions to prepare compound **21** are currently being investigated.

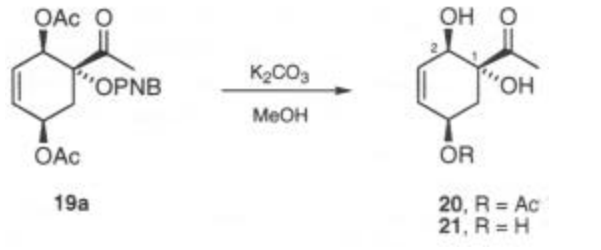


Figure 4.

In order to approach the synthesis of the cyclohexene moiety of milbemycins β1 (**7**) and E (**8**) (Fig. 1), diene **24** was prepared by the Wittig-type reaction of methacrolein (**22**) with methyl diethylphosphonoacetate (**23**) (Fig. 5) [14]. The thermal addition of diene **24** with olefin **9a** was highly stereo- and regio-selective, giving almost exclusively the *endo* and *ortho*-adduct **25** in good yield (70%) (Table 1).

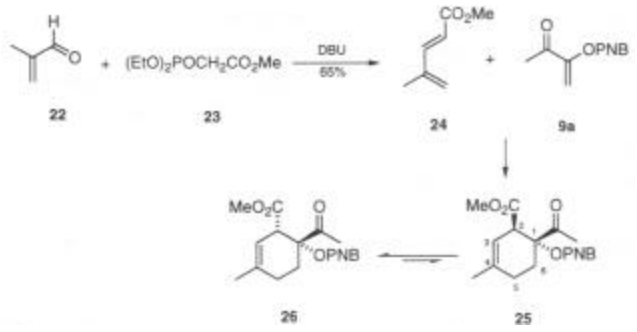


Figure 5.

Several Lewis acids were tested in order to improve the reaction conditions and yields (Table 1). The most efficient catalysts were $ZnCl_2$, $TiCl_4$, and $MgBr_2$•Et_2O, since the stereoselectivity was as high as the thermal trial. Moreover, with the last two Lewis acids, the reaction temperature and time were the lowest.

The preference for the endo selectivity and regioselectivity agrees with that observed for diene **10b**. The electronic factors at the transition state which control the selectivity also seem to be involved with diene **24** [8a]. In addition, the presence of the methyl group in **24** should enhance the regioselectivity.

Nevertheless, the major isomer **25** does not have the required relative configuration on carbons C-1 and C-2, and it should be isomerized to epimer **26** under kinetically controlled acidic or basic conditions. Indeed, when **25** was treated with imidazole in chloroform at room temperature for 24 h, a mixture of **25**/**26** (1:1) was obtained, and after stirring for 10 days, this ratio reached up to **25**/**26** (2:8) (Table 2, entries 5-12). A favorable ratio was reached faster by using more polar solvents such as DMF and acetonitrile. This isomerization was unsuccessful under acidic conditions with diverse catalysts (*p*-TsOH, H_2SO_4, HCl, and $ClSO_3H$).

The methanolysis of adduct **25** with potassium carbonate in dry MeOH was carefully studied, since an alternative product was generated when the reaction conditions were not properly maintained. Ketol **27** was isolated in 55% yield after stirring the mixture in THF with MeOH (25 mol eq) at 0 °C for 72 h, and extracting the crude with EtOAc followed by cold

Table 1. Diels-Alder cycloadditions of diene **24** and captodative olefin **9a**.[a]

Lewis Acid[b]	Solvent	T (°C)	t (h)	**25**/**26**[c]	Yield (%)[d]
——	xylene	120	72	98 : 2	70
BF_3•Et_2O	CH_2Cl_2	20	24	87 : 13	83
$ZnCl_2$	CH_2Cl_2	25	24	30 : 1	82
$TiCl_4$	CH_2Cl_2	0	8	98 : 2	85
$AlCl_3$	CH_2Cl_2	0	10	75 : 25	50
$MgBr_2$•Et_2O	CH_2Cl_2	0	8	98 : 2	88

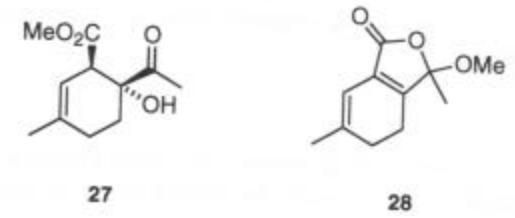
[a] All under N_2 atmosphere. Thermal trials in the presence of 1-2% hydroquinone. 1.0 mol equiv of diene **24**. [b] 10.0 mol equiv of the catalyst. [c] Determined by ^{1}H NMR from the crude mixtures. [d] Of the major isomer after column chromatography.

Table 2. Isomerization of adduct **25**.

Entry	Catalyst	Solvent	T (°C)	t (h)	Result[a]
1	*p*-TsOH	$CHCl_3$	25	5	**25** decomposed
2	H_2SO_4	$CHCl_3$	25	6	**25** decomposed
3	HCl	CH_2Cl_2	25	10	**25** decomposed
4	$ClSO_3H$	$CHCl_3$	25	48	no isomerization
5	imidazol	$CHCl_3$	25	24	**25/26** (1:1)
6	imidazol	$CHCl_3$	25	72	**25/26** (4:6)
7	imidazol	$CHCl_3$	25	144	**25/26** (27:73)
8	imidazol	$CHCl_3$	25	240	**25/26** (20:80)
9	imidazol	DMF	25	120	**25/26** (32:68)
10	imidazol	DMF	60	24	**25/26** (30:70)
11	imidazol	CH_3CN	25	120	**25/26** (30:70)
12	imidazol	C_6H_6	70	120	**25/26** (40:60)

[a] The **25**/**26** ratio was determined by integration of vinylic signals in ^{1}H NMR (200 MHz).

washings with aqueous saturated solution of NH_4Cl until neutral, and drying with anhydrous Na_2SO_4. If this procedure is not carefully followed, ketol **27** is obtained in low yield, and a new compound is produced as the main component of the reaction mixture. The usual spectroscopic analyses (IR, ^1H and ^{13}C NMR) and elemental analysis provided enough information for assigning the structure **28** to this compound. This new bicyclic lactone was very stable, in spite of the usually low stability of a dienic moiety. An optimized procedure for the preparation of **28** consisted in the treatment of **25** with a high excess of MeOH (250 mol eq) at room temperature for 48 h, which provided 65% of the desired product.



The formation of the bicyclic lactone **28** may be explained by the mechanism depicted in Fig. 6. The *syn* relative configuration of the acetyl group on carbon C-1, and the methoxycarbonyl group on carbon C-2 of adduct **25**, allows an easy intramolecular transesterification and lactonization via intermediates **29** and **30**, to give precursor **31**. The cyclization process would be favored by the stability of the five-membered ring. It is likely that the dehydration step may be the last process due to the fact that α-hydroxy ketones are relatively stable to basic and acidic conditions. Therefore, after lactonization, the elimination of the hydroxy group in the *beta* position to the γ-lactone carbonyl group in the intermediate **32** will be favored by the formation of the very stable γ-butenolide system of **28**. This would be also stabilized by the conjugated cyclohexenyl dienic skeleton.

In summary, we have demonstrated the synthetic potential of captodative olefin **9a** as a valuable synthon for the preparation of cyclohexene rings properly functionalized. This methodology may also be considered as a selective approach toward the preparation of the A rings of the aglycones of aclacynomicin (**3**), α-rhodomycin (**17**), and β-rhodomycin (**4**), and the cyclohexene moiety of milbemycins β_1 (**7**) and E (**8**).

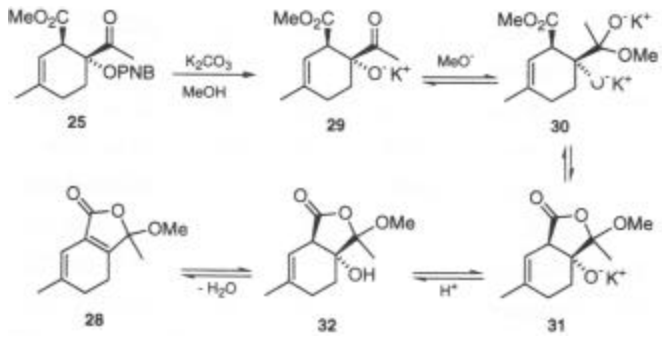


Figure 6.

Experimental

General. Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian EM-390 (90 MHz), Varian Gemini-300 (300 MHz), and Brucker DMX-200 (200 MHz) instruments, with $CDCl_3$ as solvent and TMS as internal standard. The mass spectra (MS) were taken on a Hewlett-Packard 5971A spectrometer. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ). All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Benzene, toluene, and xylene were freshly distilled from sodium, and methylene chloride from calcium hydride, prior to use. K_2CO_3 was dried overnight at 120 °C before use. All other reagents were used without further purification. Compounds **9a**, **11a**, **11b**, and **19a** were prepared as described [8a, 9b].

[1*R,2*R**,5*R**]-1-Acetyl-2-acetoxy-5-trifluoroacetoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (15a). [1*R**,2*R**,5*S**]-1-Acetyl-2-acetoxy-5-trifluoroacetoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (15b).** To a solution of 0.10 g (0.29 mmol) of **11a** in dry CH_2Cl_2 (1 mL) under an N_2 atmosphere, and at 20 °C, 0.051 g (0.29 mmol) of NBS (recrystallized from benzene) in CCl_4 (1 mL) were added. After being stirred at room temperature for 35 min under light irradiation (60 watts), CF_3CO_2Ag (0.06 g, 0.27 mmol) in dry ethyl ether (4 mL) was added, and the mixture was stirred and heated to 40 °C for 12.5 h. The mixture was diluted with CH_2Cl_2 (20 mL), filtered, and washed with cold water (3 × 5 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on Florisil (8 g, hexane/EtOAc, 8:2) to give 0.038 g (29%) of **15a**/**15b** (60:40) as a colorless oil. **15a** R_f 0.33 (hexane/EtOAc, 6:4); IR (film) 1740, 1720, 1710, 1530, 1365, 1300, 1240-1130, 800 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.09 (s, 3H, CH_3CO_2), 2.24 (s, 3H, CH_3CO), 2.50 (dd, J = 14.2, 7.6 Hz, 1H, H-6), 2.80 (dd, J = 14.2, 6.2 Hz, 1H, H-6), 4.18-4.24 (m, 1H, H-5), 5.62-5.65 (m, 1H, H-2), 5.82 (ddd, J = 10.1, 3.8, 1.7 Hz, 1H, H-3), 6.12 (ddd, J = 10.1, 2.2, 1.2 Hz, 1H, H-4), 8.08-8.17 (m, 2H, ArH), 8.28-8.33 (m, 2H, ArH). Signals attributed to the minor isomer **15b** R_f 0.39 (hexane/EtOAc, 6:4): ^1H NMR (90 MHz, $CDCl_3$) δ 2.30 (s, CH_3CO). Anal. Calcd for $C_{19}H_{16}F_3NO_9$: C, 49.68; H, 3.51. Found: C, 49.87; H, 3.28.

[1*R,2*R**,5*R**]-1-Acetyl-2-methoxycarbonyl-5-trifluoroacetoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (16a). [1*R**,2*R**,5*S**]-1-Acetyl-2-methoxycarbonyl-5-trifluoroacetoxy-3-cyclohexen-1-yl *p*-Nitrobenzoate (16b).** The same procedure as for **15a**/**15b** was used, with 0.15 g (0.43 mmol) of **11b**, and

0.085 g (0.48 mmol) of NBS. The reaction was irradiated at 20 °C for 23 h, and 0.95 g (0.43 mmol) of CF_3CO_2Ag were added. The mixture was heated to 40 °C for 13 h. Column chromatography on Florisil (12 g, hexane/EtOAc, 6:4) yielded 0.04 g (30%) of **16a**/**16b** (60:40) as a colorless oil: **16a** R_f 0.21 (hexane/EtOAc, 6:4); IR (film) 1710, 1705, 1530, 1365, 1300, 1295, 1130, 760 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3CO), 2.73-3.23 (m, 2H, H-6), 3.66 (s, 3H, CO_2CH_3), 3.68-5.77 (m, 1H, H-2), 4.19-4.28 (m, 1H, H-5), 5.79-5.88 (m, 1H, H-3), 6.02-6.12 (m, 1H, H-4), 8.08-8.17 (m, 2H, ArH), 8.26-8.35 (m, 2H, ArH). Signals attributed to the minor isomer **16b** R_f 0.36 (hexane/EtOAc, 6:4): ^1H NMR (90 MHz, $CDCl_3$) δ 2.34 (s, CH_3CO), 3.70 (s, 3H, CO_2CH_3), 4.65-4.73 (m, H-5); MS (70 eV) 163 (M^+-296, 100), 147 (20), 120 (2), 105 (8), 77 (27), 75 (17).

[1*R,2*R**,5*R**]-1-Acetyl-5-acetoxy-1,2-dihydroxy-3-cyclohexene (20).** To a solution of 0.5 g (1.23 mmol) of **19a** in dry CH_2Cl_2 (6 mL) under an N_2 atmosphere, and at 20 °C, 0.1 g (0.73 mmol) of K_2CO_3 in MeOH (2.5 mL) was added. After being stirred at room temperature for 2 h, the mixture was diluted with CH_2Cl_2 (20 mL), and washed with cold saturated solution of NH_4Cl (3 × 5 mL) and cold brine until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (10 g, hexane/EtOAc, 9:1) to give 0.18 g (92%) of **20** as a dark yellow oil: R_f 0.24 (hexane/EtOAc, 6:4); IR (film) 3450, 1715, 1705, 1540, 1345, 1310, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H, CH_3CO_2), 2.35 (s, 3H, CH_3CO), 2.15-2.24 (m, 1H H-6β), 2.50-2.58 (m, 1H, H-6α), 4.07-4.13 (m, 1H, H-2), 4.50 (br, 2H, OH), 5.41-5.48 (m, 1H, H-5), 5.80-6.05 (m, 2H, H-3, H-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2 (CH_3CO_2), 26.4 (CH_3CO), 33.1 (C-6), 67.5 (C-2), 70.8 (C-5), 96.2 (C-1), 128.6 (C-3 or C-4), 130.7 (C-4 or C-3), 170.2 (CH_3CO_2), 211.0 (*C*OMe).

Methyl (*E*)-4-methyl-2,4-pentadienoate (24) [15]. To a suspension of 0.510 g (0.012 mol) of LiCl in 60 mL of dry acetonitrile, under an N_2 atmosphere and at room temperature, 2.18 g (0.012 mol) of trimethyl phosphonoacetate, 1.52 g (0.010 mol) of DBU, and 0.70 g (0.01 mol) of methacrolein were added dropwise. The mixture was stirred at room temperature for 24 h. The solvent was evaporated under vacuum, the residue was extracted with EtOAc (120 mL), and washed successively with 5% aqueous solution of HCl (2 × 40 mL), saturated solution of $NaHCO_3$ (3 × 30 mL), and water until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by distillation, using a Kugelrohr apparatus, to give 0.86 g (68%) of **24** as a pale yellow oil: R_f 0.92 (hexane/EtOAc, 7:3).

[1*R,2*R**]-1-Acetyl-2-methoxycarbonyl-4-methyl-3-cyclohexen-1-yl *p*-Nitrobenzoate (25). Method A.** A mixture of 0.10 g (0.42 mmol) of **9a**, 0.159 g (1.26 mmol) of **24**, and hydroquinone (3 mg) in dry xylene (2 mL), was placed in a threaded ACE glass pressure tube with a Teflon screw cap, under an N_2 atmosphere, in the dark. The mixture was stirred and heated to 130 °C for 4 days. After cooling, it was diluted with EtOAc (60 mL) and washed with water (2 × 15 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (3 g, hexane/EtOAc, 8:2) to give 0.107 g (70%) of **25** as a pale yellow powder: R_f 0.89 (hexane/EtOAc, 7:3); mp 111-113 °C.

Method B. To a solution of 0.10 g (0.42 mmol) of **9a** in dry CH_2Cl_2 (5 mL), under an N_2 atmosphere at 0 °C, 0.779 g (4.10 mmol) of $TiCl_4$, and 0.053 g (0.42 mmol) of **24** were added dropwise. The mixture was stirred for 8 h at 0 °C, diluted with EtOAc (60 mL), and washed successively with water (2 x 10 mL), saturated solution of $NaHCO_3$ (3 × 15 mL), and water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (3 g, hexane/EtOAc, 8:2) to give 0.13 g (85%) of **25** as a pale yellow powder: IR (KBr) 2920, 1700, 1510, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 3H, Me-4), 1.90-2.08 (m, 1H, H-5α), 2.10-2.16 (dd, *J* = 18.0, 6.0 Hz, 1H, H-5β), 2.43 (s, 3H, CH_3CO), 2.56 (ddd, *J* = 14.1, 11.4, 6.0 Hz, 1H, H-6β), 2.66 (dddd, *J* = 14.1, 6.3, 1.8, 1.5 Hz, 1H, H-6α), 3.69 (s, 3H, CO_2CH_3), 3.71-3.78 (m, 1H, H-2), 5.48-5.50 (m, 1H, H-3), 8.09-8.13 (m, 2H, ArH), 8.28-8.31 (m, 2H, ArH); MS (CI-NH_3) 379 (M^++18, 4), 362 (M^++1, 6), 332 (20), 195 (100), 163 (13), 155 (18), 138 (18), 120 (21). Anal. Calcd for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.30. Found: C, 59.88; H, 5.40.

[1*R,2*R**]-1-Acetyl-2-methoxycarbonyl-4-methyl-3-cyclohexen-1-ol (27).** A solution of 0.20 g (0.55 mmol) of **25** in dry THF (5 mL), under an N_2 atmosphere and at 0 °C, was treated with 0.911 g (6.60 mmol) of anhydrous K_2CO_3 in dry MeOH (0.306 mL, 13.7 mmol). After being stirred for 72 h at 0 °C, EtOAc (60 mL) was added, and the mixture was washed with aqueous 5% HCl (3 × 20 mL) and with cold water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc, 9:1) to give 0.064 g (55%) of **27** as a pale yellow oil: R_f 0.80 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 3455, 1709, 1439, 1355, 1271, 1197 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (dd, *J* = 8.7, 3.7 Hz, 1H, H-6), 1.77 (br s, 3H, CH_3C-4), 1.90-2.00 (m, 1H, H-5), 2.28-2.53 (m, 2H, H-5, H-6), 2.36 (s, 3H, CH_3CO), 3.69 (s, 3H, CO_2CH_3), 3.79-3.85 (m, 1H, H-2), 4.18 (s, 1H, OH), 5.48-5.52 (m, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3 (CH_3), 24.0 (CH_3CO), 25.7 (CH_2), 30.9 (CH_2), 47.5 (C-2), 52.1 (CO_2CH_3), 77.6 (C-1), 115.4 (C-3), 135.9 (C-4), 172.9 (CO_2CH_3), 212.3 (*C*OMe); MS (70 eV) 213 (M^++1, 1), 194 (2), 169 (76), 153 (10), 137 (35), 109 (100), 95 (13), 81 (13). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.59. Found: C, 62.50; H, 7.62.

3-Methoxy-3,6-dimethyl-4,5-dihydro-1[1*H*]-isobenzofuranone (28). A solution of 0.20 g (0.55 mmol) of **25** in dry THF (5 mL), under an N_2 atmosphere and at 0 °C, was treated with

0.911 g (6.60 mmol) of anhydrous K_2CO_3 in dry MeOH (3.06 mL, 0.137 mol). After being stirred for 48 h at room temperature, EtOAc (75 mL) was added, and the mixture was washed with aqueous 5% HCl (3 × 20 mL) and with cold water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc, 9:1) to give 0.069 g (65%) of **28** as a pale yellow oil: R_f 0.85 (hexane/EtOAc, 7:3); IR (CH_2Cl_2) 1769, 1537, 1292, 1185, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 3H, CH_3C-3), 1.92 (br s, 3H, CH_3C-6), 2.40-2.56 (m, 4H, H-4, H-5), 3.21 (s, 3H, CH_3O), 5.98-6.00 (m, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9 (C-5), 22.8 (CH_3), 23.1 (CH_3), 28.1 (C-4) 50.9 (CH_3O), 108.1 (C-3), 111.1 (C-7), 128.2 (C-6), 140.6 (C-7a), 154.2 (C-3a), 168.5 (C-1). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.87; H, 7.13.

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