Brief Articles

New Stereocontrolled Synthesis and Biological Evaluation of 5-(1′-Hydroxyalkyl)-3-methylidenetetrahydro-2-furanones as Potential Cytotoxic Agents

Tomasz Janecki,*,† Edyta Błaszczyk,† Kazimierz Studzian,‡ Marek Różalski,§ Urszula Krajewska,§ and Anna Janecka‡

Institute of Organic Chemistry, Technical University, Żeromskiego 116, 90-924 Łódź, Poland, Department of Medicinal Chemistry, Medical University, Lindleya 6, 90-131 Łódź, Poland, and Institute of Biochemistry, Medical University, Muszyńskiego 1, Łódź, Poland

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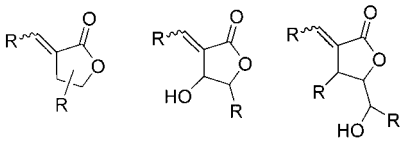
A series of 3-methylidenetetrahydro-2-furanones **7** bearing various hydroxyalkyl substituents in position 5 were synthesized using novel diastereo- and enantioselective methodology. In vitro cytotoxicity data demonstrated that all prepared compounds were active against L-1210 and HL-60 tissue culture cells with **7e** being the most potent ($IC_{50} = 6.9\ \mu M$). Also an increase in activity with an increase in lipophilicity of the substituents in the order H < alkyl < phenyl was observed.

Introduction

3-Methylidenetetrahydro-2-furanones **1** (α-methylene-γ-butyrolactones) constitute an important group of natural products and possess wide-ranging biological activities.[1,2] The α-methylene-γ-butyrolactone ring is an internal building block of the sesquiterpene lactones such as vernolepin, aromaticin, or elephantopin, isolated from plant extracts. All these compounds have cytotoxic, antitumoral, and often bactericidal properties. Although none of them has demonstrated enough selectivity to be considered for clinical use, these compounds are of interest as leads to the synthesis of analogues, which may achieve necessary selectivity.



1 **2** **3**

The cytotoxic activity of 3-methylidenetetrahydro-2-furanones **1** is mainly associated with the exocyclic, conjugated double bond which acts as an alkylating agent in a Michael-type reaction with thiol rich bionucleophiles. However, it has also been postulated that there are other factors which may enhance the biological properties of these compounds, e.g., the presence of conjugate side chain ester or stereochemically defined carbinol units at strategic positions.[3] The fact that many natural furanones **1** showing in vivo antitumor activity contain hydroxyl groups led to the conclusion that these groups enhance activity[4] and might be involved in direct binding to receptor sites in tumor cells.[5] Neighboring hydroxyl groups might also play an important role in the rate and/or selectivity of the tiols addition to furanones **1**. Although no evidence was found so far to prove this assumption,[6] the influence of adjacent hydroxyl groups on selectivity of the Michael additions to enones is well known[7] and was also documented for tiols as nucleophiles.[8]

Despite these encouraging observations, the number of general synthetic methods leading to 3-methylidenetetrahydro-2-furanones with hydroxyl functionality is very limited. Main synthetic efforts were focused on 3-alkylidene-4-hydroxytetrahydro-2-furanones **2** which are a class of natural products isolated from plants of the *Lauraceae* family.[9] Much less attention was given to the synthesis of 5-hydroxyalkyl-3-methylidenetetrahydro-2-furanones **3**. So far, their preparation was realized by palladium-catalyzed carbonylation of vinyl halides,[10] the methylenation of 5-hydroxymethyltetrahydro-2-furanone,[11] bromination of isosaccharinic acid,[12] Reformatsky reaction of α-(bromomethyl)acrylate with trialkylsilyloxyacetone,[13] or the lactonization of α-methylidene-γ-hydroxy-δ-alkoxyesters.[14] All these methods have been shown to be of very limited applicability and often give racemic products. Also, cytotoxicity of the compounds prepared was not assayed.

Continuing our investigations focused on the application of organophosphorus reagents in the synthesis of 3-methylidenetetrahydro-2-furanones,[15,16] we have recently presented,[17] as a preliminary communication, our newly developed diastereo- and enantioselective techniques for the preparation of 5-(1′-hydroxyalkyl)-3-methylidenetetrahydro-2-furanones **7**. In this paper we report full experimental details of our methodology as well as cytotoxic evaluation of 5-(1′-hydroxyalkyl)-3-

* To whom correspondence should be addressed. Phone: +(42) 6313142. Fax: +(42) 6365530. E-mail: tjanecki@ck-sg.p.lodz.pl.
† Technical University.
‡ Department of Medicinal Chemistry, Medical University.
§ Institute of Biochemistry, Medical University.

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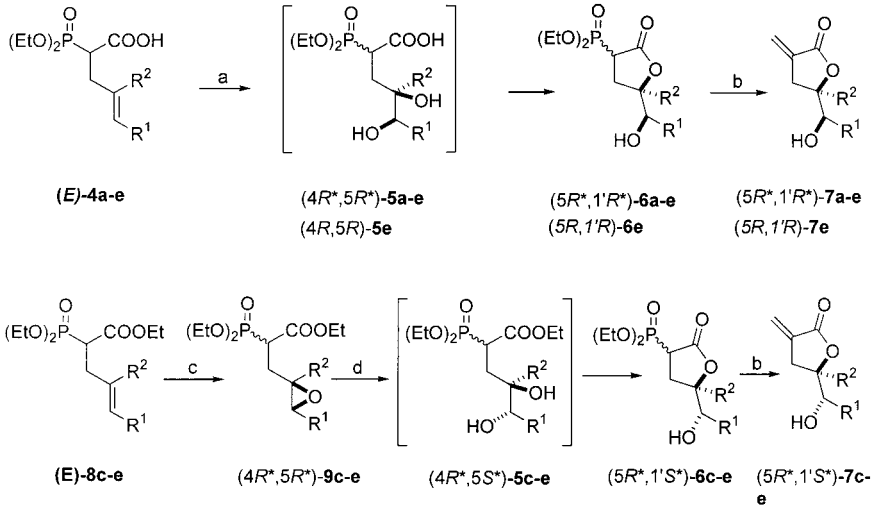
Scheme 1[a]



a R^1= H, R^2= H
b R^1= H, R^2= Me
c R^1= Me, R^2= H
d R^1= n-Pr, R^2= H
e R^1= Ph, R^2= H

[a] Reagents: (a) OsO_4 cat., NMO, H_2O/acetone, rt, 24 h; or AD-mix-β, 50% aqueous *t*-BuOH, 0 °C to rt, 48 h; (b) 36% formalin, K_2CO_3, 0−5 °C, 15 min; (c) MCPBA, CH_2Cl_2, rt, 24 h; (d) 30% $HClO_4$, rt, 24 h.

methylidenetetrahydro-2-furanones **7**, which were assayed in vitro against human leukemia HL-60 and mouse leukemia L-1210 cells. Some structure−activity relationships of the new compounds are also discussed.

Chemistry

Synthesis of the target diastereoisomeric and enantiomeric 5-hydroxyalkyl-2-furanones **7** was accomplished applying described methodology[17] and is summarized in the Scheme 1. Starting (*E*)-2-diethoxyphosphoryl-4-alkenoates (*E*)-**8a**−**e** were prepared by alkylation of ethyl diethoxyphosphoryl acetate with appropriate allyl bromides. Chemoselective hydrolysis of (*E*)-**8a**−**e** produced other key substrates, 2-diethoxyphosphoryl-4-alkenoic acids (*E*)-**4a**−**e**.

Acids (*E*)-**4a**−**e** and alkenoates (*E*)-**8c**−**e** were next transformed into diols (5*R**,1′*R**)-**5a**−**e** and (5*R**,1′*S**)-**5c**−**e**, respectively, using fully diastereoselective *syn*- or *anti*-dihydroxylation procedures (OsO_4/*N*-methylmorpholine oxide or oxidation of (*E*)-**8c**−**e** with MCPBA and cleavage of the epoxides (4*R**,5*R**)-**9c**−**e** with perchloric acid). Spontaneous lactonization of these diols gave 3-diethoxyphosphoryltetrahydro-2-furanones (5*R**,1′*R**)-**6a**−**e** and (5*R**,1′*S**)-**6c**−**e**. Due to the additional stereogenic center at C-3, furanones **6** were obtained as mixtures of diastereoisomers with close to 1:1 ratio. Horner−Wadsworth−Emmons olefination of formaldehyde using (5*R**,1′*R**)-**6a**−**e** and (5*R**,1′*S**)-**6c**−**e** yielded target 3-methylidenetetrahydro-2-furanones (5*R**,1′*R**)-**7a**−**e** and (5*R**,1′*S**)-**7c**−**e**.

All furanones **7** except **7c** were obtained as single diastereoisomers. Compounds **7c**, obtained by employing *syn*- or *anti*-dihydroxylation procedures, were mixtures of diastereoisomers (5*R**,1′*R**)/(5*R**,1′*S**) = 80/20 or (5*R**,1′*S**)/(5*R**,1′*R**) = 20/80, respectively. This is a consequence of using commercially available *E*/*Z* mixture of crotyl bromide (*E*/*Z* ∼ 85/15) in the alkylation of ethyl diethoxyphosphoryl acetate. For that reason alkenoate **8c** and alkenoic acid **4c** were prepared as a mixtures of diastereoisomers (*E*/*Z* = 80/20) and also furanones **6c** were mixtures of four diastereoisomers.

Table 1. Lipophilicity and Cytotoxic Activity of 3-Methylidenetetrahydro-2-furanones **7a**−**e**

compound	lipophilicity (log *P*)	IC_{50} (μM) L-1210	IC_{50} (μM) HL-60
7a	0.15	27.2 ± 6.1	72.4 ± 16.9
7b	0.44	26.7 ± 4.1	51.3 ± 3.2
(5*R**,1′*R**)-**7c**	0.55	19.3 ± 3.7	47.3 ± 3.7
(5*R**,1′*S**)-**7c**		17.3 ± 2.1	46.8 ± 2.9
(5*R**,1′*R**)-**7d**	1.59	18.5 ± 4.4	51.9 ± 5.1
(5*R**,1′*S**)-**7d**		16.9 ± 3.9	52.6 ± 4.9
(5*R**,1′*R**)-**7e**	1.80	8.0 ± 2.1	40.2 ± 2.4
(5*R**,1′*S**)-**7e**		7.5 ± 2.5	41.2 ± 2.8
(5*R*,1′*R*)-**7e**		6.9 ± 1.9	36.4 ± 3.5
carboplatin		9.7 ± 1.2	2.9 ± 01

Enantioselective synthesis of (5*R*,1′*R*)-**7e** (ee 90%) was accomplished using commercially available Sharpless reagent, AD-mix-β[18] in *syn*-dihydroxylation of the alkenoic acid (*E*)-**4e**. The enantiomeric excess and absolute configuration was determined by transformation of (5*R*,1′*R*)-**7e** into corresponding Mosher's ester,[19] followed by the analysis of the resulting diastereoisomers by ^1H NMR.

Results and Discussion

The obtained compounds were evaluated in vitro for their cytotoxic activity against two cell lines: mouse L-1210 leukemia and human HL-60 leukemia. The activity is expressed as the concentration (μM) required to inhibit tumor cell proliferation by 50% after 72 h exposure of the cells to the compounds (IC_{50}). The results are presented in Table 1. The data for carboplatin[20] (*cis*-diamine[1,1-cyclobutanedicarboxylato]-platinum) are included for comparison. All tested compounds displayed anticancer activity and were 2−4 times more potent against the growth of L-1210 than

HL-60 cells. Matching relationships between the substituent on the carbinol carbon atom C-1′ and activity were observed for both cell lines, with furanone **7e** (R^1 = Ph) being the most potent and furanone **7a** (R^1 = H) the least potent compound. Furanones **7c**,**d** with alkyl substituents (R^1 = Me, Pr) displayed intermediate activity. Both diastereoisomers of compounds **7c**−**e** were tested, but no significant differences in activity were found. Also, the optically active (5*R*,1′*R*) **7e** (90% ee) and racemic (5*R**,1′*R**) **7e** were almost equipotent. The most potent compound in the series, furanone **7e**, had the activity comparable to carboplatin against L-1210 cells.

In the search for more clear structure−activity relationships in furanones **7a**−**e**, we decided to determine their lipophilicity. Correlation between lipophilic character of the compound, expressed as the partition coefficient *P* in 1-octanol/water system, and its biological activity have proven meaningful.[21] Moreover, structure−cytotoxicity investigations among sesquiterpene lactones revealed that an increase in cytotoxicity usually accompanies increased lipophilicity.[4] Lipophilicities of furanones **7a**−**e** were calculated using the standard software package Pallas (CompuDrug Chemistry, Hungary) and the results, expressed as log *P*, are given in Table 1. To test the accuracy of the calculations, the lipophilicity of **7a** was also determined experimentally using a spectrophotometric method.[4] Pleasingly, experimental and calculated values for **7a** were very similar (log *P* = 0.09 and 0.15, respectively). Examination of the calculated log *P* values revealed straightforward correlation between lipophilicity and cytotoxicity, with the more lipophilic compound being also more cytotoxic. However, significant difference in lipohilicity between **7c** (log *P* = 0.55) and **7d** (log *P* = 1.59) is reflected in only a marginal increase of cytotoxicity. Obviously and not surprisingly, other factors such as steric bulk/steric hindrance and/or electronic effects might also influence cytotoxicity of these compounds.

In conclusion, we synthesized a series of 1′-hydroxyalkyl-3-methylidenetetrahydro-2-furanones **7a**−**e** with different substituents on the carbinol carbon atom C-1′ using a unique combination of *syn*- or *anti*-dihydroxylation of 4-alkenoic acids (*E*)-**4** or alkenoates (*E*)-**8** and the Horner−Wadsworth−Emmons olefination reaction. All prepared compounds were evaluated for their cytotoxic activity against L-1210 and HL-60 leukemia cells and invariably were more cytotoxic against the former ones. The effect of the substitution at the carbinol carbon atom C-1′ was also consistent for both cell lines, with activity increasing from unsubstituted through alkyl to phenyl substituted compounds. Calculated lipophilicity increased in the same order. No significant differences in cytotoxicity of stereoisomers were found. Further studies to increase the activity of furanones **7** by introducing more lipophilic substituents (R^1) and also by changing their steric bulk and electronic character are currently in progress in our laboratory.

Experimental Section

All reactions requiring anhydrous and oxygen-free conditions were conducted in an argon atmosphere. THF was freshly distilled from NaH before use. Pyridine was distilled and stored over KOH. All other solvents were of pure grade and used as received. Column chromatography was performed on Fluka silica gel 60 (230−400 mesh). IR spectra were recorded on Specord M80 spectrometer. ^{1}H NMR (250 MHz), ^{13}NMR (62.9 MHz), and ^{31}P NMR (101 MHz) spectra were recorded on Brucker DPX250 spectrometer with TMS as an internal standard and 85% H_3PO_4 as an external standard, respectively. ^{31}P NMR spectra were recorded using broadband proton decoupling.

General Procedure for the Preparation of 5-(1′-Hydroxyalkyl)-3-methylidenetetrahydro-2-furanones 7. A mixture of phosphonate 6 (2.0 mmol), K_2CO_3 (0.829 g; 6.0 mmol), and aqueous 36% formaldehyde solution (1.1 mL; 14.0 mmol) was stirred at 0−5 °C for 15 min. The reaction mixture was extracted with Et_2O (4 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried, and evaporated. The crude product was purified by column chromatography (silica gel, $CHCl_3$:acetone = 9:1 as eluent).

5-(Hydroxymethyl)-3-methylidenetetrahydro-2-furanone (7a): oil, 70% yield (lit.[10] 55%); R_f = 0.20 ($CHCl_3$: acetone = 9:1); IR (film) ν 3432 (O−H), 1760 (C=O), 1664 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (t, J = 6.50 Hz, 1H, O−H), 2.86 (ddt, J = 17.26, 6.00, 3.00 Hz, 1H, HC-4), 3.00 (ddt, J = 17.26, 8.00, 3.00 Hz, 1H, HC-4), 3.66 (ddd, J = 12.51, 6.50, 4.75 Hz, 1H, H−C-1′), 3.91 (ddd, J = 12.51, 6.50, 3.00 Hz, 1H, H−C-1′), 4.66 (dddd, J = 8.00, 6.00, 4.75, 3.00 Hz, 1H, HC-5), 5.68 (t, J = 3.00 Hz, 1H, =CH), 6.26 (t, J = 3.00 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ 27.8 (C-4), 63.0 (C-1′), 76.6 (C-5), 121.4 (=CH_2), 133.4 (C-3), 169.7 (C-2). Anal. ($C_6H_8O_3$) C, H.

5-(Hydroxymethyl)-5-methyl-3-methylidenetetrahydro-2-furanone (7b): 63% yield, white solid; mp 67−68 °C (lit.[13] 63%, mp 66−68 °C); R_f = 0.26 ($CHCl_3$:acetone = 9:1); IR (film) ν 3480 (O−H), 1756 (C=O), 1664 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H, CH_3C-5), 2.18 (bs, 1H, O−H), 2.63 (dt, J = 17.01, 2.75 Hz, 1H, HC-4), 3.08 (dt, J = 17.01, 2.75 Hz, 1H, HC-4), 3.53 (d, J = 12.01 Hz, 1H, HC-1′), 3.72 (d, J = 12.01 Hz, 1H, HC-1′), 5.65 (t, J = 2.75 Hz, 1H, =CH), 6.24 (t, J = 2.75 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ 22.4 (CH_3C-4), 34.7 (C-4), 66.9 (C-1′), 82.9 (C-5), 121.1 (=CH_2), 134.8 (C-3), 169.4 (C-2). Anal. ($C_7H_{10}O_3$) C, H.

(5*R,1′*R**)-5-(1′-Hydroxyethyl)-3-methylidenetetrahydro-2-furanone (7c):** mixture of (5*R**,1′*R**)- and (5*R**,1′*S**)-(**7c**) in 80/20 ratio; oil, 44% yield; R_f = 0.30 ($CHCl_3$:acetone = 9:1); IR (film) ν 3460 (O−H), 1754 (C=O), 1664 (C=C) cm^{-1}; data for (5*R**,1′*R**)-**7c**: ^{1}H NMR[22] ($CDCl_3$) δ 1.28 (d, J = 6.50 Hz, 3H, H_3C-2′), 2.13 (bs, 1H, O−H), 2.78 (ddt, J = 17.26, 5.50, 2.75 Hz, 1H, HC-4), 2.99 (ddt, J = 17.26, 8.00, 2.75 Hz, 1H, HC-4), 3.78 (quin, J = 6.50 Hz, 1H, HC-1′), 4.37 (ddd, J = 8.00, 6.50, 5.50 Hz, 1H, HC-5), 5.67 (t, J = 2.75 Hz, 1H, = CH), 6.25 (t, J = 2.75 Hz, 1H, =CH); ^{13}C NMR[22] ($CDCl_3$) δ 17.4 (C-2′), 28.7 (C-4), 68.6 (C-1′), 79.7 (C-5), 121.5 (=CH_2), 133.0 (C-3), 169.0 (C-2). Anal. ($C_7H_{10}O_3$) C, H.

(5*R,1′*S**)-5-(1′-Hydroxyethyl)-3-methylidenetetrahydro-2-furanone 7c:** mixture of (5*R**,1′*S**)- and (5*R**,1′*R**)-**7c** in 80/20 ratio; oil, 59% yield; R_f = 0.30 ($CHCl_3$:acetone = 9:1); IR (film) ν 3456 (O−H), 1752 (C=O), 1664 (C=C) cm^{-1}; data for (5*R**,1′*S**)-**7c**:^{1}H NMR[22] ($CDCl_3$) δ 1.21 (d, J = 6.50 Hz, 3H, H_3C-2′), 1.99 (bs, 1H, O−H), 2.88 (ddt, J = 17.26, 8.00, 2.50 Hz, 1H, HC-4), 2.99 (ddt, J = 17.26, 6.50, 2.50 Hz, 1H, HC-4), 4.12 (qd, J = 6.50, 3.25 Hz, 1H, HC-1′), 4.43 (ddd, J = 8.00, 6.50, 3.25 Hz, 1H, HC-5), 5.67 (t, J = 2.50 Hz, 1H, = CH), 6.26 (t, J = 2.50 Hz, 1H, =CH); ^{13}C NMR[22] ($CDCl_3$) δ 16.6 (C-2′), 26.1 (C-4), 66.5 (C-1′), 79.3 (C-5), 121.2 (=CH_2), 133.4 (C-3), 169.5 (C-2). Anal. ($C_7H_{10}O_3$) C, H.

(5*R,1′*R**)-5-(1′-Hydroxybutyl)-3-methylidenetetrahydro-2-furanone (5*R**,1′*R**)-7d:** oil, 62% yield; R_f = 0.33 ($CHCl_3$:acetone = 9:1); IR (film) ν 3450 (O−H), 176054 (C=O), 1664 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.25 Hz, 3H, H_3C-4′), 1.33−1.68 (m, 4H, H_2C-2′ and H_2C-3′), 1.95 (bs, 1H, O−H), 2.85 (ddt, J = 17.26, 6.25, 3.00 Hz, 1H, HC-4), 2.98 (ddt, J = 17.26, 8.00, 3.00 Hz, 1H, HC-4), 3.54−3.63 (m, 1H, HC-1′), 4.44 (ddd, J = 8.00, 6.25, 4.50 Hz, 1H, HC-5), 5.66 (t, J = 3.00 Hz, 1H, =CH), 6.24 (t, J = 3.00 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ 13.8 (C-4′), 18.6 (C-3′), 29.5 (C-4), 34.7 (C-2′), 72.8 (C-1′), 79.5 (C-5), 121.9 (=CH_2), 134.2 (C-3), 170.3 (C-2). Anal. ($C_9H_{14}O_3$) C, H.

(5*R,1′*S**)-5-(1′-Hydroxybutyl)-3-methylidenetetrahydro-2-furanone (5*R**,1′*S**)-7d:** oil, 68% yield; R_f = 0.33 ($CHCl_3$:acetone = 9:1); IR (film) ν 3440 (O−H), 1760 (C═O), 1664 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 6.75 Hz, 3H, H_3C-4′), 1.25−1.65 (m, 4H, H_2C-2′ and H_2C-3′), 1.83 (bs, 1H, O−H), 2.86 (ddt, J = 17.26, 8.00, 2.50 Hz, 1H, HC-4), 3.01 (ddt, J = 17.26, 6.00, 2.50 Hz, 1H, HC-4), 3.96 (ddd, J = 11.59, 6.50, 3.50 Hz, 1H, HC-1′), 4.46 (ddd, J = 8.00, 6.25, 3.50 Hz, 1H, HC-1′), 5.66 (t, J = 3.00 Hz, 1H, ═CH), 6.24 (t, J = 3.00 Hz, 1H, ═CH); ^{13}C NMR ($CDCl_3$) δ 13.9 (C-4′), 18.7 (C-3′), 27.1 (C-4), 33.8 (C-2′), 71.1 (C-1′), 79.6 (C-5), 121.9 (═CH_2), 134.6 (C-3), 170.4 (C-2). Anal. ($C_9H_{14}O_3$) C, H.

(5*R,1′*R**)-5-(Hydroxy-phenyl-methyl)-3-methylidenetetrahydro-2-furanone (5*R**,1′*R**)-7e:** oil, 63% yield; IR (film) ν 3432 (O−H), 1764 (C═O), 1664 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (bs, 1H, OH), 2.65−2.86 (m, 2H, H_2C-4), 4.63−4.73 (m, 2H, C-5H, H C1′), 5.59 (t, ^4J = 2.50 Hz, 1H, ═CH), 6.21 (t, ^4J = 2.5 Hz, 1H, ═CH), 7.34−7.42 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.56 (C-4), 75.13 (C-5), 79.11 (C-1′), 121.35 (═CH_2), 126.14, 127.59, 127.65, and 137.28 (Ph), 132.91 (C-3), 169.16 (C-2). Anal. ($C_{12}H_{12}O_3$) C, H.

(5*R,1′*S**)-5-(Hydroxy-phenyl-methyl)-3-methylidenetetrahydro-2-furanone (5*R**,1′*S**)-7e:** oil, 41% yield; IR (film) ν 3425 (OH), 1766 (C═O), 1665 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (bs, 1H, OH), 2.63 (ddt, ^2J = 17.50 Hz, ^3J = 8.25 Hz, ^4J = 2.50 Hz, 1H, C-4H), 3.02 (ddt, ^2J = 17.50 Hz, ^3J = 5.75 Hz, ^4J = 2.50 Hz, 1H, C-4H), 4.73 (ddd, ^3J = 8.25 Hz, ^3J = 5.75 Hz, ^3J = 3.25 Hz, 1H, C-5H), 5.14 (d, ^3J = 3.25 Hz, 1H, C-1′H), 5.60 (t, ^4J = 2.50 Hz, 1H, ═CH), 6.21 (t,^4J = 2.50 Hz, 1H, ═CH), 7.30−7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.52 (C-4), 72.91 (C-5), 80.11 (C-1′), 121.94 (═CH_2), 125.96, 128.03, 128.56 and 138.21 (Ph), 134.46 (C-3), 170.58 (C-2). Anal. ($C_{12}H_{12}O_3$) C, H.

Cells and Cytotoxicity Assays. Mouse leukemia L-1210 cells were cultured in RPMI 1640 medium (Sigma, USA) supplemented with 10% fetal calf serum (Gibco, USA), gentamycin (50 μg/mL), and 0.02 M HEPES buffer (Gibco, USA) in a 5% CO_2−95% air atmosphere. Cytotoxic effects were assayed by measuring the inhibitory effects on L-1210 cell proliferation. In this assay, cells were seeded in 2 mL aliquots in 6 mL tissue culture tubes (Corning, USA) at a concentration of 5×10^3 cells/mL and exposed to drugs for 72 h at 37 °C. The cell number relative to control was then determined by the colorimetric tetrazolium dye method.[23]

Human promyelocytic leukemia HL-60 cells were cultured in RPMI 1640 medium supplemented with 10% foetal calf serum and gentamycin (50 μg/mL) in a 5% CO_2−95% air atmosphere. Expotentially growing HL-60 cells were seeded at 6×10^5 per each well of 6-well plate (Numc), and cells were then exposed to the compounds. Stock solutions were prepared freshly in RPMI 1640, then dilutions in complete culture medium were made. HL-60 cells were exposed to compounds for 72 h. The number of viable cells was counted in a Burker hemocytometer using trypan-blue exclusion assay. All the data were expressed as means ± SD.

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Supporting Information Available: General procedures and detailed ^1H, ^{13}C, and ^{31}P NMR assignments for all nontarget compounds and (5*R*,1′*R*)-**7e**, description of the software package Pallas, some statistics to the log *P* calculations, and experimental determination of the log *P* for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Paquette, L. A.; Mendez-Andino, J. A Direct, Highly Convergent Route to α-Methylene-γ-lactones Fused to Medium and Large Rings. *Tetrahedron Lett*. **1999**, *40*, 4301−4304 and references therein.

(2) Lee, K.-H.; Huang, B.-R.; Tzenga, Ch-Ch. Synthesis and Anticancer Evaluation of Certain α-Methylene-γ-(4-substituted phenyl)-γ-butyrolactone Bearing Thymine, Uracyl, and 5-Bromouracyl. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 241−244 and references therein.

(3) Nair, V.; Sinhababu, A. K. Carbohydrate Models of α-Methylene-γ-butyrolactones. *J. Org. Chem*. **1980**, *45*, 1893−1897 and references therein.

(4) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. Tumor Inhibitors. 69. Structure-Cytotoxicity Relationships among the Sesquiterpene Lactones. *J. Med. Chem*. **1971**, *14*, 1147−1152.

(5) Fujita, E.; Nagao, Y. Tumor Inhibitors Having Potential for Interaction with Mercapto Enzymes and/or Coenzymes. *Bioorg. Chem*. **1977**, *6*, 287−309.

(6) Cassady, J. M.; Byrn, S. R.; Stamos, I. K.; Evans, S. M.; McKenzie, A. Potential Antitumor Agents. Synthesis, Reactivity, and Cytotoxicity of α-Methylene Carbonyl Compounds. *J. Med. Chem*. **1978**, *21*, 815−819.

(7) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-Directable Chemical Reactions. *Chem. Rev*. **1993**, *93*, 1307−1370.

(8) Argade, A. B.; Haugwitz, R. D.; Devraj, R.; Kozlowski, J.; Fanwick, P. E.; Cushman, M., Highly Efficient Diastereoselective Michael Addition of Various Thiols to (+)-Brefeldin A. *J. Org. Chem*. **1998**, *63*, 273−278.

(9) Harcken, Ch.; Brückner, R. Stereopure 1,3-butadiene-2-carboxylates and their conversion into nonracemic α-alkylidenebutyrolactone natural products by asymmetric dihydroxylation. *Tetrahedron Lett.* **2001**, *42*, 3967−3971 and references therein.

(10) Martin, L. D.; Stille, J. K. Palladium-catalyzed Carbonylation of Vinyl Halides: A Route to the Synthesis of α-Methylene Lactones. *J. Org. Chem*. **1982,** *47*, 3630−3633.

(11) Tomioka, K.; Kawasaki, H.; Iitaka, Y.; Koga, K. Enantiospecific Total Synthesis of (−)-Megaphone by a Highly Controlled Consecutive 1,4- and 1,3-Asymmetric Induction. *Tetrahedron Lett*. **1985**, *26*, 903−906.

(12) Bock, K.; Castilla I. M.; Lundt, I.; Pedersen, Ch. Synthesis of an Optically Active α-Methylene Lactone Starting from Isosaccharinic Acid. *Acta Chem. Scand*. **1987**, *B41*, 13−17.

(13) Still, I. W. J.; Drewery, M. J. Synthesis of 2-Butenolide and Tetronic Acid Analogues of Thiolactomycin. *J. Org. Chem*. **1989**, *54*, 290−295.

(14) Isaac, M. B.; Paquette, L. A. Experimental Test of Setting Three Contiguous Stereogenic Centers in Water. Diastereoselective Coupling of Geometrically Biased Allylic Bromides to α-Oxy Aldehydes with Indium. *J. Org. Chem*. **1997**, *62*, 5333−5338.

(15) Janecki, T.; Kuś, A.; Krawczyk, H.; Błaszczyk, E. A New, General Approach to Substituted 3-Diethoxyphosphoryl-2,5-dihydro-2-furanones. *Synlett*. **2000**, 611−614.

(16) Janecki, T.; Błaszczyk, E. A Convenient Synthesis of 3-Alkylidenetetrahydro-2-furanones from 3-Diethoxyphosphoryl-2,5-dihydro-2-furanones. *Synthesis* **2001**, 403−408.

(17) Janecki, T.; Błaszczyk, E. Stereocontrolled Synthesis of 5-(1′-Hydroxyalkyl)-3-methylidenetetrahydro-2-furanones. *Tetrahedron Lett*. **2001**, *42*, 2919−2922.

(18) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev*. **1994**, *94*, 2483−2547.

(19) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, pp 128−134.

(20) Canetta, R.; Goodlow, J.; Sinaldone, L. Pharamcologic Characteristic of Carboplatin: Clinical Experience, Current Perspectives and Future Directions. *Saunders* **1990**, 19−38.

(21) Leo, A.; Hansch, C.; Church, C. Comparison of Parameters Currently Used in the Study of Structure−Activity Relationships. *J. Med. Chem*. **1969**, *12*, 766−771.

(22) Values for specific isomers were taken from the spectrum of the mixture of isomers.

(23) Carmichael, J.; DeGraff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. Evaluation of Tetrazolium-based Semiautomatic Colorimetric Assay: Assessment of Chemosensitivity Testing. *Cancer Res*. **1987**, *47*, 936−942.

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