Journal of Medicinal Chemistry

ARTICLE

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Synthesis of Tetrahydronaphthalene Lignan Esters by Intramolecular Cyclization of Ethyl *p*-Azidophenyl-2-phenylalkanoates and Evaluation of the Growth Inhibition of Human Tumor Cell Lines

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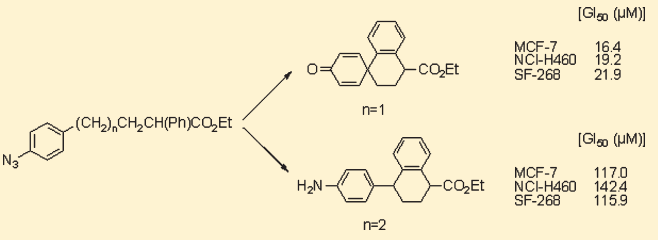
Supporting Information

ABSTRACT: Intramolecular cyclization via nitrenium ion of 2-phenylpentanoic/2-phenylbutanoic acid esters with a terminal *p*-azidophenyl group gives direct access to tetrahydronaphthalene lignan esters. The *p*-azidophenyl-substituted butanoate led to an ethyl spirodienone carboxylate, while its homologue pentanoate gave ethyl 4-(4-aminophenyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate in good yield. In contrast, the *m*-azidophenyl-substituted esters suffered aromatic nucleophilic addition of trifluoromethanesulfonate. X-ray crystallography established unequivocally the end products structure, and density functional theory studies were performed to rationalize the cyclization outcome. Reaction intermediates and end products were evaluated for their capacity to inhibit in vitro growth of the cell lines MCF-7 (breast cancer), NCI-H460 (lung cancer), SF-268 (CNS cancer), and UACC-62 (melanoma). Growth inhibition of breast, lung, and CNS cancer cell lines was observed with the spirodienone carboxylate, the *m*-nitrophenylalkyl iodides, and *p*-phenyl-substituted elongated ethyl esters, namely, the *p*-nitrophenylpentanoate and *p*-aminophenylbutanoate, with the latter being also effective on the melanoma cell line.



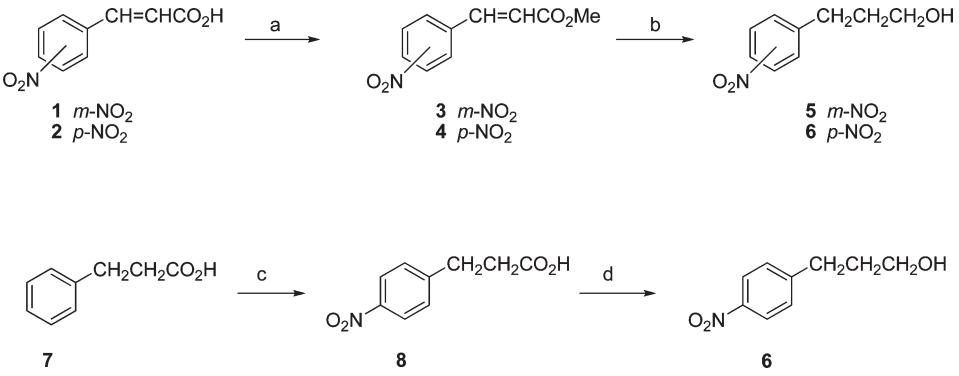
INTRODUCTION

Tetrahydronaphthalene lignans[1] are a group of naturally occurring compounds spread within the plant kingdom and classified as cyclolignans since their structure results from the modification of the carbon skeleton of a lignan, which has an additional carbocyclic ring formed by direct bonding between two atoms of the lignan backbone.[2] Synthetic strategies for structurally diverse cyclolignans have been developed, namely, for aryltetrahydronaphthalene lactones[3] and tetrahydronaphthalenes with various substitution patterns,[4] requiring multistep approaches. This family of compounds exhibits a variety of biological activities, namely, antitumor,[5] antiviral,[6] anti-inflammatory,[7] and platelet antiaggregating activity.[8] Some tetrahydronaphthalenes of synthetic origin were found to be selective MT_2 melatonin receptor antagonists,[9] while others act as ligands for histamine H_1 receptors[4a−4c,10] or stimulate tyrosine hydroxylase activity and dopamine synthesis.[11] This type of lignans includes clinically approved therapeutics and lead structures to new drugs[12] and is of valuable interest in medicinal chemistry.

The nitrenium ion chemistry has attracted special attention from the scientific community, primarily due to its possible involvement in the mechanism of action of amino- and nitroaromatic metabolites of mutagenic and carcinogenic processes and in the mechanism of action of antitumor drugs.[13] Its wide application in (bio)organic synthesis is justified since it involves simple, versatile, economical, and high yield methodologies. Nitrenium ions have been engaged in a variety of synthetic approaches including electrophilic amination of aromatic and heterocyclic compounds,[14] rearrangements[15] of nitrogen-containing compounds with nucleophiles,[16] and intramolecular cyclizations to afford new C−C,[17] C−O,[18] and C−N bonds.[19] Abramovitch and co-workers have extensively used this type of reaction for the preparation of six and seven homo- and heterocyclic rings via acid-catalyzed decomposition of aryl azides.[20] Intramolecular cyclization of nitrenium ions formed by treatment of *N*-acylaminophthalimides with hypervalent iodine compounds was also reported to afford lactams and spiro-fused lactams.[21]

Received: September 10, 2010
Published: April 19, 2011

Scheme 1[a]



[a] Reagents and conditions: (a) MeOH, H_2SO_4, reflux, 1.5 h 94% (**3**), 96% (**4**). (b) $LiBH_4$, dec-1-ene, THF, room temperature, 18 h, 71% (**5**), 56% (**6**). (c) HNO_3 fumaric/AcOH, room temperature, 6 h, 92%. (d) B_2H_6-THF, THF, room temperature, 3 h, 95%.

We now report on the antitumor activity and synthesis of tetrahydronaphthalene lignan esters containing a spirodienone or a 4-aryl substitution via intramolecular cyclization of open-chain nitrenium ions, whose formation was interpreted by density functional theory (DFT) calculations. Intramolecular cyclization of the 1,3-substituted aromatic precursors was also predicted by such calculations, but experimentally, the single products obtained resulted from a *p*-nucleophilic addition of trifluoromethanesulfonate. To date, most attention has been devoted to lignans antitumor activity. Hence, the growth inhibitory activity of the new cyclized products as well as those of some synthetic intermediates on human tumor cell lines of breast, lung, and central nervous system (CNS) cancer and melanoma was assessed.

RESULTS AND DISCUSSION

Chemistry. The starting materials 3-(3-nitrophenyl)acrylic acid (**1**), 3-(4-nitrophenyl)acrylic acid (**2**), 2-(3-nitrophenyl)ethanol (**9**), and 2-(4-nitrophenyl)ethanol (**10**) were used for the synthesis of the key ethyl ω-(azidophenyl)-2-phenylalkanoate precursors **24**−**27**, respectively, through a multistep strategy. Accordingly, as depicted in Scheme 1, the 3-(3-nitrophenyl)propan-1-ol (**5**) and 3-(4-nitrophenyl)propan-1-ol (**6**) were prepared in moderate to good yield from the corresponding acids **1** and **2** after esterification followed by complete reduction of the α,β-unsaturated esters **3** and **4** promoted by $LiBH_4$. Alternatively, the alcohol **6** was obtained in excellent yield by nitration of 3-phenylpropanoic acid (**7**) followed by reduction of the carboxylic acid with diborane (Scheme 1).

The alcohols **5**, **6**, **9**, and **10** were converted into the corresponding (ω-iodoalkyl)nitrobenzenes **11**−**14** in 96−98% yield, employing the I_2/PPh_3/imidazole system in toluene (Scheme 2).

Arylation methodologies involving the iodoalkyl derivatives **11**−**14** were then investigated to prepare the 4-/5-nitrophenyl-2-phenylalkanoate precursors **16**−**19**, namely, by condensation with thalium salts, Wittig reactions (using the bromoalkyl precursors instead), and under microwave irradiation in the presence of ammonium halides and aluminum oxide. However, these strategies gave low yields (<26%) or failed to give the target molecules. Compounds **16**−**19** were efficiently synthesized by S_N2 reaction of the (iodoalkyl)nitrobenzenes **11**−**14** with the anion of ethyl phenylacetate **15** generated in situ using lithium diisopropylamide (LDA) in THF as the base (Scheme 2). Reduction of the nitro function of derivatives **16**−**19** with Raney-Ni/H_2N-$NH_2\cdot H_2O$ provided the corresponding aminophenyl compounds **20**−**23**, which were then transformed into the key ethyl 4-/5-azidophenyl-2-phenylalkanoate precursors **24**−**27** after treatment with sodium nitrite, sodium azide, and hydrochloric acid.

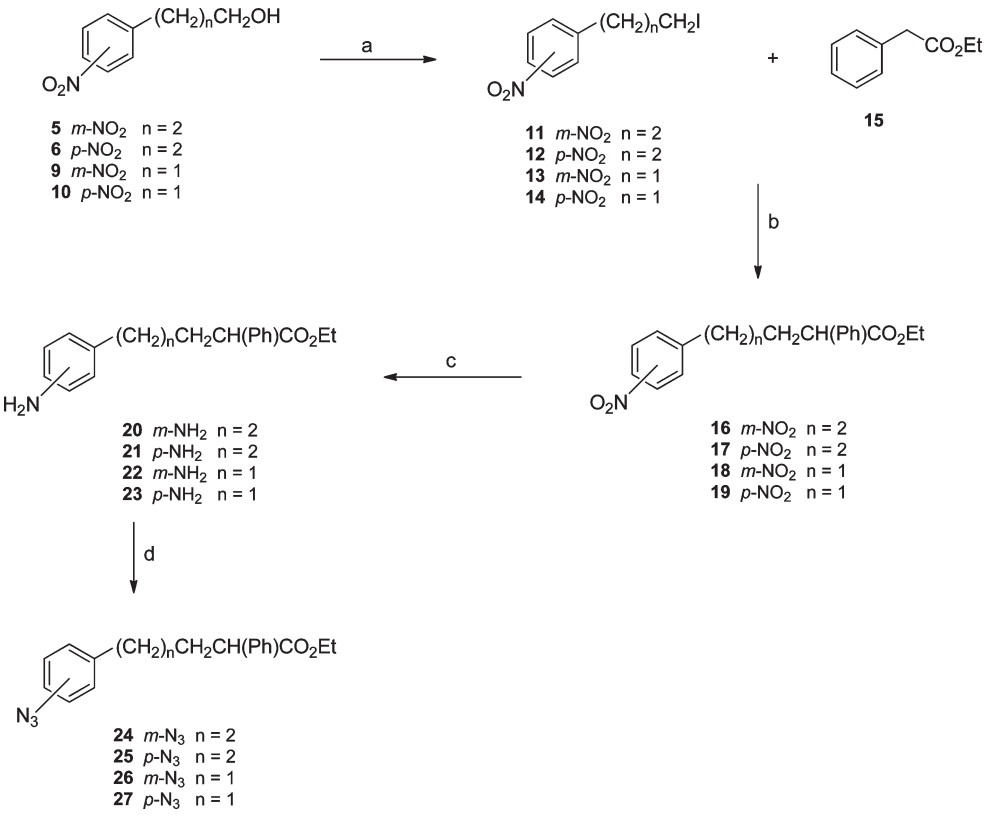
The intramolecular cyclization of the aryl azides **24**−**27** catalyzed by acid led to distinct results (Scheme 3). Treatment of the 1,3-substituted derivatives **24** and **26** with trifluoromethanesulphonic acid (TFMSA) at 0 °C did not lead to any cyclization. Instead, compounds **28** and **29** were obtained in 65 and 63% yield, respectively, suggesting the nucleophilic addition of trifluoromethanesulfonate to an intermediate carbenium ion. These results may be regarded as the introduction of a protected hydroxyl group into an aniline ring system, and consequently, these reactions could be of great value for arene chemistry.

The 1,4-substituted precursors **25** and **27** led to the synthesis of ethyl 4-(4-aminophenyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (**30**) and ethyl 4-oxo-3′,4′-dihydro-2′*H*-spiro(cyclohexa[2,5]diene-1,1′-naphthalene)-4′-carboxylate (**31**), respectively. The structure of both final products, besides the usual spectroscopic methods, was unequivocally assigned by means of X-ray crystallography (Figure 1).

Compounds **30** and **31** crystallized in a monoclinic crystal system but in different space groups: in $P2_1$ and $P2_1/n$ space groups, respectively. Although compound **30** crystallized in a noncentrosymmetric space group, the structure determination revealed that only 60% of the molecules in the crystal have the conformation shown in Figure 1a. This has been shown by the measure of a null specific optical rotation observed, confirming a practically racemic mixture in this compound.

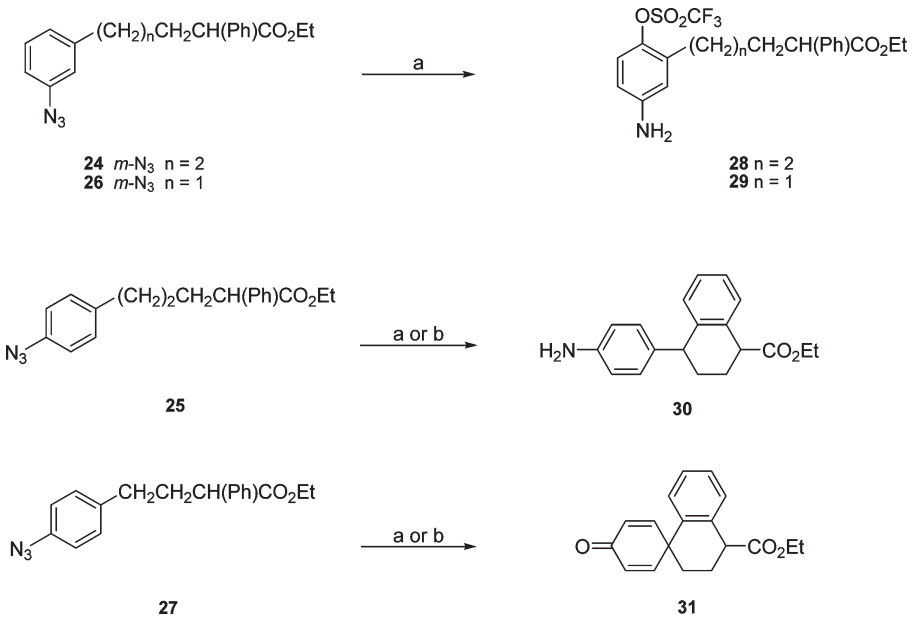
The new stereogenic center of compound **30** resulted from the nucleophilic attack to the carbenium ion at C-5, formed by electron delocalization of the intermediate iminium ion (Figure 2a) to give a racemic mixture. The formation of the six-membered ring in compound **30**, instead of an eight-membered ring, is very peculiar, especially taking in consideration the examples described in the literature for reactions of this type with similar compounds, where six-membered rings are formed as secondary products in very low yield.[22] However, this result can be rationalized through the mechanism depicted in Figure 2a,

Scheme 2[a]



[a] Reagents and conditions: (a) I_2, PPh_3, imidazole, toluene, room temperature, 3 h, 96−98%. (b) LDA, THF, −78 °C to room temperature, 72−86%. (c) Ra−Ni, H_2N-NH_2.H_2O, MeOH, room temperature, quant. (d) $NaNO_2$, NaN_3, 20% HCl, 40 °C to room temperature, 71−93%.

Scheme 3[a]



[a] Reagents and conditions: (a) TFMSA, CCl_4, 0 °C to room temperature, 65% (**28**), 63% (**29**), 67% (**30**), 62% (**31**). (b) TFMSA, CH_2Cl_2, 0 °C to room temperature, 49% (**30**), 47% (**31**).

and its interpretation (see below) was possible by DFT calculations.[23] The formation of **31**, isolated in 62% yield, can be explained by an *ipso*-substitution, followed by hydrolysis of the intermediate imine (Figure 2b). This is a particularly exciting

dx.doi.org/10.1021/jm101182s |*J. Med. Chem.* 2011, 54, 3175–3187

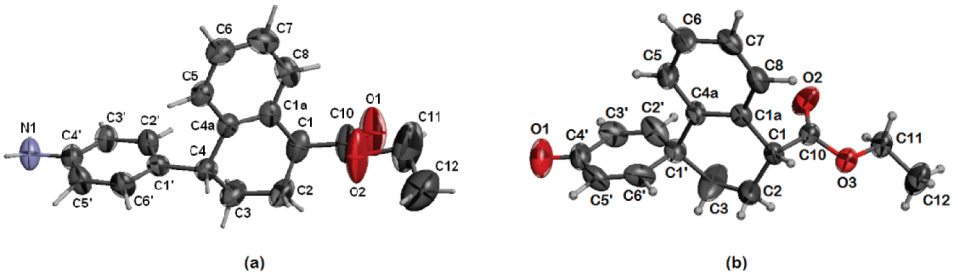


Figure 1. RASTER plot of the asymmetric units of compounds **30** (a) and **31** (b) showing the labeling scheme.

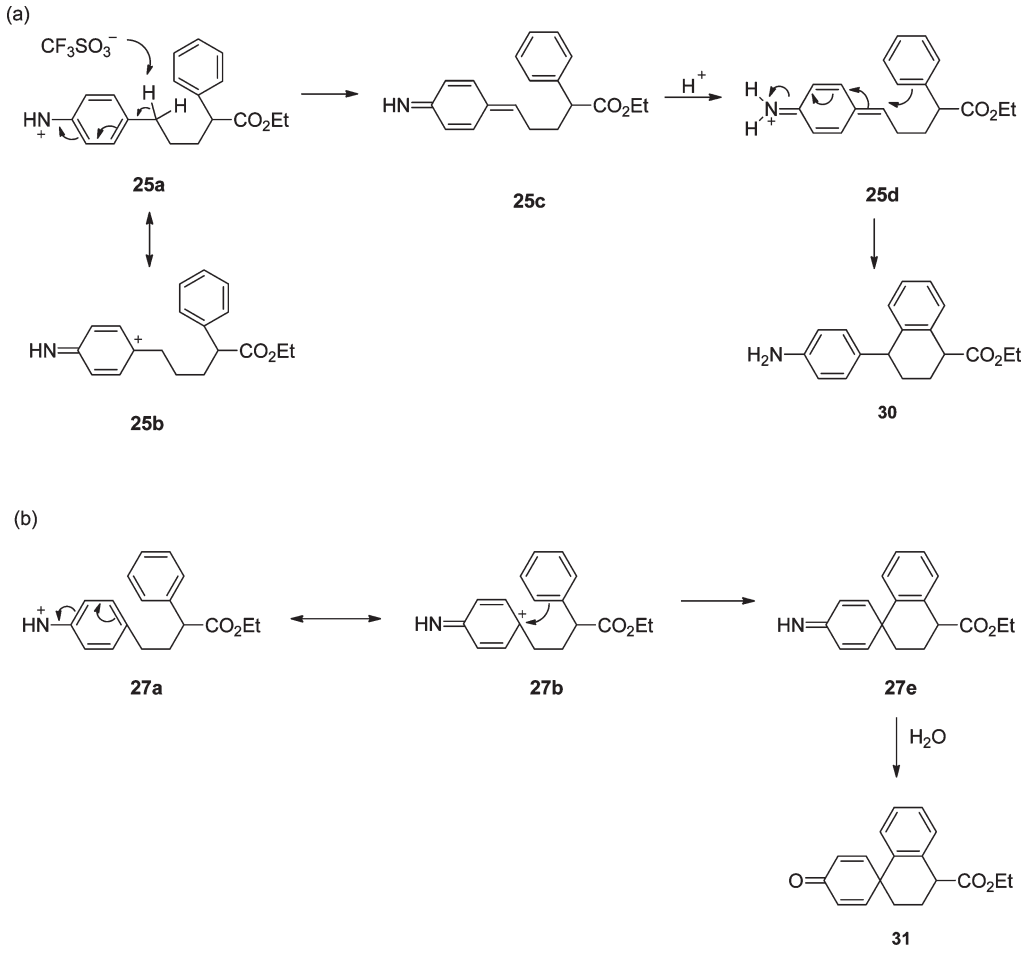


Figure 2. Mechanisms proposed for the formation of compounds **30** (a) and **31** (b).

direct procedure to obtain spirodienones by intramolecular cyclization of a nitrenium ion. Such a compound type bearing a 1-azaspiro[4.5]decane ring system has also been synthesized by the intramolecular *ipso* attack of a nitrenium ion starting from *N*-methoxy-(4-halogenophenyl)amides generated with [hydroxy-(tosyloxy)iodo]benzene in trifluoroethanol.[24]

DFT Calculations. DFT calculations[23] (Gaussian03)[25] were performed on several of the intermediates shown in Figure 2, and the two alternative pathways leading to the formation of cyclization product **30** and its analogue derived from **27a**, or **31** and its analogue derived from **25a** were analyzed.

To check the reliability of the computational approach (see the Experimental Section for details), we optimized the two final products that were structurally characterized by single crystal X-ray diffraction. The calculated structural parameters agree with the experimental ones.

The optimized structures of the precursors, **25a** and **27a**, are shown in Figure 3. The main difference between them consists of the length of the aliphatic side chain, with, respectively, three (**25a**) or two (**27a**) carbon atoms, and it has no effect on the atomic charges, as can be seen from the selected charges given in Figure 3. Therefore, the contribution of the resonance hybrids **25a,b** or **27a,b** to the structure of each molecule will be identical.

Indeed, the charge on the nitrogen is negative, because of its large electronegativity, while the carbon atom where cyclization should occur has a positive charge. The C−C bond lengths in the

dx.doi.org/10.1021/jm101182s |*J. Med. Chem.* 2011, 54, 3175–3187

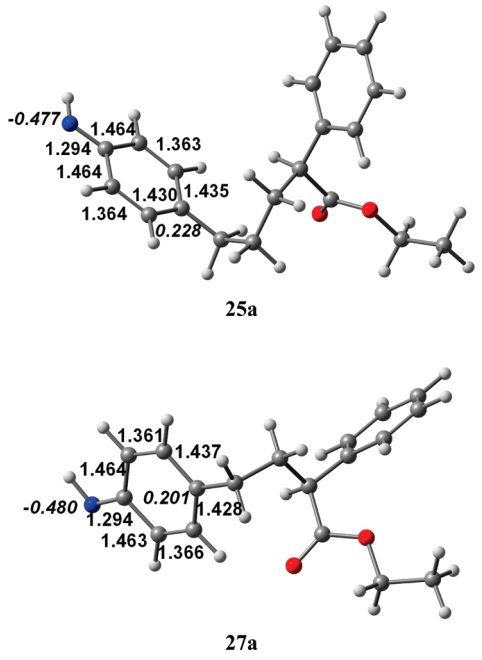


Figure 3. Optimized DFT structure of precursors **25a** and **27a**, showing selected bond lengths and charges on nitrogen and the carbon involved in the cyclization.

phenyl ring bearing the NH group indicate a large contribution of the **25b** or **27b** resonance form. The N−C bond is short, with a considerable double bond character, the same happening to two of the C−C bonds. Also, in this form, the nitrogen does not carry a formal positive charge. It is not surprising that a cyclization reaction proceeds from **25b** and **27b**, since it seems to be adequate for such a reaction.

Let us now consider the alternative pathway that leads to the formation of **30** in the long chain compound. According to Figure 2, the deprotonation of the precursor must take place at the first carbon atom of the chain (**25c**), assisted by the triflate anion, being followed by protonation at the nitrogen, to afford **25d**. The formation of a C−C bond leads to the final product **30**.

The relative energies are much lower for the tetrahydronaphtalene compounds type **30** than for the cyclization product **27e**, for both chain lengths. Indeed, the final product **31** results from hydrolysis of **27e**. Therefore, only the precursor **25a** leads to the thermodynamically preferred product. The relative energies of the relevant intermediates are collected in Table 1. The first column contains the values calculated for gas-phase compounds. Because some intermediates are neutral and others are cationic, the calculations were repeated, adding one triflate anion to the cationic species and one triflic acid to the neutral ones, to stay in the same scale (column 2). Finally, a solvent was introduced in a continuum model (CH_2Cl_2, column 3, and CCl_4, column 4). Despite the small changes observed in the relative energies when triflate and solvent are added, the tetrahydronaphtalene type compounds remain the preferred ones. The addition of triflate anion and triflic acid to the species mentioned puts all of them in the same energy scale. All of the products have negative energies, showing that they are thermodynamically more stable than the reagents. The inclusion of solvents compensates for the separation of charges, but no significant changes occur.

The formation of **30** requires the deprotonation/protonation steps, which is expected to be favored in the slightly polar

Table 1. Relative Energies of Selected Intermediates, Adding OTf^- or HOTf in the Gas Phase, in CH_2Cl_2 and in CCl_4 (kcal mol^{-1})

	gas phase	OTf^- or HOTf	CH_2Cl_2	CCl_4
25a	0.0	0.0	0.0	0.0
25c	217.2	−97.3	−17.9	−48.1
25d	−44.1	−44.1	−41.7	−43.2
"25e"	220.7	−93.8	−13.1	−43.9
30	186.2	−128.3	−48.4	−78.9
27a	0.0	0.0	0.0	0.0
27c	218.4	−96.1	−19.7	−48.4
27d	−41.2	−41.2	−40.0	−40.6
27e	214.6	−99.8	−22.5	−51.8
"30"	185.9	−128.5	−51.6	−80.6

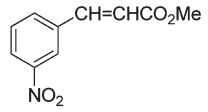
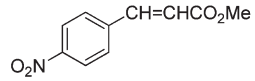
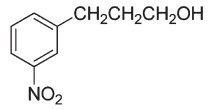
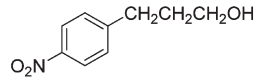
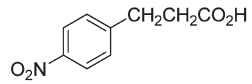
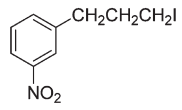
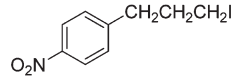
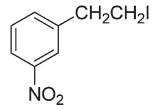
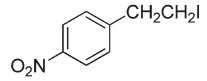
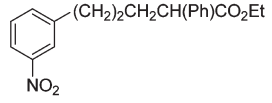
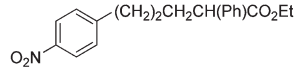
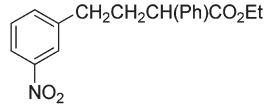
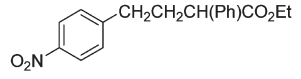
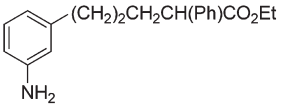
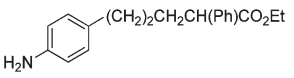
dichloromethane, while in the presence of the nonpolar CCl_4, the pathway leading to the formation of species **27e**/**31**, without charge separation, is more likely to take place. However, reaction in CCl_4 leads to higher yields of both **30** and **31** than in dichloromethane, which may also be inferred from the data given in Table 1, in which the intermediate reactive species have lower relative energies in CCl_4 than in CH_2Cl_2.

As a conclusion, one may say that the solvent CCl_4, selected for optimized solubility for reagents and products, acts as a reaction driving force conducting to lower relative energies of intermediate and end products. However, the features of the two precursors are quite similar, and the energy difference between the two alternative products is rather large. The outcome cannot be rationalized on the basis of the energy of intermediates, but their energy differences are large enough to suggest that a detailed study of the transition states would not bring any new relevant information to the problem. It should be added that different reaction outcomes observed for related products involved side chains in different positions of the phenyl ring relative to the NH group, while in this work the side chains occupy the same position differing only in their size.

Effect of Compounds on the Growth of Human Tumor Cell Lines. The effects of compounds for their ability to inhibit the in vitro growth of four human tumor cell lines representing different tumor types, namely, breast adenocarcinoma (MCF-7), nonsmall cell lung cancer (NCI-H460), CNS cancer (SF-268), and melanoma (UACC-62), after a continuous exposure for 48 h, were evaluated. The obtained results are summarized in Table 2. Interestingly, the *meta*-substituted iodides **11** and **13** show activity for three cell lines, while their isomeric *para*-substituted forms, in particular the iodopropyl derivative, show no activity on any of the cell lines studied. However, both the *para*-substituted ethyl nitrophenyl pentanoate **17** and the ethyl aminophenylbutanoate **23** exhibit bioactivity on three cell lines and on all of the cell lines tested, respectively, with the latter compound being slightly more effective against melanoma. Interestingly, the spirodienone moiety seems to be determinant for the observed cell growth inhibitory effects, which could not be detected with compound **30** nor with the related compound 1-(4-hydroxy-3,5-dimethoxyphenyl)-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydronaphthalene-2,3-dimethanol diacetate tested against malignant lung (VA-13) and hepatoma (HepG2) cells.[8] Hence, the spirodienone **31**, with this unique scaffold, shows potential as a hit compound regarding the

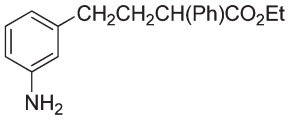
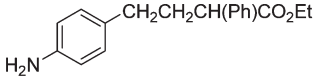
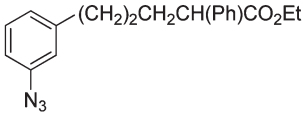
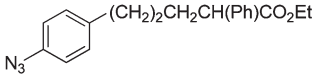
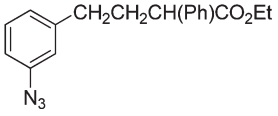
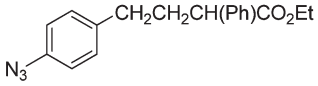
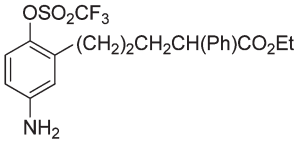
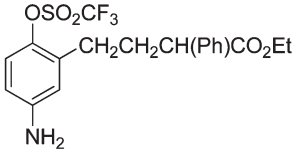
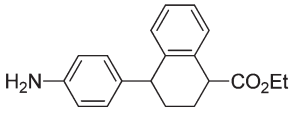
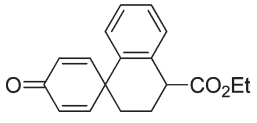
dx.doi.org/10.1021/jm101182s |*J. Med. Chem.* 2011, 54, 3175–3187

Table 2. Effect of Compounds on the Growth of Human Tumor Cell Lines [GI_{50} (μM)][a]

Compound		MCF-7 (Breast)	NCI-H460 (Lung)	SF-268 (CNS)	UACC-62 (Melanoma)
3		74.1 ± 5.9	174.7 ± 17.4	179.6 ± 14.6	ND
4		214.2 ± 27.4	> 240	> 240	ND
5		> 250	> 250	> 250	> 250
6		> 250	> 250	> 250	> 250
8		> 250	> 250	> 250	ND
11		**21.8 ± 0.9**	**37.4 ± 2.7**	**34.3 ± 3.5**	ND
12		142.6[b]	132.3[b]	> 170[b]	ND
13		**19.1 ± 1.2**	**35.3 ± 0.5**	**35.7 ± 2.1**	ND
14		55.8 ± 12.6	111.9 ± 25.3	95.7 ± 34.3	ND
16		148.8 ± 4.1	> 150	> 150	ND
17		**16.4 ± 1.8**	**19.4 ± 3.2**	**23.2 ± 5.8**	ND
18		92.7 ± 33.9	149.1 ± 10.7	> 150	ND
19		134.2[b]	> 150[b]	> 150[b]	ND
20		108.9 ± 2.6	153.8 ± 10.0	> 160	124.6 ± 3.4
21		155.4 ± 5.3	> 160	> 160	> 100

dx.doi.org/10.1021/jm101182s |J. Med. Chem. 2011, 54, 3175–3187

Table 2. Continued

Compound		MCF-7 (Breast)	NCI-H460 (Lung)	SF-268 (CNS)	UACC-62 (Melanoma)
22		104.2[b]	132.5[b]	159.0[b]	102.5 ± 14.7
23		**36.3 ± 1.3**	**40.8 ± 4.6**	**51.8 ± 4.2**	**23.3 ± 0.9**
24		119.2 ± 10.3	> 150	> 150	ND
25		> 150	> 150	> 150	ND
26		119.7[b]	> 160[b]	> 160[b]	ND
27		124.6 ± 37.2	> 160[b]	> 160[b]	ND
28		48.8 ± 5.9	74.3 ± 2.7	73.5[b]	ND
29		54.6 ± 2.2	65.8 ± 6.8	81.4 ± 9.7	ND
30		117.0[b]	142.4[b]	115.9[b]	ND
31		**16.4 ± 0.8**	**19.2 ± 1.6**	**21.9 ± 2.8**	ND

[a] Results are given in concentrations that were able to cause 50% of cell growth inhibition (GI_{50}) after a continuous exposure of 48 h and represent means ± SEMs of 3−6 independent experiments performed in duplicate and carried out independently. [b] Results from one or two independents experiments performed in duplicate. Doxorubicin was used as a positive control, GI_{50} (nM): MCF-7 = 42.8 ± 8.2, NCI-H460 = 94.0 ± 8.7, SF-268 = 94.0 ± 7.0, and UACC-62 = 94.0 ± 9.4; ND, not determined.

development of new anticancer agents easily accessed by synthesis.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on an Electrothermal melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a Brüker AMX-300, a Brüker AC-300, or a Brüker AMX-500 for solutions in $CDCl_3$ at room temperature, using tetramethylsilane as an internal reference. Additional correlation spectroscopy (COSY), nuclear Overhauser enhancement spectroscopy (NOESY), total correlation spectroscopy (TOCSY), heteronuclear multiple bond coherence (HMBC), and heteronuclear multiple quantum coherence (HMQC) measurements to verify the proposed assignments were performed in the same spectrometers. Chemical shifts are reported in δ (ppm). Gas chromatography/mass spectrometry (GC/MS) spectra were obtained on a Hewlett Pachard 5890 MSD or on a GC/MS TRIO 1000 spectrometer operating at an ionization energy of

dx.doi.org/10.1021/jm101182s |J. Med. Chem. 2011, 54, 3175–3187

70 eV. Infrared (IR) spectra were rerecorded on a Hitachi 270-50 or on a Nicolet Magna−IR Spectometer 55. The specific analytical method used to determine purity was elemental analysis, which confirmed a purity ≥95% for the compounds tested. Elemental analyses were determined on an autoanalyzer EA 1108. Column chromatography was performed on Merck silica gel 60G (230−400 mesh, 0.040−0.063 mm). Preparative and analytical thin-layer chromatography (TLC) were carried out on silica gel plates (Kieselgel 60 F254, E. Merck A.G., Germany) using UV light for detection. Solvents and reagents were purchased from Sigma-Aldrich, Acros, or Fluka. Anhydrous solvents were freshly distilled under argon from Na/benzophenone (THF, Et_2O, and toluene) or P_2O_5 (CH_2Cl_2). Other anhydrous solvents were dried over a bed of activated molecular sieves (ethanol and methanol). Dry DMSO was purchased from Sigma-Aldrich. Solvents for column chromatography (hexane and EtOAc) were distilled before use.

Esterification of the Nitrophenyl Acrylic Acids: General Procedure. In a typical experiment, a methanolic solution (30 mL) of substrate (10 mmol) was added dropwise over a period of 15 min. The reaction mixture was refluxed until the TLC revealed no trace of starting material (usually 90 min). At the end of the reaction, the methanol was removed under reduced pressure, and the remaining residue was dissolved in EtOAc (60 mL) and washed with a saturated aqueous solution of Na_2CO_3 (60 mL). The organic layer was separated, washed with water (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc 5:1). The products were crystallized from $CHCl_3$.

*Methyl 3-(3-Nitrophenyl)prop-2-enoate (**3**).* White solid (94% yield); mp 125−126 °C ($CHCl_3$). IR (KBr): 1704, 1636, 1612, 1524, 1338 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.41 (s, 1 H, H-2′), 8.26 (d, J = 7.8 Hz, 1 H, H-4′), 7.85 (d, J = 7.8 Hz, 1 H, H-6′), 7.75 (d, 1 H, H-2), 7.61 (t, J = 7.8 Hz, 1 H, H-5′), 6.58 (d, J = 16.2 Hz, 1 H, H-3), 3.66 (s, 3 H, OCH_3). GC/MS (EI): m/z 207 (M^+). Elemental anal. calcd for $C_{10}H_9O_4N$: C, 57.98; H, 4.38; N, 6.76. Found: C, 57.93; H, 4.27; N, 6.79.

*Methyl 3-(4-Nitrophenyl)prop-2-enoate (**4**).* White solid (96% yield); mp 155−155.5 °C ($CHCl_3$). IR (KBr): 1718, 1636, 1592, 1512, 1338 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.25 (d, J = 8.7 Hz, 2 H, H-3′, H-5′), 7.75−7.66 (m, 3 H, H-2′, H-6′, H-2), 6.59 (d, J = 15.9 Hz, 1 H, H-3), 3.84 (s, 3 H, OCH3). GC/MS (EI): m/z 207 (M^+). Elemental anal. calcd for $C_{10}H_9O_4N$: C, 57.98; H, 4.38; N, 6.76. Found: C, 58.17; H, 4.27; N, 6.66.

Ester Reduction: General Procedure. To a solution of $LiBH_4$ (11 mmol) in anhydrous THF (8 mL) under N_2 atmosphere was added dropwise during 1 h a solution of starting material (6 mmol) together with dec-1-ene (12 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred overnight, and the completion of the reaction was monitored by TLC. The excess of $LiBH_4$ was then decomposed by dropwise addition of acidified water. The solvent was evaporated, and the remaining residue was dissolved in CH_2Cl_2 (20 mL) and washed with a 10% aqueous solution of NaCl (2 × 15 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexane/EtOAc 3:1) afforded the target alcohols.

*3-(3-Nitrophenyl)propan-1-ol (**5**).* Oil (71% yield). IR (KBr): 3316, 1578, 1527, 1353 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.07−8.04 (m, 2 H, H-2′, H-4′), 7.54 (d, J = 9.0 Hz, 1 H, H-6′), 7.45 (t, J = 9.0 Hz, 1 H, H-5′), 3.69 (t, J = 6.0 Hz, 2 H, H-1), 2.84 (t, J = 6.0 Hz, 2 H, H-3), 1.93 (m, 2 H, H-2). GC/MS (EI): m/z 181 (M^+). Elemental anal. calcd for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.50; H, 6.09; N, 7.50.

*3-(4-Nitrophenyl)propan-1-ol (**6**).* Oil (56% yield). IR (KBr): 3322, 1599, 1512, 1347 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.13 (d, J = 9.0 Hz, 2 H, H-3′, H-5′), 7.36 (m, 2 H, H-2′, H-6′), 3.68 (t, J = 6.0 Hz, 2 H, H-1), 2.83 (t, J = 6.0 Hz, 2 H, H-3), 1.92 (m, 2 H, H-2). GC/MS (EI): m/z 181 (M^+). Elemental anal. calcd for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.89; H, 6.09; N, 7.57.

*Alternative Synthetic Strategy to the Synthesis of 3-(4-Nitrophenyl)propan-1-ol (**6**).* Nitric acid (8.4 mL, 0.2 mol) was carefully added dropwise during 1 h to an ice cooled solution of 3-phenylpropanoic acid (**7**) (4.3 g, 28.4 mmol) in glacial acetic acid (10 mL). The reaction mixture was stirred at room temperature for 3 h and then poured into ice (50 g). The precipitated formed was recovered by filtration and washed with cold water (3 × 100 mL). The product was crystallized in ethanol and dried under vacuum to afford the 3-(4-nitrophenyl)propanoic acid (**8**) (5.1 g, 92%).

To a solution of carboxylic acid **8** (4.9 g, 25.0 mmol) in anhydrous THF (15 mL) under N_2 was added dropwise a 1 M solution of diborane in THF (33 mL, 33 mmol). After the solution was stirred for 2 h at room temperature, TLC revealed no trace of starting material. The excess of diborane was carefully decomposed by addition of a 7% aqueous solution of K_2CO_3. The reaction mixture was concentrated under reduced pressure and then dissolved in EtOAc (50 mL) and washed with a saturated solution of $NaHCO_3$ (3 × 25 mL). The organic phase was dried and filtered, and the solvent was evaporated. Purification by flash column chromatography (hexane/EtOAc 7:1) afforded the alcohol **6** (4.3 g, 95%).

Iodination: General Procedure. To a vigorously stirred solution of triphenylphosphane (4 mmol) and imidazole (4 mmol) in anhydrous toluene (20 mL) was added dropwise a solution of iodine (3.9 mmol) in anhydrous toluene (10 mL) under N_2 stream. After it was stirred for 30 min at room temperature, a solution of alcohol (3 mmol) in toluene (10 mL) was added dropwise, and the reaction continued until TLC revealed no trace of starting material (typically 3 h). A saturated solution of $NaHCO_3$ (10 mL) was added, and the mixture was stirred for 10 min. The organic phase was recovered and then stirred with LiI (4 mmol) for 10 min. Aqueous sodium thiosulfate (20 mL) was added, and the organic layer was separated and washed with water (2 × 10 mL). The phosphonium oxide was directly precipitated from the organic layer by addition of cold petroleum ether. The filtrate was concentrated and purified by flash column chromatography (hexane/EtOAc 8:1).

*1-(3-Iodopropyl)-3-nitrobenzene (**11**).* Oil (96% yield). IR (NaCl): 1578, 1527, 1350 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.08−8.06 (m, 2 H, H-2′, H-4′), 7.55 (d, J = 9.0 Hz, 1 H, H-6′), 7.47 (t, J = 9.0 Hz, 1 H, H-5′), 3.18 (t, J = 6.0 Hz, 2 H, H-3), 2.66 (t, J = 6.0 Hz, 2 H, H-1), 2.17 (m, 2 H, H-2). GC/MS (EI): m/z 291 (M^+). Elemental anal. calcd for $C_9H_{10}O_2N$: C, 37.14; H, 3.46; N, 4.81. Found: C, 37.41; H, 3.39; N, 4.78.

*1-(3-Iodopropyl)-4-nitrobenzene (**12**).* Oil (97% yield). IR (NaCl): 1599, 1512, 1344 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.15 (d, J = 9.0 Hz, 2 H, H-3′, H-5′), 7.35 (d, 2 H, H-2′, H-6′), 3.17 (t, J = 6.0 Hz, 2 H, H-3), 2.85 (t, J = 6.0 Hz, 2 H, H-1), 2.15 (m, 2 H, H-2). GC/MS (EI): m/z 291 (M^+). Elemental anal. calcd for $C_9H_{10}O_2N$: C, 37.14; H, 3.46; N, 4.81. Found: C, 37.29; H, 3.23; N, 4.75.

*1-(2-Iodoethyl)-3-nitrobenzene (**13**).* Oil (98% yield). IR (NaCl): 1580, 1530, 1350 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.18−8.10 (m, 2 H, H-2′, H-4′), 7.58−7.50 (m, 2 H, H-5′, H-6′), 3.42 (t, J = 7.2 Hz, 2 H, H-2), 3.32 (t, J = 7.1 Hz, 2 H, H-1). GC/MS (EI): m/z277 (M^+). Elemental anal. calcd for $C_8H_8O_2NI$: C, 34.68; H, 2.91; N, 5.06. Found: C, 34.64; H, 2.96; N, 5.06.

*1-(2-Iodoethyl)-4-nitrobenzene (**14**).* Oil (97% yield). IR (NaCl): 1594, 1512, 1342 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 2 H, H-3′, H-5′), 7.39 (d, J = 8.5 Hz, 2 H, H-2′, H-6′), 3.42 (t, J = 6.9 Hz, 2 H, H-2), 3.32 (t, J = 6.9 Hz, 2 H, H-1). GC/MS (EI): m/z 277 (M^+). Elemental anal. calcd for $C_8H_8O_2NI$: C, 34.68; H, 2.91; N, 5.06. Found: C, 34.86; H, 2.90; N, 5.01.

S_N2 Type Arylation: General Procedure. To an ice-cooled solution of diisopropylamine (0.15 mol) in anhydrous THF (150 mL) was added dropwise a 1.6 M solution of *n*-BuLi (0.15 mol) under

continuous nitrogen flow. After 45 min, the reaction mixture was cooled to −15 °C, and a solution of ethyl 2-phenylacetate (**15**) (0.075 mol) in anhydrous THF (150 mL) was added dropwise over a period of 15 min. The resulting mixture was stirred for 2 h at −15 °C and then cooled to −78 °C. A solution of (ω-iodoalkyl)nitrobenzenes (0.038 mol) in anhydrous THF (100 mL) was slowly added during approximately 50 min. The reaction mixture was allowed to reach room temperature and stirred until the TLC showed the completion of the reaction (typically 3 h). The solvent was removed under reduced pressure, and the remaining residue was dissolved in EtOAc (100 mL) and washed with water (2 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc 8:1).

*Ethyl 5-(3-Nitrophenyl)-2-phenylpentanoate (**16**).* Oil (82% yield). IR (NaCl): 1726, 1602, 1573, 1538, 1348, 741, 704 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.05−7.99 (m, 2 H, H-2′, H-4′), 7.45−7.25 (m, 7 H, H-5′, H-6′, Ph″), 4.16−4.04 (m, 2 H, OCH_2), 3.55 (t, *J* = 7.5 Hz, 1 H, H-2), 2.70 (dt, *J* = 7.8 Hz, *J* = 1.8 Hz, 2 H, H-5), 2.16−2.05 (m, 1 H, H-3a), 1.85−1.75 (m, 1 H, H-3b), 1.73−1.59 (m, 2 H, H-4), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.4 (C═O), 149.0 (C-3′), 144.7 (C-1′), 139.7 (C-1″), 135.4 (C-6′), 129.9 (C-5′), 129.4 (C-3″, C-5″), 128.6 (C-2″, C-6″), 128.0 (C-4″), 123.8 (C-2′), 121.7 (C-4′), 61.4 (OCH_2), 52.2 (C-2), 35.9 (C-5), 33.7 (C-3), 29.6 (C-4), 14.8 (CH_3). GC/MS (EI): *m*/*z* 327 (M^+). Elemental anal. calcd for $C_{19}H_{21}O_4N$: C, 69.76; H, 6.47; N, 4.28. Found: C, 69.38; H, 6.38; N, 4.14.

*Ethyl 5-(4-Nitrophenyl)-2-phenylpentanoate (**17**).* Oil (86% yield). IR (NaCl): 1725, 1599, 1515, 1350, 735, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 2 H, H-3′, H-5′), 7.31−7.20 (m, 7 H, H-2′, H-6′, Ph″), 4.15−4.02 (m, 2 H, OCH_2), 3.56 (t, *J* = 7.2 Hz, 1 H, H-2), 2.67 (t, *J* = 7.8 Hz, 2 H, H-5), 2.15−2.10 (m, 1 H, H-3a), 1.85−1.77 (m, 1 H, H-3b), 1.68−1.58 (m, 2 H, H-4), 1.16 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.4 (C═O), 150.6 (C-1′), 147.0 (C-4′), 139.7 (C-1″), 129.9 (C-2′, C-6′), 129.4 (C-3″, C-5″), 128.6 (C-2″, C-6″), 128.0 (C-4″), 124.2 (C-3′, C-5′), 60.4 (OCH_2), 51.2 (C-2), 35.1 (C-5), 32.7 (C-3), 28.4 (C-4), 13.8 (CH_3). GC/MS (EI): *m*/*z* 327 (M^+). Elemental anal. calcd for $C_{19}H_{21}O_4N$: C, 69.76; H, 6.47; N, 4.28. Found: C, 70.03; H, 6.30; N, 4.18.

*Ethyl 4-(3-Nitrophenyl)-2-phenylbutanoate (**18**).* Oil (81% yield). IR (NaCl): 1725, 1599, 1581, 1527, 1353, 732, 696 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.09−8.00 (m, 2 H, H-2′, H-4′), 7.47−7.39 (m, 2 H, H-5′, H-6′), 7.33−7.26 (m, 5 H, Ph″), 4.18−4.04 (m, 2 H, OCH_2), 3.54 (t, *J* = 7.8 Hz, 1 H, H-2), 2.70−2.64 (m, 2 H, H-4), 2.48−2.38 (m, 1 H, H-3a), 2.18−2.08 (m, 1 H, H-3b), 1.21 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.7 (C═O), 148.7 (C-3′), 143.7 (C-1′), 138.8 (C-1″), 135.0 (C-6′), 129.6 (C-5′), 129.1 (C-3″, C-5″), 128.2 (C-2″, C-6″), 127.8 (C-4″), 123.6 (C-2′), 121.6 (C-4′), 61.2 (OCH_2), 51.3 (C-2), 34.9 (C-3), 33.6 (C-4), 14.4 (CH_3). GC/MS (EI): *m*/*z* 313 (M^+). Elemental anal. calcd for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.37; H, 6.20; N, 4.36.

*Ethyl 4-(4-Nitrophenyl)-2-phenylbutanoate (**19**).* Oil (72% yield). IR (NaCl): 1722, 1596, 1582, 1516, 1346, 738, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.14 (d, *J* = 8.7 Hz, 2 H, H-3′, H-5′), 7.37−7.26 (m, 7 H, H-2′, H-6′, Ph″), 4.19−4.07 (m, 2 H, OCH_2), 3.53 (t, *J* = 7.5 Hz, 1 H, H-2), 2.68 (dt, *J* = 7.2 Hz, *J* = 2.1 Hz, 2 H, H-4), 2.46−2.39 (m, 1 H, H-3a), 2.16−2.12 (m, 1 H, H-3b), 1.21 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.2 (C═O), 149.1 (C-1′), 146.3 (C-4′), 138.3 (C-1″), 129.1 (C-2′, C-6′), 128.6 (C-3″, C-5″), 127.7 (C-2″, C-6″), 127.3 (C-4″), 123.5 (C-3′, C-5′), 60.7 (OCH_2), 50.7 (C-2), 34.3 (C-3), 33.3 (C-4), 14.0 (CH_3). GC/MS (EI): *m*/*z* 313 (M^+). Elemental anal. calcd for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.93; H, 6.10; N, 4.51.

Nitro Reduction: General Procedure. Hydrazine monohydrate (150 mmol) was added to a solution of nitrophenyl compound (2 mmol) in methanol (25 mL) under N_2 atmosphere. After it was stirred for 5 min at room temperature, a suspension of Raney-Ni (216 mg) in ethanol (2 mL) was carefully added in 5 portions. The frequency of the addition was determined by the decomposition rate of the hydrazine (until the release of gas stop). The reaction mixture was stirred for 4 h at room temperature and then refluxed for 30 min. The mixture was filtered, the solvent was evaporated, and the residue was dissolved in EtOAc (50 mL) and washed with water (3 × 25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (hexane/EtOAc 5:1) using neutral Al_2O_3 activitation grade III.

*Ethyl 5-(3-Aminophenyl)-2-phenylpentanoate (**20**).* Oil (99% yield). IR (NaCl): 3418, 3334, 1725, 1623, 732, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30−7.24 (m, 5 H, Ph″), 7.03 (t, *J* = 7.5 Hz, 1 H, H-5′), 6.60−6.50 (m, 3 H, H-2′, H-4′, H-6′), 4.07 (dq, *J* = 10.8 Hz, *J* = 7.2 Hz, 2 H, OCH_2), 3.62−3.57 (m, 3 H, H-2, NH_2), 2.56−2.46 (m, 2 H, H-5), 2.16−2.03 (m, 1 H, H-3a), 1.83−1.76 (m, 1 H, H-3b), 1.61−1.46 (m, 2 H, H-4), 1.18 (t, *J* = 7.2 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.6 (C═O), 146.8 (C-3′), 143.8 (C-1′),139.6 (C-1″), 129.7 (C-5′), 129.1 (C-3″, C-5″), 128.4 (C-2″, C-6″), 127.7 (C-4″), 119.2 (C-6′), 115.7 (C-2′), 113.2 (C-4′), 61.3 (OCH_2), 52.1 (C-2), 36.1 (C-5), 33.7 (C-3), 29.8 (C-4), 14.6 (CH_3). GC/MS (EI): *m*/*z* 297 (M^+). Elemental anal. calcd for $C_{19}H_{23}O_2N$: C, 76.79; H, 7.80; N, 4.71. Found: C, 76.88; H, 7.86; N, 4.69.

*Ethyl 5-(4-Aminophenyl)-2-phenylpentanoate (**21**).* Oil (100% yield). IR (NaCl): 3419, 3334, 1725, 1623, 732, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.37−7.26 (m, 5 H, Ph″), 6.95 (d, *J* = 8.4 Hz, 2 H, H-2′, H-6′), 6.60 (d, *J* = 9.0 Hz, 2 H, H-3′, H-5′), 4.19−4.07 (m, 2 H, OCH_2), 3.57 (t, *J* = 7.5 Hz, 1 H, H-2), 3.47 (br s, 2H, NH_2), 2.55 (t, *J* = 7.8 Hz, 2 H, H-5), 2.20−2.07 (m, 1 H, H-3a), 1.89−1.79 (m, 1 H, H-3b), 1.67−1.49 (m, 2 H, H-4), 1.23 (t, *J* = 7.2 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.9 (C═O), 144.1 (C-4′), 139.1 (C-1″), 131.9 (C-1′), 129.0 (C-2′, C-6′), 128.4 (C-3″, C-5″), 127.8 (C-2″, C-6″), 127.0 (C-4″), 115.0 (C-3′, C-5′), 60.5 (OCH_2), 51.6 (C-2), 34.6 (C-5), 33.0 (C-3), 29.5 (C-4), 14.0 (CH_3). GC/MS (EI): *m*/*z*297 (M^+). Elemental anal. calcd for $C_{19}H_{23}O_2N$: C, 76.79; H, 7.80; N, 4.71. Found: C, 76.74; H, 7.81; N, 4.71.

*Ethyl 4-(3-Aminophenyl)-2-phenylbutanoate (**22**).* Oil (100% yield). IR (NaCl): 3424, 3340, 1725, 1617, 1602, 1527, 735, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.32−7.24 (m, 5 H, Ph″), 7.05 (t, *J* = 7.5 Hz,1 H, H-5′), 6.56−6.48 (m, 3 H, H-2′, H-4′, H-6′), 4.22−4.09 (m, 2 H, OCH_2), 3.59−3.52 (m, *J* = 8.0 Hz, 3 H, H-2, NH_2), 2.50−2.34 (m, 3 H, H-4, H-3a), 2.07−2.02 (m, 1H, H-3b), 1.19 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.7 (C═O), 146.4 (C-3′), 142.3 (C-1′), 138.8 (C-1″), 129.0 (C-5′), 128.4, 127.8 (C-2″, C-3″, C-5″, C-6″), 127.0 (C-4″), 118.5 (C-6′), 115.0 (C-2′), 112.6 (C-4′), 60.5 (OCH_2), 50.8 (C-2), 34.6 (C-3), 33.3 (C-4), 13.9 (CH_3). GC/MS (EI): *m*/*z* 283 (M^+). Elemental anal. calcd for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.35; H, 7.30; N, 4.84.

*Ethyl 4-(4-Aminophenyl)-2-phenylbutanoate (**23**).* Oil (100% yield). IR (NaCl): 3412, 3334, 1719, 1623, 732, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.33−7.21(m, 5 H, Ph″), 6.92 (d, *J* = 8.4 Hz, 2 H, H-2′, H-6′), 6.59 (d, *J* = 8.6 Hz, 2 H, H-3′, H-5′), 4.12−4.07 (m, 2 H, OCH_2), 3.54−3.51 (m, 3 H, H-2, NH_2), 2.46 (t, *J* = 7.6 Hz, 2 H, H-4), 2.38−2.31 (m, 1 H, H-3a), 2.06−1.99 (m, 1 H, H-3b), 1.19 (t, *J* = 7.1 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.4 (C═O), 144.9 (C-4′), 139.6 (C-1″), 131.7 (C-1′), 129.7 (C-2′, C-6′), 129.0(C-3″, C-5″), 128.5 (C-2″, C-6″), 127.6 (C-4″), 115.7 (C-3′, C-5′), 61.1 (OCH_2), 51.4 (C-2), 35.8(C-3), 33.1 (C-4), 14.6 (CH_3). GC/MS (EI): *m*/*z* 283 (M^+). Elemental anal. calcd for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.29; H, 7.45; N, 4.85.

Diazotation: General Procedure. A solution of aminophenyl compound (0.24 mmol) in 20% hydrochloric acid (3 mL) was heated at 40 °C and vigorously stirred for 30 min. The reaction mixture was cooled to 0 °C, and a solution of $NaNO_2$ (0.40 mmol) in H_2O (2 mL) was added. After 1 h, a solution of NaN_3 (0.43 mmol) in H_2O (2 mL) was added dropwise, and the mixture was stirred at room temperature until

completion of the reaction detected by TLC (typically 4 h). The reaction mixture was diluted with EtOAc (20 mL) and washed with water (3 × 15 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash column chromatography (hexane/EtOAc 5:1) using neutral Al_2O_3 retention grade III.

*Ethyl 5-(3-Azidophenyl)-2-phenylpentanoate (**24**).* Oil (93% yield). IR (NaCl): 2104, 1728, 1602, 1581, 735, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30−7.19 (m, 6 H, H-5′, Ph″), 6.89 (d, J = 8.0 Hz, 1 H, H-6′), 6.82 (d, J = 9.5 Hz, 1 H, H-4′) 6.76 (s, 1 H, H-2′), 4.16−4.04 (m, 2 H, OCH_2), 3.53 (t, J = 9.0 Hz, 1 H, H-2), 2.64−2.54 (m, 2 H, H-5), 2.13−2.06 (m, 1 H, H-3a), 1.83−1.76 (m, 1 H, H-3b), 1.65−1.50 (m, 2 H, H-4), 1.18 (t, J = 7.0 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.1 (C═O), 144.4 (C-1′), 140.3 (C-3′), 139.4 (C-1″), 129.9 (C-5′), 128.9 (C-3″, C-5″), 128.2 (C-2″, C-6″), 127.5 (C-4″), 125.4 (C-6′), 119.2 (C-2′), 116.8 (C-4′), 61.0 (OCH_2), 51.9 (C-2), 35.7 (C-5), 33.3 (C-3), 29.4 (C-4), 14.4 (CH_3). GC/MS (EI): m/z 323 (M^+). Elemental anal. calcd for $C_{19}H_{21}O_2N_3$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.66; H, 6.43; N, 12.87.

*Ethyl 5-(4-Azidophenyl)-2-phenylpentanoate (**25**).* Oil (71% yield). IR (NaCl): 2104,1725, 1602, 732, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.34−7.24 (m, 5 H, Ph″), 7.10 (d, J = 8.1 Hz, 2 H, H-2′, H-6′), 6.91 (d, J = 9.0 Hz, 2 H, H-3′, H-5′), 4.15−4.05 (m, 2 H, OCH_2), 3.52 (t, J = 8.1 Hz, 1H, H-2), 2.61−2.57 (m, 2 H, H-5), 2.12−2.05 (m, 1 H, H-3a), 1.82−1.75 (m, 1 H, H-3b), 1.63−1.48 (m, 2 H, H-4), 1.18 (t, J = 7.0 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.2 (C═O), 139.5 (C-1″), 139.2 (C-1′), 137.9 (C-4′), 130.0(C-2′, C-6′), 128.9 (C-3″, C-5″), 128.2 (C-2″, C-6″), 127.5 (C-4″), 119.3 (C-3′, C-5′), 61.0 (OCH_2), 52.0 (C-2), 35.3 (C-5), 33.4 (C-3), 29.6 (C-4), 14.5 (CH_3). GC/MS (EI): m/z 323 (M^+). Elemental anal. calcd for $C_{19}H_{21}O_2N_3$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.72; H, 6.51; N, 12.71.

*Ethyl 4-(3-Azidophenyl)-2-phenylbutanoate (**26**).* Oil (81% yield). IR (NaCl): 2104, 1728, 1602, 1584, 735, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.32−7.22 (m, 6 H, H-5′, Ph″), 6.92 (d, J = 8.0 Hz, 1 H, H-6′), 6.85 (d, J = 9.5 Hz, 1 H, H-4′) 6.79 (s, 1 H, H-2′), 4.16−4.06 (m, 2 H, OCH_2), 3.53 (t, J = 7.8 Hz, 1 H, H-2), 2.57 (t, J = 7.5 Hz, 2 H, H-4), 2.45−2.36 (m, 1 H, H-3a), 2.11−2.05 (m, 1H, H-3b), 1.20 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.9 (C═O), 143.7 (C-1′), 140.3 (C-3′), 139.1 (C-1″), 130.0 (C-5′), 129.0 (C-3″, C-5″), 128.3 (C-2″, C-6″), 127.6 (C-4″), 125.4 (C-6′), 119.4 (C-2′), 117.0 (C-4′), 61.1 (OCH_2), 51.2 (C-2), 35.0 (C-3), 33.7 (C-4), 14.4 (CH_3). GC/MS (EI): m/z 309 (M^+). Elemental anal. calcd for $C_{18}H_{19}O_2N_3$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.19; H, 6.10; N, 13.20.

*Ethyl 4-(4-Azidophenyl)-2-phenylbutanoate (**27**).* Oil (84% yield). IR (NaCl): 2120, 1736, 1610, 1586, 740, 706 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.33−7.23 (m, 5 H, Ph″), 7.11 (d, J = 8.5 Hz, 2 H, H-2′, H-6′), 6.93 (d, J = 8.5 Hz, 2 H, H-3′, H-5′), 4.16−4.06 (m, 2 H, OCH_2), 3.52 (t, J = 7.5 Hz, 1 H, H-2), 2.55 (t, J = 7.5 Hz, 2 H, H-4), 2.41−2.34 (m, 1 H, H-3a), 2.10−2.03 (m, 1 H, H-3b), 1.19 (t, J = 7.5 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.0 (C═O), 139.2 (C-1″), 138.5 (C-1′), 138.1 (C-4′), 130.1 (C-2′, C-6′), 129.0 (C-3″, C-5″), 128.3 (C-2″, C-6″), 127.6 (C-4″), 119.3 (C-3′, C-5′), 61.0 (OCH_2), 51.3 (C-2), 35.3 (C-3), 33.3 (C-4), 14.4 (CH_3). GC/MS (EI): m/z 309 (M^+). Elemental anal. calcd for $C_{18}H_{19}O_2N_3$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.77; H, 6.28; N, 13.76.

Intramolecular Cyclization by Acid-Catalyzed Decomposition of the Aryl Azides: General Procedure. To a solution of aryl azide (0.80 mmol) in anhydrous CH_2Cl_2 or CCl_4 (10 mL) was added dropwise TFMSA (2 mmol) at 0 °C under continuous N_2 stream. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature until the TLC revealed no trace of starting material. The mixture was concentrated, and the residue was dissolved in Et_2O (10 mL) and washed with a saturated solution of $NaHCO_3$ (3 × 5 mL) and water (3 × 5 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (hexane/EtOAc 4:1) using neutral Al_2O_3 activity grade III.

*Ethyl 5-[5-Amino-2-(trifluoromethylsulfonyloxy)phenyl]-2-phenylpentanoate (**28**).* Oil (65% yield). IR (NaCl): 3346, 3004, 1725, 1629, 879, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.42−7.33 (m, 5 H, Ph″), 7.11 (d, J = 8.4 Hz, 1 H, H-3′), 6.67 (d, J = 2.1 Hz, 1 H, H-6′) 6.60 (dd, J = 8.4 Hz, J = 2.1 Hz, 1 H, H-4′), 4.25−4.14 (m, 2 H, OCH_2), 3.92 (br s, 2 H, NH_2), 3.60 (t, J = 7.5 Hz, 1 H, H-2), 2.56 (t, J = 7.8 Hz, 2 H, H-5), 2.18−2.12 (m, 1 H, H-3a), 1.87−1.83 (m, 1 H, H-3b), 1.67−1.58 (m, 2 H, H-4), 1.20 (t, J = 7.4 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.7 (C═O), 147.5 (C-2′), 140.6 (C-5′), 139.8 (C-1″), 136.1 (C-1′), 129.4, 128.6 (C-2″, C-3″, C-5″, C-6″), 128.0 (C-4″), 122.8 (C-3′), 121.5 (CF_3), 116.8 (C-6′), 114.1(C-4′), 61.5 (OCH_2), 52.3 (C-2), 33.7 (C-3), 30.5 (C-5), 28.3 (C-4), 14.7 (CH_3). GC/MS (EI): m/z 445 (M^+). Elemental anal. calcd for $C_{20}H_{22}O_5NS$: C, 53.92; H, 4.98; N, 3.14; S, 7.20. Found: C, 54.26; H, 5.13; N, 2.87; S, 7.16.

*Ethyl 4-[5-Amino-2-(trifluoromethylsulfonyloxy)phenyl]-2-phenylbutanoate (**29**).* Oil (63% yield). IR (NaCl): 3472, 3380, 1734, 1598, 888, 706 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.32−7.25 (m, 5 H, Ph″), 6.97 (d, J = 8.5 Hz, 1 Hz, H-3′), 6.50−6.47 (m, 2 H, H-4′, H-6′), 4.14−3.95 (m, 2 H, OCH_2), 3.72 (br s, 2 H, NH_2), 3.56 (t, J = 7.5 Hz, 1 H, H-2), 2.49 (t, J = 7.5 Hz, 2 H, H-4), 2.28−2.23 (m, 1 H, H-3a), 2.05−1.93 (m, 1 H, H-3b), 1.20 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.3 (C═O), 146.3 (C-2′), 139.5 (C-5′), 138.3 (C-1″), 134.6 (C-1′), 128.4, 127.5 (C-2″, C-3″, C-5″, C-6″), 127.0 (C-4″), 121.8 (C-3′), 120.6 (CF_3), 115.9 (C-6′), 113.2 (C-4′), 60.6 (OCH_2), 50.9 (C-2), 33.1 (C-3), 27.7 (C-4), 13.7 (CH_3). GC/MS (EI): m/z 431 (M^+). Elemental anal. calcd for $C_{19}H_{20}O_5NS$: C, 52.90; H, 4.67; N, 3.25; S, 7.43. Found: C, 52.98; H, 4.40; N, 3.17; S, 7.12.

*Ethyl 4-(4-Aminophenyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (**30**).* White solid (67% in CCl_4; 49% in CH_2Cl_2); mp 127−128 °C (ethanol). IR (KBr): 3376, 3304, 1713, 1635, 1611, 831, 726 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.20 (d, J = 7.5 Hz, 1 H, H-8), 7.14 (t, J = 7.5 Hz, 1 H, H-7), 7.09 (t, J = 7.5 Hz, 1 H, H-6), 6.90 (d, J = 7.5 Hz, 1 H, H-5), 6.83 (d, J = 9.0 Hz, 2 H, H-2′, H-6′), 6.60 (d, J = 9.0 Hz, 2 H, H-3′, H-5′), 4.22−4.17 (m, 2 H, OCH_2), 4.07 (t, J = 6.0 Hz, 1 H, H-4), 3.91 (t, J = 6.5 Hz, 1 H, H-1), 3.58 (br s, 2 H, NH_2), 2.35−2.29 (m, 1 H, H-3e), 2.15−2.06 (m, 2 H, H-2), 1.87−1.81 (m, 1 H, H-3a), 1.28 (t, J = 7.0 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 175.7 (C═O), 145.3 (C-4′), 140.9 (C-4a), 137.6 (C-1′), 134.6 (C-1a), 131.2 (C-5), 130.2 (C-2′, C-6′), 129.4 (C-8), 127.6 (C-6), 126.8 (C-7), 115.8 (C-3′, C-5′), 61.5 (OCH_2), 46.1 (C-1), 44.9 (C-4), 31.3 (C-3), 24.9 (C-2), 15.0 (CH_3). GC/MS (EI): m/z 295 (M^+). Elemental anal. calcd for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.71. Found: C, 77.30; H, 7.20; N, 4.61.

*Ethyl 4-Oxo-3′,4′-dihydro-2′H-spiro(cyclohexa[2,5]diene-1,1′-naphthalene)-4′-carboxylate (**31**).* White solid (62% in CCl_4, 47% in CH_2Cl_2); mp 59−60 °C (hexane/EtOAc 4:1). IR (KBr): 1734, 1670, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.29 (br d, J = 7.6 Hz, 1 H, H-15), 7.23 (dt, J = 7.3 Hz, J = 1.4 Hz, 1 H, H-13), 7.17 (dt, J = 7.7 Hz, J = 1.2 Hz, 1 H, H-14), 7.05−6.99 (m, 3 H, H-8, H-10, H-12), 6.34 (dd, J = 9.9 Hz, J = 1.8 Hz, 1 H, H-7 or H-11), 6.27 (dd, J = 9.9 Hz, J = 1.9 Hz, 1 H, H-7 or H-11), 4.21 (q, J = 7.2 Hz, 2 H, OCH_2), 3.94 (t, J = 5.5 Hz, 1 H, H-3), 2.36−2.16 (m, 3 H, H-4a, H-5a, H-5e), 1.92−1.87 (m, 1 H, H-4e), 1.30 (t, J = 7.2 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 186.5 (C═O, quinone), 174.3 (C═O), 155.5, 154.7 (C-8, C-10), 134.3 (C-2), 133.4 (C-1), 130.9 (C-15), 129.4 (C-12), 128.2 (C-14), 128.1 (C-13), 127.8, 127.2 (C-7, C-11), 61.6 (OCH_2), 44.9 (C-3), 44.7 (C-6), 31.3 (C-5), 22.8 (C-4), 14.6 (CH_3). GC/MS (EI): m/z 282 (M^+). Elemental anal. calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.42; H, 6.84.

X-ray Structure Determination. X-ray data were collected on a TURBOCAD4 Enraf−Nonius diffractometer with a rotating anode and Cu-K_α1 radiation (λ = 1.54439 Å), at room temperature for compounds **30** and **31**. Data collection and data reduction were done with CAD4 and XCAD programs.[26]

All structures were solved by direct methods with SIR97[27] and refined by full-matrix least-squares on F^2 with SHELXL97,[28] both included in

the package of programs WINGX-Version 1.70.01.[29] Nonhydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were located in a Fourier map, and their positions and isotropic displacement parameters, Uiso(H), were refined freely, except those of the methyl groups in both compounds, which were refined using a riding model (1.5 times the attached oxygen atom), and the hydrogen atoms attached to the C11 atom (compound **30**) and those hydrogens attached to the C2 and C3 in compound **31**, which were also allowed to refine riding on the parent C atom (1.2 times the attached oxygen atom).

Graphical representations were prepared using RASTER3D.[30] A summary of the crystal data, structure solution and refinement parameters for both compounds is given in Table S1 in the Supporting Information.

DFT Studies. DFT calculations[23] were performed with the Gaussian03 software package[25] using the B3LYP hybrid functional. This functional includes a mixture of Hartree−Fock[31] exchange with DFT exchange-correlation, given by Becke's three parameter functional[32] with the Lee, Yang, and Parr correlation functional, which includes both local and nonlocal terms.[33] All intermediates were optimized without symmetry constraints. The standard 6-31G* basis set was employed for all the elements.[34] Frequency calculations were performed in all species at this level of theory to confirm the nature of the stationary points and to calculate electronic energies corrected for ZPE (ΔE_{0DFT}) and free energies (ΔG_{DFT}). The free energies in dichloromethane or CCl_4 solution (ΔG_s) were obtained by performing self-consistent reaction field (SCRF) calculations using the polarizable continuum model (PCM) and the universal force field (UFF)[35] to define the atomic radii of the atoms on the gas-phase optimized geometries. Three-dimensional representations of structures were obtained with Chemcraft.[36]

Biological Activity. *Reagents.* RPMI-1640, fetal bovine serum (FBS), L-glutamine, phosphate-buffered saline (PBS), and trypsin were from Gibco Invitrogen Co. (Scotland, United Kingdom). Acetic acid, dimethyl sulfoxide (DMSO), doxorubicin, ethylenediaminetetraacetic acid (EDTA), penicillin, streptomycin, sulforhodamine B (SRB), and trypan blue were from SigmaChemical Co. (St. Louis, MO). Trichloroacetic acid (TCA) and Tris were sourced from Merck (Darmstadt, Germany).

Samples. Stock solutions of compounds were prepared in DMSO and kept at −20 °C. Appropriate dilutions of the compounds were freshly diluted just prior to every assay.

Cell Cultures. Four human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (nonsmall cell lung cancer), SF-268 (CNS cancer), and UACC-62 (melanoma), were grown as a monolayer and routinely maintained in RPMI-1640 medium supplemented with 5% heat-inactivated fetal bovine serum, 2 mM glutamine, and antibiotics (100 U/mL penicillin and 100 μg/mL streptomycin), at 37 °C in an humidified atmosphere containing 5% CO_2.

Tumor Cell Growth Assay. The effects of the compounds on the growth of human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, United States) in the "In Vitro Anticancer Drug Discovery Screen" that uses the protein-binding dye sulforhodamine B to assess cell growth.[37] The optimal plating density of each cell line, which ensures exponential growth throughout all of the experimental period, was the same as originally published[38] and was, respectively, 1.5×10^5 cells/mL to MCF-7 and SF-268, 7.5×10^4 cells/mL for NCI-H460, and 1.0×10^5 cells/mL for UACC-62. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all experiments by exposing untreated control cells to the maximum concentration (0.25%) of DMSO used in each assay. Cells in 96-well plates were allowed to attach overnight and then exposed for 48 h to five serial concentrations of the compounds, starting from a maximum concentration of 100 μM. Following this incubation period, the adherent cells were fixed in situ with 50% TCA, washed with distillate water, and stained with 0.4% SRB (solubilized in 1% acetic acid). The bound stain was solubilized in 10 mM Tris, and the absorbance was measured at 492 nm in a microplate reader (EAR400 STL-Labinstruments). For each test compound and for each cell line, a dose−response curve was obtained, and the growth inhibition of 50% (GI_{50}), corresponding to the concentration of compound that inhibited 50% of the net cell growth, was calculated as described elsewhere.[38] Doxorubicin, used as a positive control, was tested in the same manner.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic details for compounds **16**−**31** and crystal data and structure refinement for compounds **30** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by Fundação Luso-Americana para o Desenvolvimento (FLAD), FCT (CQB-FCUL, UI&D4040), FEDER, and POCI. M.J.C. and P.D.V. also thank FCT for financial support (PDCT/QUI/58925/2004). We are grateful to NCI (United States) for the generous gift of the tumor cell lines.

■ ABBREVIATIONS USED

CNS, central nervous system; COSY, correlation spectroscopy; DFT, density functional theory; GC/MS, gas chromatography/mass spectrometry; GI_{50}, 50% growth inhibition; HMBC, heteronuclear multiple bond coherence; HMQC, heteronuclear multiple quantum coherence; IR, infrared; LDA, lithium diisopropylamide; NOESY, nuclear Overhauser enhancement spectroscopy; TFMSA, trifluoromethanesulphonic acid; TLC, thin-layer chromatography; TOCSY, total correlation spectroscopy; UV, ultraviolet

■ REFERENCES

(1) (a) Moraes, R. M. The Lignans of Podophyllum. In *Studies in Natural Product Chemistry*; Ralman, A., Ed.; Elsevier Science B.V.: Amsterdam, 2002; Vol. 26, Bioactive Natural Products, Part G, pp 149−182. (b) Rios, J. L.; Giner, R. M.; Prieto, J. M. New Findings on the Bioactivity of Lignans. In *Studies in Natural Product Chemistry*; Ralman, A., Ed.; Elsevier Science B.V.: Amsterdam, 2002; Vol. 26, Bioactive Natural Products, Part G, pp 183−291. (c) Ward, R. S. Lignans, neolignans and related compounds. *Nat. Prod. Rep.* **1999**, *16*, 75–96. (d) Hearon, W. M.; McGregor, W. S. The Naturally Occurring Lignans. *Chem. Rev.* **1955**, *55* (5), 957–1068.

(2) Moss, G. P. The nomenclature of lignans and neolignans (IUPAC Recommendations 2000). *Pure Appl. Chem.* **2000**, *72* (8), 1493–1523.

(3) Sellars, J. D.; Steel, P. G. Advances in the synthesis of aryltetralin lignan lactones. *Eur. J. Org. Chem.* **2007**, 3815–3828.

(4) (a) Tanaka, K.; Sawada, Y.; Aida, Y.; Thammathevo, M.; Tanaka, R.; Sagae, H.; Otake, Y. Rhodium-catalyzed convenient synthesis of functionalized tetrahydronaphthalenes. *Tetrahedron* **2010**, *66*, 1563–1569. (b) Benda, K.; Regenhardt, W.; Schaumann, E.; Adiwidjaja, G. 2-Hydroxybenzocyclobutenone Ethylene Dithioacetals

as Precursors of Highly Substituted 1,4-Dihydronaphthalenes. *Eur. J. Org. Chem.* **2009**, 1016–1021. (c) Lucarini, S.; Bedini, A.; Spadoni, G.; Piersanti, G. An improved synthesis of cis-4-phenyl-2-propionamidotetralin (4-P-PDOT): A selective MT2 melatonin receptor antagonist. *Org. Biomol. Chem.* **2008**, *6*, 147–150. (d) Stadler, D.; Bach, T. Concise stereoselective synthesis of (−)-podophyllotoxin by an intermolecular iron(III)-catalyzed Friedel-Crafts alkylation. *Angew. Chem., Int. Ed.* **2008**, *47*, 7557–7559. (e) Hughes, N. J.; Pullin, R. D. C.; Sanganee, J.; Sellars, M. J. D.; Steel, P. G.; Turnera, M. J. Hosomi−Sakurai reactions of silacyclohexenes. *Org. Biomol. Chem.* **2007**, *5*, 2841–2848. (f) Ghoneim, O. M.; Legere, J. A.; Golbraikh, A.; Tropsha, A.; Booth, R. G. Novel ligands for the human histamine H1 receptor: Synthesis, pharmacology, and comparative molecular field analysis studies of 2-dimethylamino-5-(6)-phenyl-1,2,3,4-tetrahydronaphthalenes. *Bioorg. Med. Chem.* **2006**, *14*, 6640–6658. (g) Moniri, N. H.; Covington-Strachan, D.; Booth, R. Ligand-directed functional heterogeneity of histamine H_1 receptors: Novel dual-function ligands selectively activate and block H_1-mediated phospholipase C and adenine cyclase signaling. *J. Pharmacol. Exp. Ther.* **2004**, *311* (1), 274–281. (h) Agrawal, V. K.; Karmarkarb, S.; Khadikarb, P. V. QSAR Study on competition binding of rodenticides (PATs) to H1 receptor in rat and Guinea Pig Brain. *Bioorg. Med. Chem.* **2002**, *10*, 2913–2918. (i) Harris, M. C. J.; Jackson, M.; Lennon, I. C.; James, A. R.; Samuel, H. A novel asymmetric route to 2-amino-1,2,3,4-tetrahydronaphthalenes. *Tetrahedron Lett.* **2000**, *41*, 3187–3191. (j) Ward, R. S. The synthesis of lignans and neolignans. *Chem. Soc. Rev.* **1982**, *11*, 75–125.

(5) (a) Dong, Y.; Shi, Q.; Nakagawa-Goto, K.; Wu, P.; Bastow, K. F.; Morris-Natschke, S. L.; Lee, K.-H. Antitumor agents 269. Non-aromatic ring-A neotanshinlactone analog, TNO, as a new class of potent antitumor agents. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6289–6292. (b) Lee, K.-H.; Xiao, Z. Lignans in treatment of cancer and other diseases. *Phytochem. Rev.* **2003**, *2*, 341–362. (c) LaLonde, R. T.; Ramdayal, F.; Sarko, A.; Yanai, K.; Zhang, M. Modes of methyleneoxy bridging and their effect on tetrahydronaphthalene lignan cytotoxicity. *J. Med. Chem.* **2003**, *46*, 1180–1190. (d) Engelhardt, U.; Sarkar, A.; Linker, T. Efficient enantioselective total synthesis of (-)-epipodophyllotoxin. *Angew. Chem.-Int. Ed.* **2003**, *42* (22), 2487–2489.

(6) (a) Chen, S. W.; Wang, Y. H.; Jin, Y.; Tian, X.; Zheng, Y. T.; Luo, D. Q.; Tu, Y. Q. Synthesis and anti-HIV-1 activities of novel podophyllotoxin derivatives. *Bioorg. Med. Chem. Lett.* **2007**, *17* (7), 2091–2095. (b) Castro, M. A.; del Corral, J. M. M.; Gordaliza, M.; Gomez-Zurita, M. A.; de la Puente, M. L.; Betancur-Galvis, L. A.; Sierra, J.; Feliciano, A. S. Synthesis, cytotoxicity and antiviral activity of podophyllotoxin analogues modified in the E-ring. *Eur. J. Med. Chem.* **2003**, *38* (10), 899–911. (c) Hara, H.; Fujihashi, T.; Sakata, T.; Kaji, A.; Kaji, H. Tetrahydronaphthalene lignan compounds as potent anti-HIV type 1 agents. *Aids Res. Hum. Retroviruses* **1997**, *13* (8), 695–705.

(7) Li, N.; Wu, J.; Hasegawa, T.; Sakai, J.; Bai, L.; Wang, L.; Kakuta, S.; Furuya, Y.; Oguro, H.; Kataoka, T.; Tomida, A.; Tsuruo, T.; Ando, M. Bioactive Lignans from *Peperomia duclouxii*. *J. Nat. Prod.* **2007**, *70*, 544–548.

(8) Kim, S. Y.; Yun-Choi, H. S. Platelet anti-aggregating activities of bupleurumin from the aerial parts of *Bupleurum falcatum*. *Arch. Pharm. Res.* **2007**, *30* (5), 561–564.

(9) Lucarini, S.; Bedini, A.; Spadoni, G.; Piersanti, G. An improved synthesis of *cis*-4-phenyl-2-propionamidotetralin (4-P-PDOT): a selective MT_2 melatonin receptor antagonist. *Org. Biomol. Chem.* **2008**, *6*, 147–150.

(10) Bucholtz, E. C.; Brown, R. L.; Tropsha, A.; Booth, R. G.; Wyrich, S. D. Synthesis, evaluation and comparative molecular filed analysis of 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as ligands for histamine H_1 receptors. *J. Med. Chem.* **1999**, *42*, 3041–3054.

(11) Wyrick, S. D.; Booth, R. G.; Myers, A. M.; Owens, C. E.; Bucholtz, E. C.; Hooper, P. C.; Kula, N. S.; Baldessarini, R. J.; Mailman, R. B. 1-Phenyl-3-amino-l,2,3,4-tetrahydronaphthalenes and related derivatives as ligands for the neuromodulatory US receptor: Further structure-activity relationships. *J. Med. Chem.* **1995**, *38*, 3857–3864.

(12) (a) Saleem, M.; Kim, H. J.; ShaiqAliq, M.; Lee, Y. S. An update on bioactive plant lignans. *Nat. Prod. Rep* **2005**, *52*, 696–716. (b) Apers, S.; Vlietinck, A.; Pieters, L. Lignans and neolignans as lead compounds. *Phytochem. Res.* **2003**, *2*, 201–217.

(13) (a) Qi, S. F.; Wang, X. N.; Yang, Z. Z.; Xu, X. H. Effect of N7-Protonated Purine Nucleosides on Formation of C8 Adducts in Carcinogenic Reactions of Arylnitrenium Ions with Purine Nucleosides: A Quantum Chemistry Study. *J. Phys. Chem. B* **2009**, *113*, 5645–5652. (b) Yang, Z. Z.; Qi, S. F.; Zhao, D. X.; Gong, L. D. Insight into Mechanism of Formation of C8 Adducts in Carcinogenic Reactions of Arylnitrenium Ions with Purine Nucleosides. *J. Phys. Chem. B* **2009**, *113*, 254–259. (c) Novak, M.; Rajagopal, S. N-arylnitreniurn ions. *Adv. Phys. Org. Chem.* **2001**, *36*, 167–254. (d) Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; James, T. G. Involvement of Free Nitrenium Ions, Ion Pairs, and Preassociation Trapping in the Reactions of Ester Derivatives of *N*-Arylhydroxylamines and *N*-Arylhydroxamic Acids in Aqueous Solution. *J. Org. Chem.* **1995**, *60*, 8294–8304. (e) Novak, M.; Kennedy, S. A. Selective Trapping of *N*-Acetyl-*N*-(4-biphenylyl)nitrenium and *N*-Acetyl-*N*-(2-fluorenyl)nitrenium Ions by 2′-Deoxyguanosine in Aqueous Solution. *J. Am. Chem. Soc.* **1995**, *117*, 574–57. (f) Helmick, J. S.; Martin, K. A.; Heinrich, J. L.; Novak, M. Mechanism of the Reaction of Carbon and Nitrogen Nucleophiles with the Model Carcinogens *O*-Pivaloyl-*N*-arylhydroxylamines: Competing S_N2 Substitution and S_N1 Solvolysis. *J. Am. Chem. Soc.* **1991**, *113*, 3459–3466.

(14) (a) Borodkin, G. I.; Elanov, I. R.; Popov, S. A.; Pokrovskii, L. M.; Shubin, V. G. Electrophilic Amination of Methylbenzenes with the System NaN_3-$AlCl_3$-HCl. Effects of the Solvent, Crown Ether, and Substrate Structure. *Russ. J. Org. Chem.* **2003**, *39*, 672–679. (b) Mota, C. J. A.; Íons, N. *Quím. Nova* **1998**, *21*, 453–458. (c) Olah, G. A. Superelectrophiles. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767–788.

(15) (a) Borodkin, G. I.; Shubin, V. G. Nitrenium ions: Structure and reactivity. *Russ. Chem. Rev.* **2008**, *77*, 395–419 and references therein. (b) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. Organic Azides: An Exploding Diversity of a Unique Class of Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240. (c) Kantorowski, E. J.; Kurth, M. J. Expansion to Seven-Membered Rings. *Tetrahedron* **2000**, *56*, 4317–4353.

(16) (a) Glover, S. A. *N*-Acyloxy-*N*-alkoxyamides—Structure, properties, reactivity and biological activity. *Adv. Phys. Org. Chem.* **2007**, *42*, 35–123. (b) Novak, M.; Nguyen, T.-M. Unusual Reactions of the Model Carcinogen *N*-Acetoxy-*N*-acetyl-2-amino-α-carboline. *J. Org. Chem.* **2003**, *68*, 9875–9881. (c) Rajagopal, S.; Brooks, M. E.; Nguyen, T.-M.; Novak, M. Synthesis and characterization of the aqueous solution chemistry of the food-derived carcinogen model *N*-acetoxy-*N*-(1-methyl-5H-pyrido[4,5-b]indol-3-yl)acetamide and its *N*-pivaloyloxy analogue. *Tetrahedron* **2003**, *59*, 8003–8010. (d) Novak, M.; Kayser, K. J.; Brooks, M. E. Azide and Solvent Trapping of Electrophilic Intermediates Generated during the Hydrolysis of *N*-(Sulfonatooxy)-*N*-acetyl-4-aminostilbene. *J. Org. Chem.* **1998**, *63*, 5489–5496. (e) Mota, C. J. A.; Íons, N. *Quím. Nova* **1998**, *21*, 453–458. (f) Helmick, J. S.; Martin, K. A.; Heinrich, J. L.; Novak, M. Mechanism of the Reaction of Carbon and Nitrogen Nucleophiles with the Model Carcinogens *O*-Pivaloyl-*N*-arylhydroxylamines: Competing S_N2 Substitution and S_N1 Solvolysis. *J. Am. Chem. Soc.* **1991**, *113*, 3459–3466.

(17) (a) Kung, A. C.; McIlroy, S. P.; Falvey, D. E. Diphenylnitrenium Ion: Cyclization, Electron Transfer, and Polymerization Reactions. *J. Org. Chem.* **2005**, *70*, 5283–5290. (b) Rodrigues, J. A. R.; Abramovitch, R. A.; Sousa, J. D. F.; Leivaand, G. C. Diastereoselective Synthesis of Cularine Alkaloids via Enium Ions and an Easy Entry to Isoquinolines by Aza-Wittig Electrocyclic Ring Closure. *J. Org. Chem.* **2004**, *69*, 2920–2928. (c) Abramovitch, R. A.; Cooper, M.; Iyer, S.; Jeyaraman, R.; Rodrigues, J. A. R. Intramolecular Cyclization of Arylnitrenium Ions. Formation of Carbon-Carbon Bonds and of Lactones. *J. Org. Chem.* **1982**, *47*, 4819–4820.

(18) Abramovitch, R. A.; Bartnik, R.; Cooper, M.; Dassanayake, N. L.; Hwang, H. Y.; Inbasekaran, M. N.; Rusek, G. Intramolecular Cyclization of Aryloxenium Ions. C-O-C and C-C Bond Formation. A Novel Ortho Effect. *J. Org. Chem.* **1982**, *47*, 4817–4818.

(19) (a) Stokes, B. J.; Richert, K. J.; Driver, T. G. Examination of the Mechanism of Rh_2 (II)-Catalyzed Carbazole Formation Using Intramolecular Competition Experiments. *J. Org. Chem.* **2009**, *74*, 6442–6451. (b) Nagashima, A.; Sakamoto, T.; Kikugawa, Y. Intramolecular benzylic cyclization with nitrenium ions generated from *N*-acylaminophthalimides using phenyliodine(III) bis(trifluoroacetate): Formation of phenyl substituted lactams. *Heterocycles* **2007**, *74*, 273–281. (c) Wardrop, D. J.; Burge, M. S. Nitrenium Ion Azaspirocyclization-Spirodienone Cleavage: A New Synthetic Strategy for the Stereocontrolled Preparation of Highly Substituted Lactams and N-Hydroxy Lactams. *J. Org. Chem.* **2005**, *70*, 10271–10284.

(20) (a) Abramovitch, R. A.; Miller, J.; Souza, A. J. C. The formation of medium-sized rings by the intramolecular eyelization of arylnitrenium ions. *Tetrahedron Lett.* **2006**, *47*, 7271–7271. (b) Abramovitch, R. A.; Miller, J.; Souza, A. J. C. The formation of medium-sized rings by the intramolecular cyclization of arylnitrenium ions. *Tetrahedron Lett.* **2003**, *44*, 6965–6967. (c) Abramovitch, R. A.; Ye, X. C. Intramolecular cyclizations via arylnitrenium ions. Formation of a six-membered ring rather than a macrocycle. *J. Org. Chem.* **1999**, *64*, 5904–5912. (d) Abramovitch, R. A.; Cooper, M.; Iyer, S.; Jeyaraman, R.; Rodrigues, J. A. R. Intramolecular Cyclization of Arylnitrenium Ions. Formation of Carbon-Carbon Bonds and of Lactones. *J. Org. Chem.* **1982**, *47*, 4819–4820.

(21) Kikugawa, I.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. Intramolecular Cyclization with Nitrenium Ions Generated by Treatment of *N*-Acylaminophthalimides with Hypervalent Iodine Compounds: Formation of Lactams and Spiro-Fused Lactams. *J. Org. Chem.* **2003**, *68*, 6739–6744.

(22) Satyanarayana, P.; Venkateswarlu, S.; Viswanatham, K. N. Oxidative aryl-aryl, aryl-benzyl coupling of lignans-reactions of phyllanthin and haloderivatives with ttfa, ddq, li/thf: Synthesis of dibenzocyclooctadiene system and phyltetralin. *Tetrahedron* **1991**, *47*, 8277–8284.

(23) Parr, R. G.; Young, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(24) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. Synthesis of spirodienones by intramolecular ipso-cyclization of *N*-methoxy-(4-halogenophenyl)amides using [hydroxy(tosyloxy)iodo]benzene in trifluoroethanol. *J. Org. Chem.* **2003**, *68*, 5429–5432.

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2003.

(26) Harms, K.; Wocadlo, S. *CAD4 Data Reduction*; University of Marburg: Marburg, Germany, 1995.

(27) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. Completion and refinement of crystal structures with SIR92. *J. Appl. Crystallogr.* **1993**, *26*, 343–350.

(28) Sheldrick, G. M. *SHELX97—Programs for Crystal Structure Analysis (Release 97-2)*; Institüt für Anorganische Chemie der Universität: Göttingen, Germany, 1998.

(29) Farrugia, L. J. WinGX Suite for Single Crystal Small Molecule Crystallography. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

(30) Merritt, E. A.; Bacon, D. J. Raster3D: Photorealistic molecular graphics. *Methods Enzymol.* **1997**, *277*, 505–524.

(31) Lee, C.; Yang, W.; Parr, W. R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* **1988**, *37*, 785–789.

(32) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

(33) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. Results obtained with the correlation energy density functionals of Becke and Lee, Yang and Parr. *Chem. Phys. Lett.* **1989**, *157*, 200–206.

(34) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-Consistent Molecular-Orbital Methods. IX. An Extended Gaussian-Type Basis for Molecular-Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1971**, *54*, 724–728. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1972**, *56*, 2257–2261. (c) Hariharan, P. C.; Pople, J. A. Accuracy of AH_n equilibrium geometries by single determinant molecular orbital theory. *Mol. Phys.* **1974**, *27*, 209–214. (d) Gordon, M. S. The isomers of silacyclopropane. *Chem. Phys. Lett.* **1980**, *76*, 163–168. (e) Hariharan, P. C.; Pople, J. A. The influence of polarization functions on molecular orbital hydrogenation energies. *Theor. Chim. Acta* **1973**, *28*, 213.

(35) Rappé, A. K.; Kasewit, C. J.; Colwell, K. S.; Goddard, W. A., III; Skiff, W. M. UFF, a Full Periodic Table Force Field for Molecular Mechanics and Molecular Dynamics Simulations. *J. Am. Chem. Soc.* **1992**, *114*, 10024–10035.

(36) http://www.chemcraftprog.com/index.html.

(37) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening. *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112.

(38) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. Feasibility of a High-Flux Anticancer Drug Screen Using a Diverse Panel of Cultured Human Tumor Cell Lines. *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.