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Synthesis and antitumor activity of bicyclo[3.3.1]nonenol derivatives

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Abstract—Various novel bicyclo[3.3.1.]nonenol derivatives were synthesized in an efficient one-pot procedure in a remarkably stereoselective reaction. The title compounds show significant antitumor activity against human cancer cell lines. A variety of cinnamic acid derivatives were linked to the title compounds as side chains in order to enhance the antitumor activity. These compounds were subjected to the in vitro antitumor screening, and the results are discussed. It seems important with respect to antitumor activity to locate an aromatic ring at the C-7 position of the bicyclo[3.3.1]nonane framework.

1. Introduction

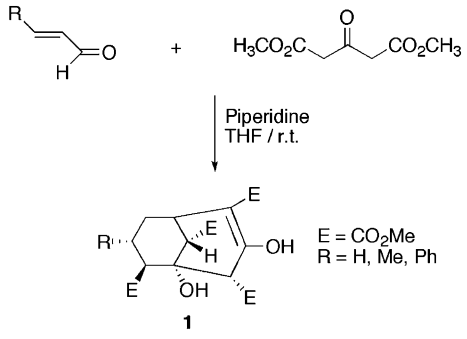
A few years ago we reported on a new method for the synthesis of novel bicyclo[3.3.1]nonenol derivatives **1** by reacting 1-aza-1,3-butadienes with dimethyl 1,3-acetonedicarboxylate.[1,2] We further observed that similar results could be obtained by replacing the 1-aza-1,3-butadienes with the corresponding α,β-unsaturated aldehyde, demonstrating that the transformation of the α,β-unsaturated aldehyde to the less reactive 1-aza-1,3-butadiene derivative obviously offered no advantages in these cases. Compounds **1** are thus accessible by a remarkably simple procedure from readily available starting materials.

In view of the fact that numerous biologically active natural products contain the bicyclo[3.3.1]nonane framework,[3,4] it was of interest to us to evaluate these compounds for their biological significance. The prepared bicyclo[3.3.1]nonenols were submitted to the National Cancer Institute for testing in vitro cytotoxicity against 60 tumor cell lines,[5] and the compounds exhibited antitumor activity in a GI_{50} range between 1 and 100 μM. These results implied cytotoxic potential and constituted an opening for further research, the results of which are disclosed in the present paper. Moreover, these compounds deserve attention in view of the fact that bicyclo[3.3.1]nonane derivatives have been used as key precursors in a synthetic strategy toward the taxane skeleton.[6–8]

2. Results and discussion

2.1. Chemistry

The bicyclo[3.3.1]nonenols **1a–c** were initially prepared by refluxing the methanol solution of dimethyl 1,3-acetonedicarboxylate and an α,β-unsaturated aldehyde in the presence of a catalytic amount of lithium methoxide. This remarkably stereoselective reaction afforded **1a–c** in 50–70% yield. It has been reported recently that the yields of **1** can be substantially increased by stirring the reactants in THF for 5–6 days at room temperature in the presence of piperidine.[9] We now use this latter method exclusively and in our hands the reaction is usually finished in less than 4 h (Scheme 1).



Scheme 1. Synthesis of bicyclo[3.3.1]nonenols, **1**.

Keywords: Bicyclo[3.3.1]nonane; Stereoselective synthesis; Antitumor activity; Cinnamoyl side chains.
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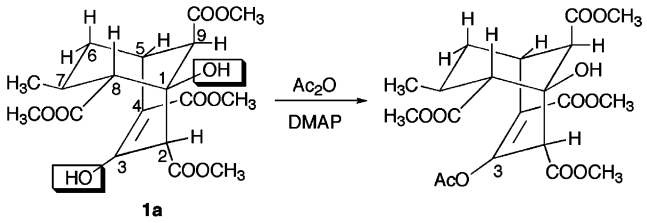
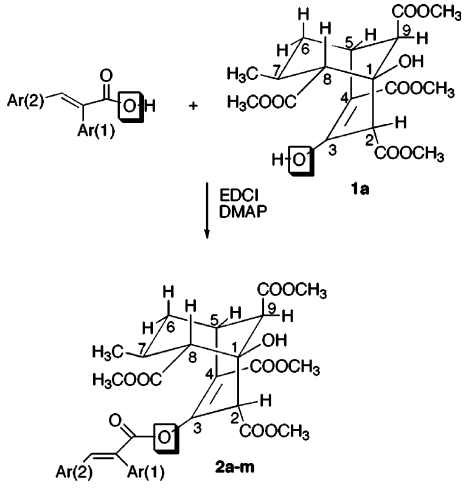


Scheme 2. Selective acetylation of the enolic hydroxyl group of **1a**.

With reference to the biological importance of the taxol C-13 side chain,[10,11] it seemed promising to link side chains of biological interest to **1** in order to possibly enhance the antitumor activity. In preliminary experiments, treatment of **1a** with acetic anhydride in the presence of DMAP led to the acetylation of the enolic hydroxyl group at C-3 (Scheme 2). All attempts to acetylate or alkylate the *tert*-hydroxyl group at C-1 were fruitless. Consequently, it seemed expedient to use the enolic oxygen atom at C-3 as a linkage for the introduction of different side chains to the molecule.

Thus far, these coupling experiments have been confined to derivatives of cinnamic acid. We chose the cinnamoyl moiety because it is found in a variety of biologically active substances,[11–13] for example, in chymotrypsin inhibitors,[14–16] and it also occurs in diverse natural products.[17–19] Related compounds are the α-phenylcinnamic acids, derivatives of which are known antifungal and antibacterial agents.[20,21] The cinnamic acids were linked to **1** with the aid of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and DMAP as coupling agents. The transformation of **1** to **2** is outlined in Scheme 3.

The compounds under study are summarized in Table 1. By examining the Table it can be seen that for compounds **1** the variations in structure are to be found in different substituents at C-7 of the bicyclo[3.3.1]nonane skeleton. For compounds **2** on the other hand, the two aromatic rings on the side chain are differently substituted in an attempt to identify a substituent pattern with pronounced antitumor activity. Treatment of **1a** and **1b**



Scheme 3. The introduction of a cinnamoyl side chain to **1**.

with benzoyl chloride and triethylamin in the presence of catalytic amount of DMAP yielded **3a** and **3b**, respectively. The compounds **3** and **4** were synthesized and tested in order to obtain an idea of the importance of the hydroxyl group at C-3 and to find out if position C-6 was sensitive to substituents, respectively. We encountered difficulties when attempting to couple the cinnamoyl moiety to **1b**, and only two compounds, **2l** and **2m**, were isolated in sufficient purity for testing. The examination of models revealed that this is possibly due to the proximity of the enolic hydroxyl group at C-3 and a large substituent at C-7.

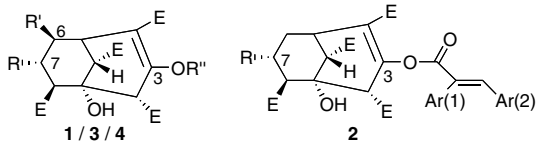
2.2. NCI 60-human tumor cell line screening

The prepared compounds **1**–**4** (Table 1) were submitted to the NCI for in vitro testing against a panel of 60-human tumor cell lines representing nine different cancer types.[5] All submitted compounds were active against some or all of these cell lines and GI_{50} values (concentration that inhibits the cell growth by 50%) for selected cell lines are shown in Table 2. It should be noted that compounds with $GI_{50} > 100\,\mu M$ are considered inactive. Compound **2j** was further screened by NCI for preliminary in vivo testing against tumor cells that were placed in the polyvinylidene fluoride hollow fibers of capsules and then implanted into the intraperitoneal or the subcutaneous compartment in mice. The compound did not obtain a satisfactory score for further evaluation.

2.3. Structure–activity relationships

The antitumor activity of compounds **1a** and **1c** were similar and we chose **1a** as the standard compound for the coupling experiments, because it was easier to prepare and the interpretation of the ^{1}H and ^{13}C NMR spectra was more straightforward. This was further based on the fact that we encountered difficulties when coupling the cinnamic acids to **1b**. The inspection of the data in Table 2 reveals that the introduction of the cinnamoyl moiety to **1a** to afford compounds **2a** and **2b**, has not any appreciable effect on the antitumor activity. On the other hand, the installation of side chains with two aromatic rings, rendering compounds **2c**–**k**, resulted in a decrease in antitumor activity as compared to the parent compound **1a**. Regardless of this, it is of interest to note that **2j** offers excellent selectivity against the five sub-panels of leukemia. This compound showed little or no cytotoxicity against colon, melanoma, ovarian, renal, prostate, and breast cancer cell lines. This selectivity aspect justified in part the preparation of derivative **2m**. The side chain of **2j** has two *p*-chlorophenyl groups, and this emphasizes the possible role of a chlorine substituent on both aromatic rings upon selectivity, because similar selectivity was not observed for **2c**, **2d**, or **2f**, which have side chains that contain two phenyl groups or one phenyl and one *p*-chlorophenyl group. An inbuilt limitation of Table 2 can be demonstrated using **2c** as an example. It might be erroneously inferred from the Table that **2c** was selective against nonsmall lung cancer, but it was screened against eight cell lines of the lung cancer panel and only the NCI-H522 had $GI_{50} < 100\,\mu M$ as disclosed in Table

Table 1. Bicyclo[3.3.1]nonene derivatives **1**–**4** prepared



Compd	R	R′	R″	Compd	R	Ar(1)	Ar(2)
1a	Me	H	H	**2a**	Me	H	Ph
1b	Ph	H	H	**2b**	Me	H	4-Chlorophenyl
1c	H	H	H	**2c**	Me	Ph	Ph
				2d	Me	Ph	4-Chlorophenyl
3a	Me	H	–COPh	**2e**	Me	Ph	2,6-Difluorophenyl
3b	Ph	H	–COPh	**2f**	Me	4-Chlorophenyl	Ph
				2g	Me	2,4-Dichlorophenyl	Ph
4a	Me	Me	H	**2h**	Me	4-Nitrophenyl	Ph
4b	Ph	Me	H	**2i**	Me	4-Methoxyphenyl	Ph
				2j	Me	4-Chlorophenyl	4-Chlorophenyl
				2k	Me	2,4-Dihlorophenyl	2,4-Dichlorophenyl
				2l	Ph	H	4-Chlorophenyl
				2m	Ph	4-Chlorophenyl	4-Chlorophenyl

Table 2. GI_{50} values (μM) of bicylco[3.3.1]nonenes **1**–**4** against human cancer cell lines

Compd	MOLT-4 (leukemia)	H522 (lung)	KM12 (colon)	SF-539 (CNS)	M14 (melanoma)	SK-OV-3 (ovarian)	A498 (renal)	DU-145 (prostate)	MCF7 (breast)
1a	26.3	25.2	23.5	18.4	20.5	26.0	(19.4)	20.2	34.8
1b	11.6	6.71	11.7	12.6	10.8	17.4	17.2	12.9	5.93
1c	29.4	10.6	21.6	18.6	22.6	19.2	16.5	44.7	35.6
2a	>100	5.59	27.9	19.8	25.5	21.4	13.3	18.0	19.3
2b	15.8	6.81	34.1	17.6	23.2	24.6	—	39.4	—
2c	—	45.4	>100	>100	>100	>100	>100	>100	>100
2d	>100	5.99	>100	>100	>100	>100	5.55	>100	>100
2e	>100	6.76	>100	>100	>100	>100	—	>100	—
2f	79.2	>100	>100	>100	>100	>100	>100	>100	>100
2g	>100	>100	>100	>100	>100	>100	>100	>100	>100
2h	3.53	77.2	>100	51.5	>100	>100	>100	>100	>100
2i	>100	35.3	>100	>100	>100	80.3	>100	>100	>100
2j	3.62	10.8	26.0	>100	>100	>100	>100	>100	>100
2k	>100	64.1	>100	>100	>100	>100	>100	>100	>100
2l	3.45	1.96	4.33	3.41	3.46	24.6	6.04	5.80	—
2m	2.22	3.84	>100	>100	30.1	64.0	—	>100	—
3a	46.1	13.2	28.4	14.5	28.3	29.5	26.4	59.2	29.0
3b	3.64	—	8.6	2.20	1.95	10.6	16.3	9.40	3.02
4a	>100	26.9	34.7	35.7	67.5	49.4	>100	>100	38.1
4b	86.0	18.9	>100	>100	88.1	>100	—	>100	—

2. This renders **2c** practically inactive against the majority of the 60 cell lines.

The data in Table 2 for compounds **1a** and **1b** demonstrate that the in vitro antitumor activity increased substantially for all cell lines when the methyl group at C-7 in **1a** was replaced by a phenyl group. With respect to antitumor activity, this suggests distinct sensitivity of the C-7 position of the bicyclo[3.3.1]nonane skeleton. The comparison of the test data for **2b** and **2l** seems to support this notion. Both derivatives have identical side chains but differ in the substituent at C-7, and the enhanced antitumor activity observed for **2l** against most cell lines can be ascribed to the phenyl group present in **2l**. The related assessment of the data for **2j** and **2m** is less conclusive, the antitumor activity being similar in both cases. Worthy of note is the observed cell line selectivity, both compounds (**2j** and **2m**) being essentially inactive against colon, melanoma, renal, prostate, and breast cancer. It was noted earlier that linking *p*-chlorocinnamic acid to **1a** to yield **2b** has little effect on the antitumor activity. On the other hand, the coupling of the same entity to **1b** affords a derivative (**2l**) with improved antitumor activity against almost all cell lines. Exactly analogous results were obtained for the derivatives **3a** and **3b**, obtained by the treatment of **1a** and **1b** with benzoyl chloride, respectively. In fact, the screening results for **2l** and **3b** are noticeably similar

for nearly all cell lines. In spite of the absence of more pertinent data, this strongly indicates that the derivatization of the enolic hydroxyl group at C-3 enhances the antitumor activity of bicyclo[3.3.1]nonanes, given the proper substituent at C-7.

In order to explore if a substituent at C-6 would affect the antitumor activity, the compounds **4a**–**b** with a methyl group at C-6 were synthesized, and subjected to in vitro antitumor screening at the NCI. The compounds should be directly compared with **1a** and **1b** in order to trace the possible effect of a substituent at C-6. The screening results show that for **4a** and **4b** the antitumor activity against all cell lines is lower as compared to **1a** and **1b**, respectively. The data indicate that position C-6 on the bicyclo[3.3.1]nonane framework is unsuited for substituents when trying to enhance the antitumor activity.

In summary, the results presented here demonstrate that bicyclo[3.3.1]nonenols **1** have noticeable antitumor activity. Somewhat to our disappointment, the antitumor activity could not be substantially increased with the linkage of cinnamic acid derivatives to **1**, but one derivative exhibited a significant cell line selectivity. It is apparently promising to modify the substituent at C-7, and work is well underway to prepare a series of **1** with a variety of differently substituted aromatic rings located at C-7. The outcome of the in vitro antitumor screening against human cancer cell lines will then be reported in due course.

3. Experimental

3.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer. Chemical shifts are reported in ppm with respect to residual $CHCl_3$ at 7.26 downfield from Me_4Si. Elemental analyses were carried out on Carlo-Elba microanalyzers, Models 1106 and 1108. Melting points were determined in open capillaries on a Büchi 520 melting point apparatus and are uncorrected. Reactions were monitored by analytical TLC using Merck silica gel 60 F-254 plates, and visualized by UV light. Silica gel from Acros Organics (particle size 0.060–0.200) was used for column chromatography, and flash column chromatography was performed on an instrument from Biotage with pre-packed columns.

3.2. Synthesis

3.2.1. General procedure for the preparation of bicyclo[3.3.1]nonenols 1 and 4. To a stirred solution of dimethyl 1,3-acetonedicarboxylate (2.0 mmol) and an α,β-unsaturated aldehyde (1.0 mmol) in dry THF (15 mL) was added in one portion piperidine (0.1 mmol) dissolved in THF (1 mL). The resulting mixture was stirred at room temperature for 2–4 h. The reaction was monitored by TLC using CH_2Cl_2/ethyl acetate (9:1) as the mobile phase. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (40 mL). The organic phase was washed successively with 10% HCl (twice), water, and saturated NaCl solution, and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the oily residue was diluted with hot MeOH and placed in the freezer for crystallization. In isolated cases, the residue had to be purified by column chromatography (silica gel, eluted with CH_2Cl_2/ethyl acetate (9:1)). Crystals were recrystallized from MeOH.

Spectroscopic data for compounds **1a**–**c** have been published elsewhere.[2] The analytical and spectral data for **4a**–**b** are as follows.

3.2.1.1. 2,4,8,9-Tetrakis(methoxycarbonyl)-6,7-dimethylbicyclo[3.3.1]non-3-ene-1,3-diol (4a). Obtained from 2-methyl-2-butenal and dimethyl 1,3-acetonedicarboxylate (73%): white crystals, mp 127–128 °C; ^{1}H NMR ($CDCl_3$): δ 0.78 (3H, d, $J = 5.4$ Hz), 0.81 (3H, d, $J = 5.8$ Hz), 1.24 (1H, ddq, $J = 3.0$, 12.0, 5.8 Hz), 1.48 (1H, tq, $J = 12.0$, 5.4 Hz), 2.78 (1H, d, $J = 12.0$ Hz), 3.47 (1H, t, $J = 3.0$ Hz), 3.53 (1H, d, $J = 3.0$ Hz), 3.70 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.78 (3H, s), 4.50 (2H, s), 12.24 (1H, s); ^{13}C NMR ($CDCl_3$): δ 16.4, 16.9, 33.2, 37.1, 38.7, 47.8, 51.6, 51.8, 51.9, 52.3, 52.4, 57.8, 71.8, 99.6, 168.4, 170.2, 171.6, 173.2, 173.6. Anal. Calcd for $C_{19}H_{26}O_{10}$: C, 55.07; H, 6.32. Found: C, 55.38; H, 6.48.

3.2.1.2. 2,4,8,9-Tetrakis(methoxycarbonyl)-6-methyl-7-phenylbicyclo[3.3.1]non-3-ene-1,3-diol (4b). Obtained from 2-methyl-3-phenylpropenal and dimethyl 1,3-acetonedicarboxylate (35%): white crystals, mp 171–172 °C; ^{1}H NMR ($CDCl_3$): δ 0.53 (d, $J = 6.8$ Hz, 3H), 1.89 (dqd, $J = 12.0$, 6.8, 3.2 Hz, 1H), 2.52 (dd, $J = 12.2$, 12.0 Hz, 1H), 3.38 (s, 3H), 3.46 (d, $J = 12.2$ Hz, 1H), 3.61 (dd, $J = 3.2$, 3.0 Hz, 1H), 3.68 (d, $J = 3.0$ Hz, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 4.47 (br s, 1H), 4.58 (s, 1H), 7.0–7.3 (m, 5H), 12.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 16.9, 36.9, 37.6, 46.0, 47.8, 51.7, 51.8, 52.1, 52.5, 52.6, 56.9, 71.9, 99.5, 127.0, 128.2 (2C), 128.5 (2C), 140.0, 168.6, 170.2, 171.7, 172.0, 173.6. Anal. Calcd for $C_{24}H_{28}O_{10}$: C, 60.50; H, 5.92. Found: C, 60.36; H, 5.87.

3.2.2. General procedure for the preparation of bicyclo[3.3.1]nonenes 2. The pertinent cinnamic acid (0.89 mmol) was added in small portions over ca. 5 min to a magnetically stirred solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.89 mmol) and DMAP (20 mg) in purified $CHCl_3$ (15 mL), and the resulting solution stirred at room temperature for 15 min; it is important to remove traces of ethanol from the $CHCl_3$ prior to use.[22] To this solution was added in one portion the bicyclo[3.3.1]non-3-en-1-ol **1** (0.75 mmol) and the resulting mixture stirred at reflux until TLC (CH_2Cl_2/ethyl acetate, 9:1) showed the disappearance of the starting material. The reaction mixture was cooled to room temperature and washed twice with water, and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate (9:1) as the mobile phase. This provided **2a**–**m** in 30–80% yields, with the following analytical and spectral data.

3.2.2.1. 2,4,8,9-Tetrakis(methoxycarbonyl)-7-methyl-3-(3-phenylpropenoyloxy)bicyclo[3.3.1]non-3-ene-1-ol (2a). Obtained from 3-phenylpropenoic acid (cinnamic acid) and **1a** (55%): white crystals, mp 142–144 °C; ^{1}H NMR ($CDCl_3$): δ 0.90 (d, J = 6.4 Hz, 3H), 1.23 (ddd, J = 14.3, 11.6, 3.5 Hz, 1H), 1.74 (dt, J = 14.3, 3.0 Hz, 1H), 2.37 (ddqd, J = 12.0, 11.6, 6.4, 3.0 Hz, 1H), 2.73 (d, J = 12.0 Hz, 1H), 3.63 (d, J = 3.0 Hz, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 3.72–3.76 (m, 1H) 3.75 (s, 3H), 3.82 (s, 3H), 4.60 (s, 1H), 4.65 (s, 1H), 6.52 (d, J = 16.0 Hz, 1H), 7.29–7.44 (m, 3H), 7.53–7.57 (m, 2H), 7.81 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.8, 33.9, 34.4, 45.9, 51.8, 52.1, 52.2, 52.4, 52.6, 58.0, 72.4, 116.2, 121.8, 128.4 (2C), 129.0 (2C), 130.8, 134.0, 147.3, 152.1, 163.96, 164.02, 169.9, 173.0, 173.4. Anal. Calcd for $C_{27}H_{30}O_{11}$: C, 61.13; H, 5.70. Found: C, 61.19; H, 5.53.

3.2.2.2. 2,4,8,9-Tetrakis(methoxycarbonyl)-7-methyl-3-[3-(4-chlorophenyl)propenoyloxy]bicyclo[3.3.1]non-3-ene-1-ol (2b). Obtained from 3-(4-chlorophenyl)propenoic acid and **1a** (65%): white crystals, mp 159–160 °C; ^{1}H NMR ($CDCl_3$): δ 0.89 (d, J = 6.4 Hz, 3H), 1.23 (ddd, J = 14.2, 12.0, 3.6 Hz, 1H), 1.73 (dt, J = 14.2, 3.0 Hz, 1H), 2.36 (tqd, J = 12.0, 6.4, 3.0 Hz, 1H), 2.73 (d, J = 12.0 Hz, 1H), 3.63 (d, J = 2.8 Hz, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 3.72–3.76 (m, 1H), 3.75 (s, 3H), 3.82 (s, 3H), 4.58 (br s, 1H), 4.63 (s, 1H), 6.49 (d, J = 16.0 Hz, 1H), 7.35–7.40 (m, 2H), 7.46–7.50 (m, 2H), 7.74 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 27.7, 33.8, 34.4, 45.8, 51.8, 52.1, 52.4, 52.52, 52.54, 57.9, 72.3, 116.8, 121.7, 129.2 (2C), 129.5 (2C), 132.4, 136.7, 145.8, 152.0, 163.6, 163.9, 169.8, 173.0, 173.3. Anal. Calcd for $C_{27}H_{29}ClO_{11}$: C, 57.40; H, 5.17. Found: C, 57.46; H, 5.21.

3.2.2.3. 2,4,8,9-Tetrakis(methoxycarbonyl)-7-methyl-3-(2,3-diphenylpropenoyloxy)bicyclo[3.3.1]non-3-ene-1-ol (2c). Obtained from 2,3-diphenylpropenoic acid and **1a** (64%): white crystals, mp 143–145 °C; ^{1}H NMR ($CDCl_3$): δ 0.88 (d, J = 6.5 Hz, 3H), 1.20 (ddd, J = 14.2, 10.8, 3.5 Hz, 1H), 1.74 (dt, J = 14.2, 3.0 Hz, 1H), 2.35 (ddqd, J = 12.2, 10.8, 6.5, 3.0 Hz, 1H), 2.70 (d, J = 12.2 Hz, 1H), 3.57 (d, J = 3.0 Hz, 1H), 3.61 (s, 3H), 3.70 (dt, J = 3.5, 3.0 Hz, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 4.59 (br s, 1H), 4.65 (s, 1H), 7.04–7.38 (m, 10H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 27.8, 33.9, 34.4, 45.9, 51.8, 52.1, 52.3, 52.4, 52.6, 57.8, 72.3, 121.4, 127.9, 128.2 (2C), 128.6 (2C), 129.5, 129.6 (2C), 130.8 (2C), 131.0, 134.1, 135.1, 142.6, 152.4, 163.9, 164.7, 169.6, 173.1, 173.4. Anal. Calcd for $C_{33}H_{33}O_{11}$: C, 65.45; H, 5.49. Found: C, 65.55; H, 5.46.

3.2.2.4. 2,4,8,9-Tetrakis(methoxycarbonyl)-7-methyl-3-[2-phenyl-3-(4-chlorophenyl)propenoyloxy]bicyclo[3.3.1]-non-3-ene-1-ol (2d). Obtained from 2-phenyl-3-(4-chlorophenyl)propenoic acid and **1a** (46%): white crystals, mp 141–142 °C; ^{1}H NMR ($CDCl_3$): δ 0.88 (d, J = 6.5 Hz, 3H), 1.21 (ddd, J = 14.2, 12.0, 3.5 Hz, 1H), 1.73 (dt, J = 14.3, 3.0 Hz, 1H), 2.34 (tqd, J = 12.0, 6.5, 3.0 Hz, 1H), 2.70 (d, J = 12.0 Hz, 1H), 3.56 (d, J = 2.8 Hz, 1H), 3.60 (s, 3H), 3.70 (ddd, J = 3.5, 3.0, 2.8 Hz, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 4.57 (s, 1H), 4.64 (s, 1H), 6.96–6.99 (m, 2H), 7.13–7.16 (m, 2H), 7.22–7.27 (m, 2H), 7.34–7.39 (m, 3H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.8, 33.9, 34.4, 45.9, 51.8, 52.1, 52.35, 52.42, 52.5, 57.9, 72.3, 121.5, 128.2, 128.6 (2C), 128.8 (2C), 129.6 (2C), 131.6, 132.0 (2C), 132.7, 134.8, 135.4, 152.4, 163.8, 164.5, 169.6, 173.1, 173.3. Anal. Calcd for $C_{33}H_{33}ClO_{11}$: C, 61.83; H, 5.19. Found: C, 61.94; H, 5.49.

3.2.2.5. 2,4,8,9-Tetrakis(methoxycarbonyl)-7-methyl-3-[2-phenyl-3-(2,6-difluorophenyl)propenoyloxy]bicyclo-[3.3.1]non-3-ene-1-ol (2e). Obtained from 2-phenyl-3-(2,6-difluorophenyl)propenoic acid and **1a** (51%): white crystals, mp 163–164 °C; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.3 Hz, 3H), 1.22 (ddd, J = 14.3, 12.1, 3.7 Hz, 1H), 1.73 (dt, J = 14.3, 3.0 Hz, 1H), 2.34 (ddqd, J = 12.1, 12.0, 6.3, 3.0 Hz, 1H), 2.71 (d, J = 12.0 Hz, 1H), 3.59 (d, J = 2.8 Hz, 1H), 3.66 (s, 3H), 3.72–3.76 (m, 1H), 3.74 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 4.59 (s, 1H), 4.69 (s, 1H), 6.76 (t, J = 8.0 Hz, 2H), 7.12–7.25 (m, 6H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 27.8, 33.8, 34.4, 45.9, 51.8, 52.2, 52.4 (2C), 52.5, 57.9, 72.4, 111.3 (dd, $^2J_{CF}$ = 22.6, $^4J_{CF}$ = 2.5), 112.9 (t, $^2J_{CF}$ = 18.8), 121.8, 127.8 (2C), 128.1, 129.2 (2C), 129.6, 130.6 (t, $^3J_{CF}$ = 10.4), 134.7, 137.4, 152.1, 160.0 (dd, $^1J_{CF}$ = 252.2, $^3J_{CF}$ = 6.9), 163.8, 163.9, 169.7, 173.0, 173.3. Anal. Calcd for $C_{33}H_{32}F_2O_{11}$: C, 61.68; H, 5.02. Found: C, 61.62; H, 5.08.

3.2.2.6. 3-[2-(4-Chlorophenyl)-3-phenylpropenoyloxy]-2,4,8,9-tetrakis(methoxycarbonyl)-7-methylbicyclo[3.3.1]-non-3-ene-1-ol (2f). Obtained from 2-(4-chlorophenyl)-3-phenylpropenoic acid and **1a** (78%): white crystals, mp 149–150 °C; ^{1}H NMR ($CDCl_3$): δ 0.88 (d, J = 6.5 Hz, 3H), 1.21 (ddd, J = 14.2, 12.0, 3.5 Hz, 1H), 1.73 (dt, J = 14.2, 3.0 Hz, 1H), 2.34 (tqd, J = 12.0, 6.5, 3.0 Hz, 1H), 2.70 (d, J = 12.0 Hz, 1H), 3.56 (d, J = 2.8 Hz, 1H), 3.62 (s, 3H), 3.70 (ddd, J = 3.5, 3.0, 2.8 Hz, 1H), 3.72 (s, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 4.57 (s, 1H), 4.64 (s, 1H), 7.06–7.10 (m, 2H), 7.17–7.27 (m, 5H), 7.30–7.37 (m, 2H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 27.8, 33.9, 34.4, 45.9, 51.8, 52.1, 52.36, 52.41, 52.5, 57.8, 72.3, 121.5, 128.4 (2C), 128.9 (2C), 129.76, 129.80, 130.8 (2C), 131.3 (2C), 133.6, 133.9, 134.0, 143.1, 152.4, 163.7, 164.3, 169.6, 173.1, 173.3. Anal. Calcd for $C_{33}H_{33}ClO_{11}$: C, 61.83; H, 5.19. Found: C, 61.80; H, 5.08.

3.2.2.7. 3-[2-(2,4-Dichlorophenyl)-3-phenylpropenoyloxy]-2,4,8,9-tetrakis(methoxycarbonyl)-7-methylbicyclo-[3.3.1]non-3-ene-1-ol (2g). Obtained from 2-(2,4-dichlorophenyl)-3-phenylpropenoic acid and **1a** (30%): white crystals, mp 115–116 °C; ^{1}H NMR ($CDCl_3$): δ 0.88 (d, J = 6.0 Hz, 3H), 1.21 (ddd, J = 14.2, 12.2, 3.5 Hz, 1H), 1.72 (dt, J = 14.3, 3.0 Hz, 1H), 2.34 (ddqd, J = 12.2, 12.0, 6.0, 3.0 Hz, 1H), 2.70 (d, J = 12.0 Hz, 1H), 3.56 (br s, 1H), 3.66 (s, 3H), 3.71 (dd, J = 3.5, 3.0 Hz, 1H), 3.76 (s, 6H), 3.80 (s, 3H), 4.58 (s, 1H), 4.66 (s, 1H), 7.04–7.08 (m, 2H), 7.14–7.30 (m, 5H), 7.48–7.50 (m, 1H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.8, 33.9, 34.4, 45.8, 51.8, 52.2, 52.3, 52.4, 52.5, 57.9, 72.4, 121.8, 127.7, 128.6 (2C), 129.5, 129.9, 130.2, 130.4

(2C), 132.3, 132.5, 133.1, 133.7, 134.9, 144.6, 152.3, 163.7, 164.1, 169.9, 173.0, 173.3. Anal. Calcd for $C_{33}H_{32}Cl_2O_{11}$: C, 58.68; H, 4.77. Found: C, 58.04; H, 4.33.

3.2.2.8. 3-[2-(4-Nitrophenyl)-3-phenylpropenoyloxy]-2,4,8,9-tetrakis(methoxycarbonyl)-7-methylbicyclo[3.3.1]-non-3-ene-1-ol (2h). Obtained from 2-(4-nitrophenyl)-3-phenylpropenoic acid and **1a** (46%): white crystals, mp 123–124 °C; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.4 Hz, 3H), 1.20 (ddd, J = 14.3, 12.0, 3.7 Hz, 1H), 1.73 (dt, J = 14.3, 3.0 Hz, 1H), 2.32 (tqd, J = 12.0, 6.4, 3.0 Hz, 1H), 2.70 (d, J = 12.0 Hz, 1H), 3.55 (d, J = 2.9 Hz, 1H), 3.61 (s, 3H), 3.71 (ddd, J = 3.7, 3.0, 2.9 Hz, 1H), 3.736 (s, 3H), 3.740 (s, 3H), 3.81 (s, 3H), 4.58 (s, 1H), 4.64 (s, 1H), 7.01–7.06 (m, 2H), 7.17–7.32 (m, 3H), 7.45–7.50 (m, 2H), 8.04 (s, 1H), 8.20–8.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 19.4, 27.8, 33.8, 34.3, 45.8, 51.8, 52.2, 52.4, 52.47, 52.52, 57.8, 72.3, 121.6, 123.8 (2C), 128.6 (2C), 129.0, 130.2, 130.7 (2C), 131.2 (2C), 133.3, 142.4, 144.3, 147.4, 152.3, 163.5, 163.6, 169.5, 173.1, 173.2. Anal. Calcd for $C_{33}H_{33}NO_{13}$: C, 60.83; H, 5.10; N, 2.15. Found: C, 60.11; H, 5.39; N, 1.97.

3.2.2.9. 3-[2-(4-Methoxyphenyl)-3-phenylpropenoyloxy]-2,4,8,9-tetrakis(methoxycarbonyl)-7-methylbicyclo-[3.3.1]non-3-ene-1-ol (2i). Obtained from 2-(4-methoxyphenyl)-3-phenylpropenoic acid and **1a** (56%): white crystals, mp 170–171 °C; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.4 Hz, 3H), 1.20 (ddd, J = 14.2, 12.0, 3.6 Hz, 1H), 1.73 (dt, J = 14.2, 3.0 Hz, 1H), 2.35 (tqd, J = 12.0, 6.4, 3.0 Hz, 1H), 2.70 (d, J = 12.0 Hz, 1H), 3.57 (d, J = 2.6 Hz, 1H), 3.63 (s, 3H), 3.68–3.72 (m, 1H, obscured signal), 3.72 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.57 (s, 1H), 4.65 (s, 1H), 6.86–6.92 (m, 2H), 7.08–7.24 (m, 7H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.8, 33.9, 34.4, 45.9, 51.8, 52.1, 52.4 (2C), 52.5, 55.2, 57.9, 72.3, 114.1 (2C), 121.5, 127.3, 128.3 (2C), 129.4, 130.7, 130.8 (2C), 130.9 (2C), 134.4, 142.3, 152.6, 159.3, 163.9, 165.0, 169.7, 173.1, 173.4. Anal. Calcd for $C_{34}H_{36}O_{12}$: C, 64.14; H, 5.70. Found: C, 64.02; H, 5.63.

3.2.2.10. 3-[2,3-Bis(4-chlorophenyl)propenoyloxy]2,4,8,9-tetrakis(methoxycarbonyl)-7-methylbicyclo[3.3.1]non-3-ene-1-ol (2j). Obtained from 2,3-bis(4-chlorophenyl)propenoic acid and **1a** (80%): white crystals, mp 156–157 °C; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.4 Hz, 3H), 1.21 (ddd, J = 15.0, 14.0, 3.8 Hz, 1H), 1.73 (dt, J = 14.0, 3.0 Hz, 1H), 2.33 (ddqd, J = 15.0, 12.0, 6.4, 3.0 Hz, 1H), 2.70 (d, J = 12.0 Hz, 1H), 3.56 (d, J = 2.8 Hz, 1H), 3.61 (s, 3H), 3.70–3.74 (m, 1H, obscured signal), 3.72 (s, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 4.56 (br s, 1H), 4.62 (s, 1H), 6.97–7.01 (m, 2H), 7.14–7.22 (m, 4H), 7.32–7.36 (m, 2H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 27.8, 33.9, 34.3, 45.9, 51.8, 52.1, 52.35, 52.43, 52.5, 57.9, 72.2, 121.5, 128.7 (2C), 129.0 (2C), 130.4, 131.2 (2C), 131.9 (2C), 132.3, 133.2, 134.2, 135.7, 141.6, 152.3, 163.6, 164.1, 169.5, 173.1, 173.3. Anal. Calcd for $C_{33}H_{32}Cl_2O_{11}$: C, 58.68; H, 4.78. Found: C, 58.64; H, 4.79.

3.2.2.11. 3-[2,3-Bis(2,4-dichlorophenyl)-3-phenylpropenoyloxy]-2,4,8,9-tetrakis(methoxycarbonyl)-7-methylbicyclo[3.3.1]non-3-ene-1-ol (2k). Obtained from 2,3-bis(2,4-dichlorophenyl)propenoic acid and **1a** (39%): white crystals, mp 191–192 °C; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, J = 6.2 Hz, 3H), 1.22 (ddd, J = 13.5, 9.2, 4.5 Hz, 1H), 1.72 (dm, J = 13.5 Hz, 1H), 2.21–2.41 (m, 1H), 2.71 (d, J = 12.0 Hz, 1H), 3.56 (br s, 1H), 3.67 (s, 3H), 3.68–3.76 (m, 1H, obscured signal), 3.75 (s, 6H), 3.81 (s, 3H), 4.59 (s, 1H), 4.67 (s, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.98 (dd, J = 8.5, 2.0 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.36–7.48 (m, 2H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.8, 33.8, 34.5, 45.8, 51.8, 52.1, 52.3, 52.5, 52.6, 57.9, 72.4, 122.0, 127.1, 127.6, 129.4, 129.7, 129.9, 130.7, 131.0, 132.1, 132.5, 134.9, 135.2, 135.8, 136.0, 139.9, 151.8, 163.0, 163.8, 169.7, 173.0, 173.3. Anal. Calcd for $C_{33}H_{30}Cl_4O_{11}$: C, 53.25; H, 4.06. Found: C, 53.12; H, 4.02.

3.2.2.12. 3-[3-(4-Chlorophenyl)propenoyloxy]-2,4,8,9-tetrakis(methoxycarbonyl)-7-phenylbicyclo[3.3.1]non-3-ene-1-ol (2l). Obtained from 3-(4-chlorophenyl)propenoic acid and **1b** (40%): white crystals, mp 185–187 °C; ^{1}H NMR ($CDCl_3$): δ 1.74–1.89 (m, 2H), 3.40 (s, 3H), 3.41 (d, J = 12.5 Hz, 1H), 3.56 (ddd, J = 12.5, 12.0, 5.3 Hz, 1H), 3.68 (s, 3H), 3.73 (d, J = 3.0 Hz, 1H), 3.75 (s, 3H), 3.84 (q, J = 3.0 Hz, 1H), 3.88 (s, 3H), 4.59 (s, 1H), 4.65 (s, 1H), 6.54 (d, J = 16.0 Hz, 1H), 7.14–7.29 (m, 5H), 7.37–7.41 (m, 2H), 7.48–7.52 (m, 2H), 7.80 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 33.3, 34.6, 39.2, 45.8, 51.7, 52.2, 52.6, 52.7, 52.8, 56.4, 72.5, 116.8, 121.6, 127.0, 127.8 (2C), 128.4 (2C), 129.3 (2C), 129.6 (2C), 132.5, 136.8, 141.1, 145.9, 152.3, 163.7, 163.8, 169.7, 172.0, 173.3. Anal. Calcd for $C_{32}H_{31}ClO_{11}$: C, 61.30; H, 4.98. Found: C, 61.38; H, 4.11.

3.2.2.13. 3-[2,3-Bis(4-chlorophenyl)propenoyloxy]-2,4,8,9-tetrakis(methoxycarbonyl)-7-phenylbicyclo[3.3.1]-non-3-ene-1-ol (2m). Obtained from 2,3-bis(4-chlorophenyl)propenoic acid and **1b** (77%): white crystals, mp 194–196 °C; ^{1}H NMR ($CDCl_3$): δ 1.70–1.94 (m, 2H), 3.38 (d, J = 12.0 Hz, 1H), 3.40 (s, 3H), 3.53 (td, J = 12.0, 4.6 Hz, 1H), 3.62 (s, 3H), 3.68 (d, J = 3.0 Hz, 1H), 3.71 (s, 3H), 3.80 (q, J = 3.0 Hz, 1H), 3.87 (s, 3H), 4.55 (s, 1H), 4.65 (s, 1H), 7.01–7.05 (m, 2H), 7.15–7.30 (m, 9H), 7.35–7.40 (m, 2H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 33.4, 34.6, 39.3, 45.9, 51.6, 52.1, 52.5 (2C), 52.6, 56.3, 72.4, 121.4, 127.0, 127.8 (2C), 128.4 (2C), 128.7 (2C), 129.0 (2C), 130.5, 131.2 (2C), 131.9 (2C), 132.4, 133.3, 134.2, 135.7, 141.0, 141.7, 152.5, 163.4, 164.1, 169.4, 172.1, 173.2. Anal. Calcd for $C_{38}H_{34}Cl_2O_{11}$: C, 61.88; H, 4.65. Found: C, 62.25; H, 4.62.

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