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Hyperconjugation Involving Strained Carbon−Carbon Bonds. Structural Analysis of Ester and Ether Derivatives and One-Bond $^{13}C-^{13}C$ Coupling Constants of α- and β-Nopinol

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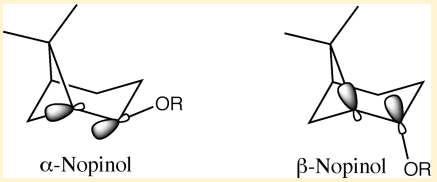
Supporting Information

ABSTRACT: $\sigma_{C-C}-\sigma^*_{C-O}$ interactions involving the strained carbon−carbon bonds of α- and β-nopinol, and their ester and ether derivatives have been demonstrated in the solid state using the variable oxygen probe. These hyperconjugative interactions are manifested as a strong response of the C−OR bond distance to the electron demand of the OR substituent. Although the effects upon the donor C−C bond distances are not large enough to be measurable by X-ray crystallography, they do result in systematic and measurable effects on the $^{13}C-^{13}C$ one-bond coupling constants. For the donor C−C bond, coupling constants decrease, consistent with weakening of this bond, while the intervening C−C bond coupling constants increase, consistent with bond strengthening, as the electron demand of OR increases.



INTRODUCTION

Interactions between donor and acceptor orbitals within a molecular framework have a profound effect on fundamental molecular properties including conformational preferences and chemical reactivity.[1] These interactions are dependent on the intrinsic donor and acceptor abilities of the orbitals involved, and upon their relative, spatial relationships. These interactions often give rise to unusual chemical and spectroscopic properties, and because of their dependence on stereochemistry, they are referred to as stereoelectronic effects.[2] Hyperconjugation (or $\sigma-\pi$ conjugation)[3] is a particularly important type of donor/acceptor interaction between a filled σ bonding orbital (σ_{C-X}) and an electron-deficient orbital such as a carbocation p orbital (Figure 1).

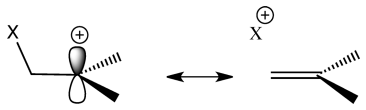
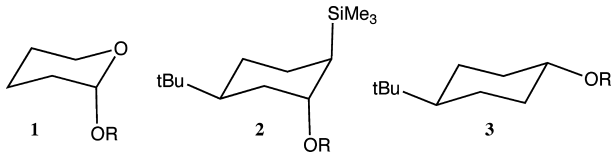


Figure 1. Hyperconjugation between σ_{C-X} and a carbocation p orbital.

The ease at which a C−X σ-bond donates electrons by hyperconjugation is an important fundamental property often referred to as the σ-donor ability. Information on the relative σ-donor abilities of a range of C−X bonds has been obtained by various means including Hammett plots,[4] measurement of the charge-transfer bands in donor−acceptor complexes,[5] ^{19}F and ^{13}C NMR spectroscopy,[6] and ab initio calculations on suitable model systems.[7] An X-ray structural method for obtaining information on σ-donor abilities was introduced by Kirby and Jones and coined as the *variable oxygen probe*.[8,9] The C−O bond distance in the C−OR fragment increases with increasing electron demand of the OR substituent, reflecting increasing contributions of the C^+-OR valence bond form to the ground-state structure of the molecule containing this fragment.

The electron demand of a given substituent (OR) is conveniently quantified by the pK_a value for the parent acid (ROH), and a linear relationship between the C−OR bond distance and pK_a (ROH) has been established. The slope is sensitive to the effects of electron donation into the C−OR σ^* antibonding orbital. The presence of good donor orbitals vicinal and antiperiplanar to the C−O bond results in a strong response of the C−OR bond distance to the electron demand of OR. This reflects increased stabilization of the cation part of the valence bond form C^+-OR. For example, plots of C−OR bond distance vs pK_a (ROH) constructed for **1**,[8] **2**,[10] and **3**[11] gave the following relationships:



$$\mathbf{1}:\ r_{C-O}\ (\text{Å}) = 1.493 - (6.49 \times 10^{-3})pK_a(\text{ROH}) \quad R^2 = 0.985 \qquad (1)$$

$$\mathbf{2}:\ r_{C-O}\ (\text{Å}) = 1.502 - (5.30 \times 10^{-3})pK_a(\text{ROH}) \quad R^2 = 0.986 \qquad (2)$$

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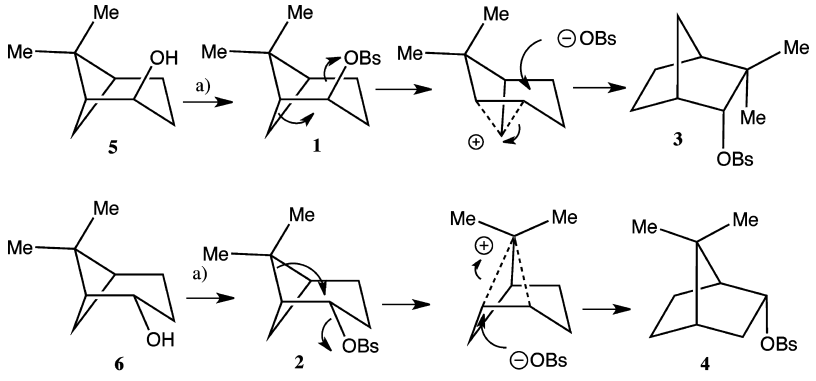
Scheme 1. Rearrangement of α- and β-Nopinyl Brosylate Derivatives



a) p-bromobenzenesulphonyl chloride / pyridine

$$\mathbf{3}:\ r_{C-O}\ (\text{Å}) = 1.479 - (2.86 \times 10^{-3})pK_a(\text{ROH})$$
$$R^2 = 0.985 \qquad (3)$$

A strong response of the C−OR bond distance to the electron demand of OR is demonstrated for **1** which has an oxygen lone pair (n_O) orbital antiperiplanar to the OR substituent (this is the basis of the well-known anomeric effect);[12] a strong response is also observed for **2** which has a C−Si bond antiperiplanar to the OR substituent (this is the basis of the silicon β-effect),[13] but a weaker response is obvious in **3** which has a σ_{C-C} bonding orbital, which is a weaker donor orbital situated antiperiplanar to the OR bond. This structural technique has also been applied to the determination of σ_{C-S}, σ_{C-Se}, σ_{C-Te},[14] and remote $\pi_{C=C}$ donor abilities.[15,16]

Examples of participation of C−C or C−H σ bonds resulting in carbocation stabilization and rearrangement are widespread in organic chemistry, particularly in terpine chemistry where the geometry of the molecule is often particularly favorable.[17,18] Examples include the pinacol rearrangement, the acid-catalyzed conversion of pinene hydrochloride to bornyl chloride,[19] and the rearrangement of camphene hydrochloride to isobornyl hydrochloride.[17] Of interest to us is rearrangement of the α- and β-nopinol system. For example α- and β-nopinyl bromobenzenesulphonates **1** and **2** undergo a particularly facile rearrangement to endocamphenilyl **3** and apobornyl bromobenzenesulphonates **4**, respectively (Scheme 1).[20] Rearrangement occurs so rapidly that attempts to prepare the brosylate derivatives **1** and **2** from α- and β-nopinol **5** and **6** under standard conditions leads to the isolation of the rearrangement products **3** and **4** in quantitative yield. The rearrangement undoubtedly occurs by concerted participation of a strained C−C bond of the four-membered ring which is antiperiplanar to the leaving group leading to the formation of a nonclassical ion intermediate and capture of the intermediate by the brosylate anion leading to the rearranged products.

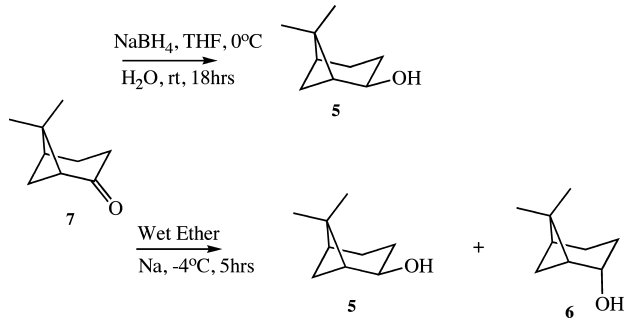
The facile rearrangement of **1** and **2** reflects the strong propensity of the strained C−C bond of the four-membered ring to participate in the formation and stabilization of the adjacent carbenium ion.[21] The presence of strain raises the energy of the σ_{C-C} electrons, resulting in a better energy match with the developing carbenium ion p orbital; furthermore, strain is ultimately released as a result of participation.[22]

We were interested in determining the σ-donor abilities of the strained C−C bonds of α- and β-nopinol (**5** and **6**) from analysis of accurate crystal structures of ester and ether derivatives of varying electron demand. The responses of the C−OR bond distance in these derivatives to the electron demand of the oxygen substituent (OR) give a measure of σ-donor abilities of the two types of C−C bond in the four-membered ring. Of interest also is whether observable structural effects consistent with the early stages of the rearrangement (Scheme 1) manifest in the carbon frameworks of **5** and **6** in response to increasing electron demand of the OR.

RESULTS AND DISCUSSION

Treatment of commercially available (1*R*,5*S*)-(+)-nopinone (**7**) with sodium borohydride gives a quantitative conversion to α-nopinol **5**, while reduction using sodium in wet ether affords a ca. 1:1 mixture of α- and β-nopinol **5** and **6** (Scheme 2); separation of the two isomers was readily achieved by dry-flash chromatography on silica gel.

Scheme 2. Synthesis of α- and β-Nopinol by Reduction of Nopinone



The alcohols were converted to the ester and ether derivatives **5a**−**h** and **6a**−**h** using standard techniques; these derivatives and the pK_a values for their corresponding parent acids are summarized in Table 1. Attempts to prepare more electron-demanding sulfonate esters of **5** and **6** (including mesylate, tosylate, and nosylate) resulted in Wagner−Meerwein rearrangement into the corresponding analogues of **3** and **4**.

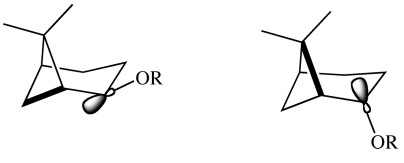


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Table 1. Ether and Ester Derivatives of α- and β-Nopinol

pK_a (ROH)[23]	R	α	β
7.15	4-$NO_2C_6H_4$	**5a**	**6a**
4.16	2-Naphthoyl	**5b**	**6b**
3.46	3-$NO_2C_6H_4CO$	**5c**	**6c**
3.43	4-$NO_2C_6H_4CO$	**5d**	**6d**
2.85	3,5-$(NO_2)_2C_6H_3CO$	**5e**	**6e**
2.82	3,4-$(NO_2)_2C_6H_3CO$	**5f**	**6f**
2.17	2-$NO_2C_6H_4CO$	**5g**	**6g**
1.43	2,4-$(NO_2)_2C_6H_3CO$	**5h**	**6h**

Crystals of suitable quality for X-ray analysis were obtained for the α-nopinyl derivatives **5a** and **5e–g**, while the only suitable crystal data obtained for the β-nopinyl derivatives were for **6a–c**. Data of insufficient quality for this analysis due to crystal twinning and/or thermal disorder were obtained for **5**, **5d**, **5h**, and **6d**.

Data for **5a**, **5e–g**, and **6a–c** were obtained at 130 K to minimize the effects of thermal libration. Derivatives **5e** and **5f** crystallized with two independent molecules in the asymmetric unit. Selected bond distances, angles, and dihedral angles for the α-isomers **5a** and **5e–g** are presented in Table 2, while a thermal ellipsoid plot for **5g**, with the numbering system representative of all α-isomers, is presented in Figure 2. Corresponding data for the β-nopinyl derivatives **6a–c** are presented in Table 3, and a thermal ellipsoid plot for **6c** is presented in Figure 3.

In the α-nopinyl derivatives **5a** and **5e–g** the C2–C3 and C3–C4 bonds have essentially eclipsed conformations. As a result, the two six-membered rings, defined by (C1–C6) and (C1–C5, C7), adopt basically identical conformations which are best described as being midway between idealized chair and boat forms, referred to as a sofa conformation.[24] Associated with the eclipsed conformations about C2–C3 and C3–C4 is an opening up of the valence angles (Table 2): C1–C2–C3, mean 113.5°; C2–C3–C4, mean 115.1°; C3–C4–C5, mean 112.5° from the standard tetrahedral angle (109.5°).

In the β-isomers **6a–c**; however, these bonds are more "*gauche*-like": **6a**, C1–C2–C3–C4 = 24.8(3)°; C2–C3–C4–C5 = −23.7(3)°; **6b**, C1–C2–C3–C4 = 13.0(2)°; C2–C3–C4–C5 = −12.3(2)°; **6c**, C1–C2–C3–C4 = 26.2(2)°; C2–C3–C4–C5 = −24.5(2)° (Table 3). The resulting six-membered ring defined by C1–C6 is a flattened chair, while

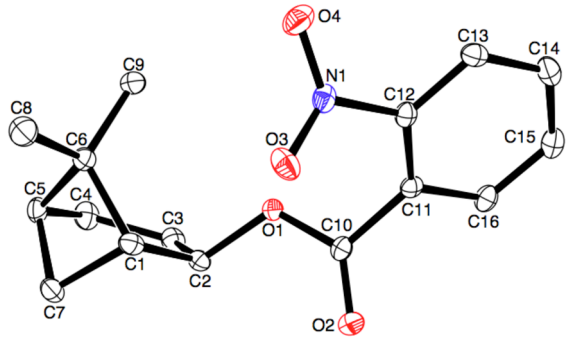

Figure 2. Thermal ellipsoid plot for α-nopinyl 2-nitrobenzoate (**5g**). Ellipsoids are at the 30% probability level.

Table 3. Selected Bond Distances (Å), Angles (deg), and Dihedral Angles (deg) for the β-Nopinyl Derivatives 6a–c

	6a	**6b**	**6c**
C2–O1	1.455(3)	1.471(2)	1.467(2)
C1–C2	1.504(3)	1.517(2)	1.511(2)
C6–C1	1.559(3)	1.560(2)	1.563(2)
C1–C2–C3	111.3(2)	112.4(1)	111.5(1)
C2–C3–C4	114.4(2)	115.0(2)	114.0(1)
C3–C4–C5	110.8(2)	112.5(1)	111.4(1)
C1–C2–C3–C4	24.8(3)	13.0(2)	26.2 (2)
C2–C3–C4–C5	−23.7(3)	−12.3(2)	−24.5 (2)
C6–C1–C2–C3	−60.8(3)	−55.3(2)	−62.5(2)
C6–C5–C4–C3	59.9(3)	53.7(2)	59.6(2)
O1–C2–C1–C7	−82.3(2)	−78.2(2)	−83.7(1)
O1–C2–C1–C6	−176.7(2)	−173.8(8)	−178.3(1)

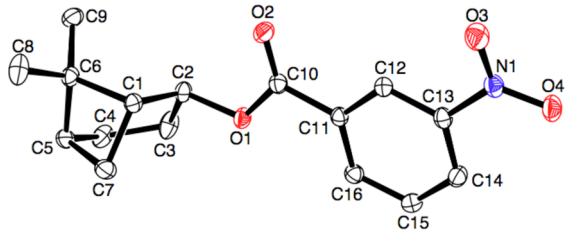

Figure 3. Thermal ellipsoid plot for β-nopinyl 3-nitrobenzoate (**6c**). Ellipsoids are at the 30% probability level.

Table 2. Selected Bond Distances (Å), Angles (deg), and Dihedral Angles (deg) for the α-Nopinyl Derivatives

		5e[a]		**5f**[a]		
	5a	**M1**	**M2**	**M1**	**M2**	**5g**
C2–O1	1.459(2)	1.469(3)	1.473(3)	1.475(3)	1.472(3)	1.475(3)
C1–C2	1.516(2)	1.492(4)	1.515(4)	1.504(4)	1.507(4)	1.517(3)
C1–C7	1.552(2)	1.548(4)	1.539(4)	1.556(3)	1.550(3)	1.547(3)
C1–C2–C3	113.3(1)	113.2(3)	113.8(3)	113.6(2)	113.8(2)	113.4(2)
C2–C3–C4	115.1(1)	115.4(3)	114.8(3)	115.4(2)	115.0(2)	115.0(2)
C3–C4–C5	112.9(1)	112.0(3)	112.7(3)	112.0(2)	112.6(2)	112.8(2)
C1–C2–C3–C4	−5.2(2)	−3.9 (4)	−2.8(4)	0.5(3)	−3.7 (3)	−5.2 (3)
C2–C3–C4–C5	2.0(2)	0.8(4)	0.0(5)	−3.8(3)	0.7(3)	2.7 (3)
C6–C1–C2–C3	−42.3(2)	−43.7(4)	−43.6(4)	−45.2(3)	−43.3(2)	−42.6(2)
C6–C5–C4-C3	48.8(2)	50.1(4)	49.8(5)	52.0(3)	49.5(3)	48.0(2)
O1–C2–C1–C7	172.9(1)	172.6(3)	174.7(3)	171.8(2)	170.9(2)	172.6(2)
O1–C2–C1–C6	78.1(1)	76.7(3)	79.4(3)	76.9(2)	76.0(2)	77.9(2)

[a]Derivatives **5e** and **5f** were crystallized with two independent molecules (**M1** and **M2**) in the asymmetric unit.

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the six-membered ring defined by C1−C5 and C7 is in a flattened boat conformation. The associated bond angles (Table 3) C1−C2−C3, mean 111.7°, C2−C3−C4, mean 114.4°, and C3−C4−C5, mean 111.5° are relaxed toward the preferred tetrahedral value compared with the α-nopinyl derivatives.

The conformation about C1−C2 and the C5−C4 bonds also differs significantly between the α- and β-derivatives. For the α-derivatives **5a** and **5e−g** the average C6−C1−C2−C3 and C6−C5−C4−C3 dihedral angles are −43.5° and 49.7°, respectively (Table 2), whereas for the β-nopinyl derivatives **6a−c** the corresponding dihedral angles are −59.5° and 57.7° (Table 3).

The differences in the conformations of the [3.1.1] bicyclic core for the α- and β-nopinyl derivatives very likely arise from the minimization of the nonbonded repulsion between the *endo*-methyl (C9) and the oxygen substituent on C2. In the α-nopinyl derivatives, tipping of the C2-oxygen substituent away from the *endo*-methyl (C9) is very likely responsible for flattening of the six-membered ring.

The dihedral angle C7−C1−C2−O1 for the α-nopinyl derivatives **5a** and **5e−g** varied from 170.9 to 174.7° (Table 2) and can be considered to be essentially antiperiplanar. This geometry allows for close to optimum overlap between the strained C7−C1 σ-bonding orbital and the O1−C2 σ*-antibonding orbital (Figure 4, compound **5**). In the β-nopinyl

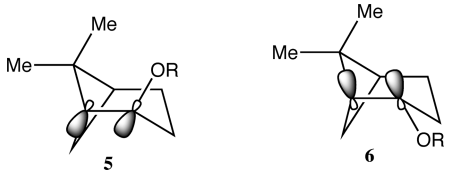


Figure 4. $\sigma_{C-C}-\sigma^*_{C-O}$ interaction for the α-nopinyl and β-nopinyl derivatives.

derivatives **6a−c** it is the C6−C1−C2−O1 dihedral angle (Table 3) that is essentially antiperiplanar. Thus, the strained C6−C1 σ-bonding orbital is optimally aligned with the C2−O1 antibonding orbital (Figure 4, compound **6**).

The structural effects of the $\sigma_{C-C}-\sigma^*_{C-O}$ interaction in the α-nopinyl derivatives **5a** and **5e−g** are best demonstrated from a plot of the C2−O1 bond distances vs the pK_a value for the parent acids for each derivative (Table 1), which is shown in Figure 5.

From this plot the following relationship between C2−O1 bond distance and the electron demand of the ester substituent is obtained:

$$r_{C-O}\ (\text{Å}) = 1.482 - (3.20 \times 10^{-3})\text{p}K_a(\text{ROH})$$
$$R^2 = 0.975 \qquad (4)$$

The slope of eq 4 (−3.20 (aside from the exponent)) is a measure of the σ-donor ability of the C7−C1 bond of the α-derivatives (which is antiperiplanar to the C2−OR bond). Thus, the cyclobutane (C7−C1) bond in the α-nopinyl derivatives is a stronger σ-donor when compared to the unstrained C−C bonds of the cyclohexane derivative **3**, for which a gradient of −2.86 was obtained (eq 3) from the application of variable oxygen probe. On the other hand, the cyclobutane C−C bond in the α-nopinyl derivatives is a weaker donor than the more highly strained cyclopropane C−C bond as indicated by application of the variable oxygen probe to

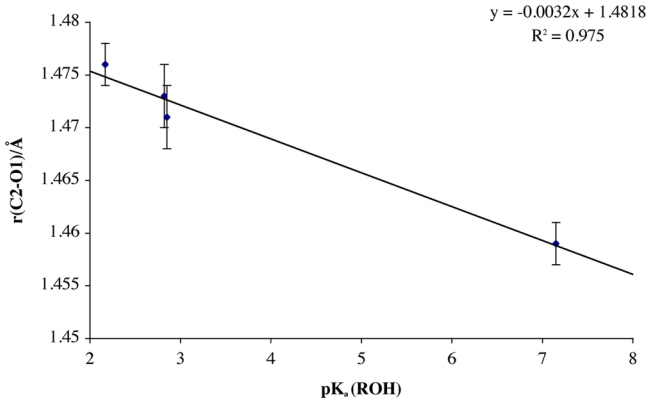
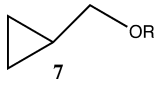


Figure 5. Plot of r_{C2-O1} vs pK_a(ROH) for the α-nopinyl derivatives **5a** and **5e−5g**. (The averages of both **M1** and **M2** values from **5e** and **5f** respectively have been used.)

derivatives of cyclopropylmethanol **7** for which a slope of −4.60 was obtained.[25]



The data set of C2−O1 bond distance and pK_a(ROH) for β-nopinyl derivatives **6a−c** can be found in Table 3 and is presented graphically in Figure 6.

From the plot in Figure 6, the following relationship between C2−O1 bond distance and the electron demand of the ester substituent for the β-nopinol derivatives is obtained:

$$r_{C-O}\ (\text{Å}) = 1.483 - (3.90 \times 10^{-3})\text{p}K_a(\text{ROH})$$
$$R^2 = 0.832 \qquad (5)$$

While eq 5 (slope = −3.90) suggests a stronger donor ability for the antiperiplanar C6−C1 bonds, it is based on a small data set with more scatter and, at best, gives a very qualitative indication of the σ-donor ability of the C6−C1 bond.

The structural data obtained for structures **5a**, **5e−g**, and **6a−c** clearly demonstrate the dependence of the C2−OR bond distance on the electron demand of the oxygen substituent (OR) and are consistent with relatively strong $\sigma_{C-C}-\sigma^*_{C-O}$ interactions involving the strained carbon−carbon bonds of the four-membered rings. However, the carbon−carbon bond distances (particularly those involved in the $\sigma_{C-C}-\sigma^*_{C-O}$ interaction), in both α- and β-nopinol derivatives do not vary significantly with the electron demand of the OR group (Tables 2 and 3), it appears that the effects are too small, and small variations in these distances may simply reflect subtle differences in the crystal packing environments for these structures. Also, it has been noted before that structural effects on the σ-donor bond participating in a σ−σ* interaction are much less that the effects on the σ* acceptor bond.[10]

The apparently small effect on the C−C distances and the relatively small number of crystalline derivatives prompted us to investigate the effects that varying electron demand of the OR substituent would have on the $^{13}C-^{13}C$ one-bond coupling constants. $^{13}C-^{13}C$ one-bond coupling constants have been shown to vary inversely with carbon−carbon bond distances[26] and are sensitive to hyperconjugative effects.[25b] This solution phase alternative technique would complement the structural information provided by the X-ray analysis and has the very real advantage of not requiring good quality crystals.

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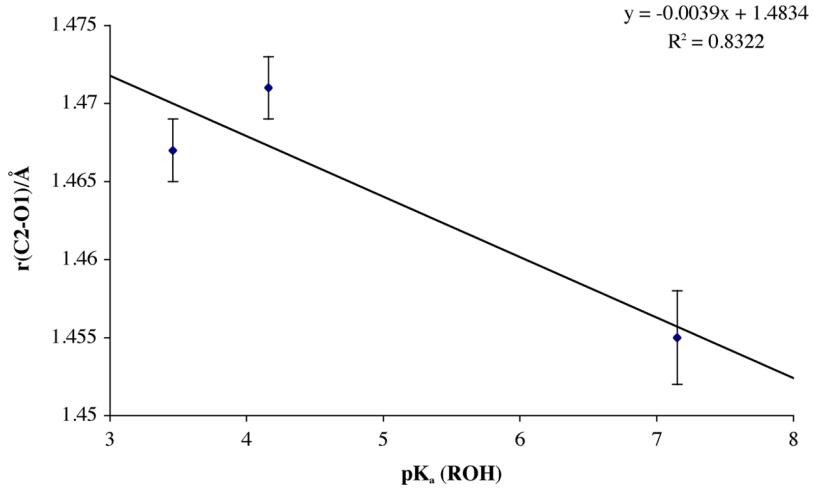

Figure 6. Plot of r_{C2-O1} vs pK_a(ROH) for the β-nopinyl derivatives **6a−c**.

The one-bond $^{13}C-^{13}C$ ($^1J_{C,C}$) scalar coupling constants are obtained via INADEQUATE (incredible natural abundance double quantum transfer experiment).[27] The assignment of all the carbons of α- and β-nopinol **5** and **6** was achieved by standard two-dimensional techniques, and the substituted derivatives were assigned by comparison and by matching up of the $^{13}C-^{13}C$ coupling constants. Each $^{13}C-^{13}C$ coupling constant is determined twice, and these values are averaged. Coupling constants obtained for α- and β-nopinol derivatives are presented in Tables 4; atom numbering is that which is shown in Figures 2 and 3.

Table 4. $^{13}C-^{13}C$ Coupling Constants for α-Nopinol Derivatives 5 and 5a−h and β-Nopinol Derivatives 6 and 6a−h[a]

pK_a (ROH)	compd	J (1,2)	J (7,1)	compd	J (1,2)	J (6,1)
16	**5**	36.9	26.9	**6**	36.6	28.2
7.15	**5a**	36.9	28.4	**6a**	36.7	27.3
4.16	**5b**	37.2	27.9	**6b**	37.2	27.9
3.46	**5c**	37.5	27.6	**6c**	37.4	28.0
3.43	**5d**	37.5	27.6	**6d**	37.4	28.0
2.85	**5e**	37.6	27.3	**6e**	37.4	27.8
2.82	**5f**	37.6	27.3	**6f**	37.6	27.9
2.17	**5g**	37.8	27.3	**6g**	37.6	27.7
1.43	**5h**	38.0	27.0	**6h**	37.6	28.0

[a]All spectra recorded in $CDCl_3$ at 298 K. $^1J_{CC}$ coupling constant (Hz) values ±0.2 Hz.

The data in Tables 4 were used to construct plots of selected $^{13}C-^{13}C$ coupling constants for the ester and ether derivatives **5a−h** and **6a−h** vs the electron demand of the −OR substituent as quantified by pK_a (ROH). The coupling constants for the parent nopinols **5** and **6** were not used for this study as the effects of the oxygen lone pair delocalization into neighboring C−C bonds would make it impossible to delineate the effects of lone pair delocalization from the effects of hyperconjugation.[28] Plots of the $^{13}C-^{13}C$ coupling constants for the antiperiplanar bonds of the cyclobutane ring for α-and β-Nopinol vs pK_a (ROH) are presented in Figure 7. While plots of $^{13}C-^{13}C$ coupling constants of the C1−C2 bonds vs pK_a (ROH) for the α-and β-nopinol derivatives **5a−h** and **6a−h** are presented in Figure 8.

Two clear and distinct trends emerged from the analysis of these $^{13}C-^{13}C$ coupling constant values for α- (**5a−h**) and β-nopinyl derivatives (**6a−h**). These trends are best interpreted by the following relationships between the $^{13}C-^{13}C$ coupling constant and pK_a values of ROH for the α-nopinol derivatives (eqs 6 and 7) and β-nopinol derivatives (eqs 8 and 9)

$$^1J^{13}C-^{13}C\ (Hz) = 26.697 + (2.48 \times 10^{-1})pK_a(ROH)$$
$$R^2 = 0.951\ (\mathbf{C7-C1}) \quad (6)$$

$$^1J^{13}C-^{13}C\ (Hz) = 38.168 - (1.91 \times 10^{-1})pK_a(ROH)$$
$$R^2 = 0.933\ (\mathbf{C1-C2}) \quad (7)$$

$$^1J^{13}C-^{13}C\ (Hz) = 27.163 + (2.33 \times 10^{-1})pK_a(ROH)$$
$$R^2 = 0.969\ (\mathbf{C6-C1}) \quad (8)$$

$$^1J^{13}C-^{13}C\ (Hz) = 37.947 - (1.70 \times 10^{-1})pK_a(ROH)$$
$$R^2 = 0.940\ (\mathbf{C1-C2}) \quad (9)$$

The slopes of plots for eq 6 and 8 and (2.48 and 2.33 (aside from the exponent)) give an indication of the sensitivity of the $^{13}C-^{13}C$ coupling constants of the antiperiplanar bonds of the α-nopinol (**5a-5h**) and β-nopinyl derivatives (**6a-6h**) to the electron demand of the OR substituent, and importantly demonstrate that as the electron demand increases (decreasing pK_a (ROH)) then the coupling constants decrease.

In contrast the $^{13}C-^{13}C$ coupling constant for the C1−C2 bond (eq 7 and 9) in the α- and β-nopinyl derivatives increase with increasing electron demand of the OR substituent. These trends are consistent with the presence of $\sigma_{C-C}-\sigma^*_{C-O}$ interaction between the antiperiplanar carbon−carbon bond and the C2−O1 antibonding orbital. This type of interaction will consequently impart some double-bond character into the C1−C2 bond as depicted in Figure 9 while weakening the antiperiplanar bond (C7−C1 for α- and C6−C1 for β-nopinol derivatives). The contributions of the double-bond no-bond resonance form increases with increasing electron demand of OR substituent.

■ CONCLUSION

Strong $\sigma_{C-C}-\sigma^*_{C-O}$ interactions involving the strained carbon−carbon bonds of α- and β-nopinol and their derivatives

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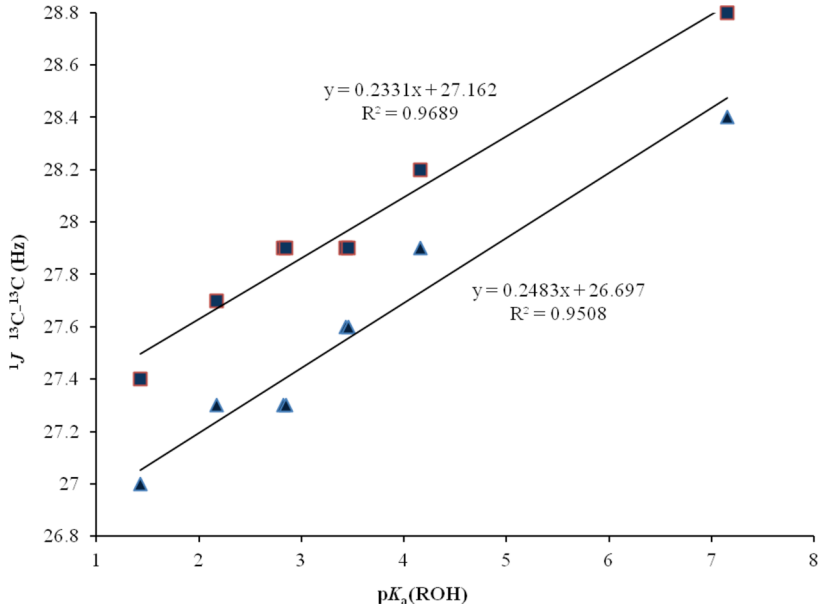

Figure 7. (▲) Plot of $^{13}C-^{13}C$ coupling constant C7−C1 vs pK_a(ROH) for α-nopinyl derivatives **5a**−**5h**. (■) Plot of $^{13}C-^{13}C$ coupling constant C6−C1 vs pK_a(ROH) for β-nopinyl derivatives **6a**−**h**.

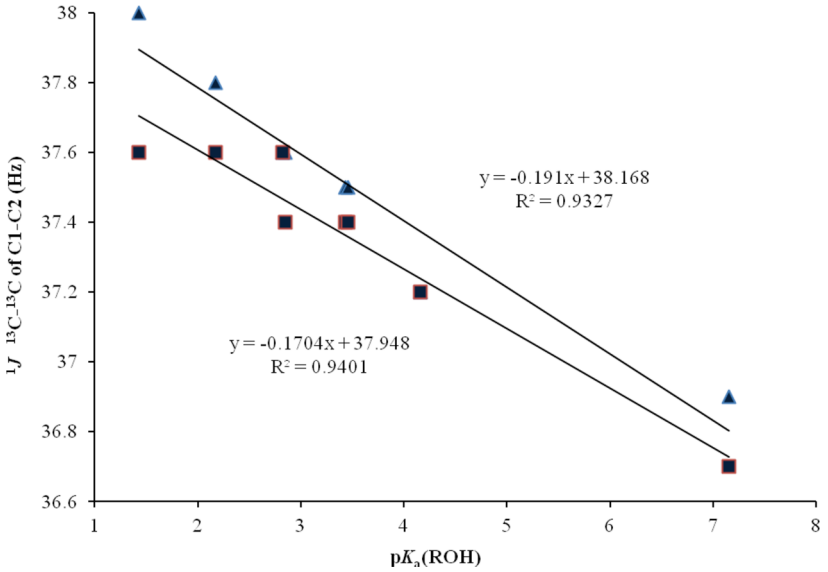

Figure 8. (▲) Plot of $^{13}C-^{13}C$ coupling constant C1−C2 vs pK_a(ROH) for α-nopinyl derivatives **5a**−**h**. (■) Plot of $^{13}C-^{13}C$ coupling constant C1−C2 vs pK_a(ROH) for β-nopinyl derivatives **6a**−**h**.

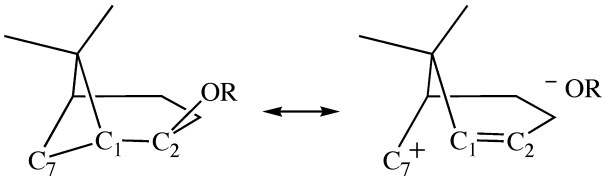

Figure 9. $\sigma_{C-C}-\sigma^*_{C-O}$ interaction between C7−C1 donor orbital and the C2−O1 antibonding orbital in α-nopinol derivatives.

are demonstrated in the solid state using X-ray crystallography, and these are manifested as a strong response of the C−OR bond distance to the electron demand of the OR substituent, however effects upon the C−C bonds are not large enough to be measurable by this technique. The $\sigma_{C-C}-\sigma^*_{C-O}$ interaction, however, does result in systematic and measurable effects on the $^{13}C-^{13}C$ one-bond coupling constants as a function of electron demand for those vicinal bonds involved in this interaction. Thus the donor C−C bond coupling constants decrease, consistent with weakening of this bond, while the intervening C−C bond coupling constants increase, consistent with bond strengthening, as the electron demand of OR increases.

■ EXPERIMENTAL SECTION

Crystallography. Intensity data were collected on a CCD diffractometer using either Cu Kα radiation (graphite crystal monochromator λ = 1.54184) or with Mo Kα radiation (graphite crystal monochromator λ = 0.71073). The temperature during data collections was maintained at 130.0(2) K.

Crystal data for **5**: $C_9H_{16}O$, M = 140.22, T = 130.0(2) K, λ = 0.71069, trigonal, space group $P3(2)$ a = 10.515(2) Å, c =6.565(3) Å, V = 628.6(3) Å^3, Z = 3, D_c = 1.111 mg M^{-3}, μ(Mo Kα) 0.070 mm^{-1},

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$F(000)$ = 308, crystal size 0.4 × 0.08 × 0.07 mm; 3184 reflections measured, 1215 independent reflections (R_{int} = 0.0761), twin law: −1.00 −1.00 0.00 0.00 1.00 0.00 0.00 0.00 −1.00, BASF 0.49, the final R was 0.0421 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.0780 (all data) (without twin correction: R = 0.21 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.35).

Crystal data for **5a**: $C_{15}H_{19}NO_3$, M = 261.31, T = 130.0(2) K, λ = 0.71069, orthorhombic, space group $P2_12_12_1$, a = 10.2043(6) Å, b = 11.1772(7) Å, c =12.1590(8) Å, V = 1386.8(2) Å^3, Z = 4, D_c = 1.252 mg M^{-3}, μ(Mo Kα) 0.087 mm^{-1}, $F(000)$ = 560, crystal size 0.5 × 0.45 × 0.4 mm; 8822 reflections measured, 3170 independent reflections (R_{int} = 0.0181), the final R was 0.0380 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.1010 (all data).

Crystal data for **5e**: $C_{16}H_{18}N_2O_6$, M = 334.32, T = 130.0(2) K, λ = 0.71069, orthorhombic, space group $P2_12_12_1$, a = 9.7057(8) Å, b = 11.5435(9) Å, c =29.504(2) Å, V = 3305.6(5) Å^3, Z = 8, D_c = 1.344 mg M^{-3} μ(Mo Kα) 0.104 mm^{-1}, $F(000)$ = 1408, crystal size 0.45 × 0.4 × 0.06 mm; 17565 reflections measured, 5806 independent reflections (R_{int} = 0.0965), the final R was 0.0438 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.0731 (all data).

Crystal data for **5f**: $C_{16}H_{18}N_2O_6$, M = 334.32, T = 130.0(2) K, λ = 0.1.5418, monoclinic, space group $P2_1$, a = 7.70798(2) Å, b = 32.9160(6) Å, c =7.4809(2) Å, β = 113.621(3)°, V = 1597.27(7) Å^3, Z = 4, D_c = 1.390 mg M^{-3}, μ(Cu Kα) 0.907 mm^{-1}, $F(000)$ = 704, crystal size 0.6 × 0.28 × 0123 mm; 7512 reflections measured, 4231 independent reflections (R_{int} = 0.0278), the final R was 0.0353 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.0957 (all data).

Crystal data for **5g**: $C_{16}H_{19}NO_4$, M = 289.32, T = 130.0(2) K, λ = 0.71069, monoclinic, space group $P2_1$, a = 7.7048(7) Å, b = 9.7610(9) Å, c = 9.6507(9) Å, β = 98.352(2)°, V = 718.1(1) Å^3, Z = 2, D_c = 1.338 mg M^{-3}, μ(Mo Kα) 0.096 mm^{-1}, $F(000)$ = 308, crystal size 0.4 × 0.4 × 0.3 mm; 3810 reflections measured, 2011 independent reflections (R_{int} = 0.0339), the final R was 0.0334 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.0804 (all data).

Crystal data for **6a**: $C_{16}H_{19}NO_3$, M = 261.31, T = 130.0(2) K, λ = 1.5418, orthorhombic, space group $P2_12_12_1$, a = 10.6165(7) Å, b = 10.959(1) Å, c =11.849(1) Å, V = 1378.6(2) Å^3, Z = 4, D_c = 1. 259 mg M^{-3}, μ(Cu Kα) 0.710 mm^{-1}, $F(000)$ = 560, crystal size 0.4 × 0.2 × 0.1 mm; 4874 reflections measured, 2349 independent reflections (R_{int} = 0.0491), the final R was 0.0373 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.0832 (all data).

Crystal data for **6b**: $C_{20}H_{22}O_2$, M = 294.38, T = 130.0(2) K, λ = 1.5418, monoclinic, space group $C2$, a = 18.5270(3) Å, b = 7.4890(1) Å, c =11.4673(2) Å, β = 96.453(2)°, V = 1580.99(4) Å^3, Z = 4, D_c = 1.237 mg M^{-3}, μ(Cu Kα) 2.470 mm^{-1}, $F(000)$ = 632, crystal size 0.36 × 0.28 × 0.07 mm, 4698 reflections measured, 2212 independent reflections (R_{int} = 0.0219) the final R was 0.0351 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.0986 (all data).

Crystal data for **6c**: $C_{16}H_{19}NO_4$, M = 289.32, T = 130.0(2) K, λ = 0.71069, monoclinic, space group $P2_1$, a = 7.2654(6) Å, b = 8.3363(7) Å, c = 12.6898(11) Å, β = 105.698(1)°, V = 739.9(1) Å^3, Z = 2, D_c = 1.299 mg M^{-3}, μ(Mo Kα) 0.093 mm^{-1}, $F(000)$ = 308, crystal size 0.5 × 0.45 × 0.35 mm, 3879 reflections measured, 2467 independent reflections (R_{int} = 0.0117) the final R was 0.0299 [$I > 2\sigma(I)$] and w$R(F^2)$ was 0.0768 (all data).

Analytical Analyses. Infrared spectra (IR) were determined on a Perkin-Elmer Spectrum One, FT ATR-IR spectrometer. High-resolution mass spectra (HRMS) were obtained via ESI using a Finnigan Linear Trap Quadrople FT hybrid mass spectrometer linear ion trap.

Nuclear Magnetic Resonance. Nuclear magnetic resonance (NMR) spectra for ^{1}H and ^{13}C nuclei were recorded using either a 400 MHz NMR operating at 399.8 and 100.5 MHz, respectively, or on a 500 NMR spectrometer operating at 500 and 125 MHz, respectively. The samples for the INADEQUATE analyses were prepared by dissolving ca. 0.4 g of sample in 0.4 mL of the reported deuterated chloroform.

Synthesis. Other general experimental details have been reported elsewhere.[29]

General Procedure A: Reaction of Alcohols with 4-Fluoronitrobenzene. Potassium hydride (1.0 equiv) was added to a solution of alcohol (1.0 equiv) in anhydrous THF. 4-Fluoronitrobenzene (1.05 equiv) was then added to this mixture and the reaction stirred at rt for 2 h. After quenching by addition of water (1 mL), the solvent was removed in vacuo. The residue was dissolved in Et_2O (20 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a black oil. Starting material was removed by column chromatography (gradient system of Et_2O/petroleum ether) to afford the required compound as dark brown oil. This compound was then later recrystallized to produce good quality crystals for X-ray crystallography.

General Procedure B: Esterification of Alcohols Using Benzoyl Chlorides. The alcohol was stirred in anhydrous solvent (DCM, Et_2O, or THF) and pyridine (1 mL) for 30 min and then treated with benzoyl chloride (1.05 equiv), which was added all at once at 0 °C. The reaction was stirred at rt for 24 h or until precipitation of pyridine hydrochloride was complete. Water was added and the mixture stirred for a further 30 min to hydrolyze the remaining acid chloride. The mixture was then extracted with Et_2O, and the combined organic extracts were washed with saturated aqueous copper sulfate ($CuSO_4$) solution, water, saturated aqueous sodium hydrogen carbonate ($NaHCO_3$) solution, and water, dried ($MgSO_4$), filtered, and concentrated in vacuo to generally afford solids of the desired compound which were subsequently recrystallized to produce crystals of X-ray quality.

*α-Nopinol (**5**).* (+)-Nopinone (1 mL, 1.02 g, 7.24 mmol, 1 equiv) was dissolved in tetrahydrofuran (10 mL) and treated with sodium borohydride (0.55 g, 14.45 mmol, 2.0 equiv) at 0 °C under nitrogen. Water (75 mL) was added dropwise over 1 h to the solution, and the resulting mixture was stirred at 25 °C for 18 h. The resultant mixture was diluted with water (5 mL) and then extracted with Et_2O. The combined organic extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo to give (1*R*,2*R*,5*S*)-(−)-α-nopinol in the form of a white crystalline solid (0.42 g, 83%). ^{1}H NMR: δ 4.27 (1H, ddd, J = 9.6, 3.5, 3.5 Hz), 2.33−1.58 (8H, m), 1.21 (3H, s), 1.10 (3H, s), 0.83 (1H, d, J = 9.9 Hz).[30] ^{13}C NMR: δ 73.2 (CH-OH), 48.0 (CH), 40.9 (CH), 37.4 (quaternary *C*), 28.2 (CH_2), 27.3 (CH_3), 25.7 (CH_2), 24.7 (CH_2), 22.5 (CH_3). IR ν_{max}: 3379, 2911, 1457, 1382, 1074 cm^{-1}.

*β-Nopinol (**6**).* Et_2O (25 mL), water (0.30 mL), and (+)-nopinone (0.51 mL, 0.50 g, 3.62 mmol) were stirred in ice when sodium metal (0.38 g, 0.016 mol) was added over 15 min. The mixture was stirred at 0 °C for 4 h. The reaction mixture was slowly quenched with EtOH and then water. When the sodium metal was fully dissolved, the organic extracts were washed with water and Et_2O, dried with $MgSO_4$, filtered, and concentrated to afford an approximately 1:2 mixture of α-(**5**) and β-nopinol (**6**). Separation was achieved by column chromatography on silica gel (gradient system of Et_2O/hexane, R_f = 0.88 for α-nopinol (**5**) and R_f = 0.75 for β-nopinol (**6**). The β-nopinol (**6**) was obtained as a pale yellow oil (0.13 g, 25%). ^{1}H NMR: δ 4.10 (1H, ddd, J = 7.2, 7.2, ca. 1.9 Hz), 2.61 (1H, bs), 2.06−1.48 (8H, m), 1.21 (3H, s), 1.18 (3H, s). ^{13}C NMR: δ 69.7 (CH−OH), 48.0 (CH), 40.5 (CH), 39.4 (quaternary *C*), 26.6 (CH_3), (CH_2), 25.7 (CH_2), 23.2 (CH_2), 22.5 (CH_2), 19.9 (CH_3). IR ν_{max}: 3343, 2912, 1462, 1367, 1018 cm^{-1}. HRMS (ESI): calcd $C_9H_{16}O$ [M + Na]$^+$ 163.10934, found [M + Na]$^+$ 163.10944.

*α-Nopinyl 4-Nitrophenoxide (**5a**).* Following general procedure **A**, potassium hydride (0.03 g, 0.71 mmol) was added to α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous THF (2 mL). 4-Fluoronitrobenzene (0.08 g, 0.75 mmol) was then added to this mixture and stirred for 2 h to afford product **5a**. Crystallization from dichloromethane yielded brown rectangular blocks (0.14 g, 75%). Mp: =77.3−78.1 °C. ^{1}H NMR: δ 8.15 (2H, d, J = 9.2 Hz), 6.83 (2H, d, J = 9.2 Hz), 4.90 (1H, ddd, J = 9.2, 3.2, 3.2 Hz), 2.43−1.81 (7H, m), 1.24 (3H, s), 1.07 (3H, s), 1.06 (1H, d, J = 9.6 Hz). δ 163.0 140.7, 125.7, 115.0, 79.3, 44.7, 40.7, 37.5, 27.3, 26.9, 24.3, 22.8, 22.5. IR ν_{max}: 2922, 1591, 1494, 1339, 1257 cm^{-1}. HRMS (ESI): calcd $C_{15}H_{19}NO_3$ [M + H]$^+$ 262.14377, found [M + H]$^+$ 262.14383.

*α-Nopinyl 2-Naphthoate (**5b**).* Following general procedure B, α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous DCM (1 mL) and pyridine was treated with 2-naphthoyl chloride (0.142 g, 1.75 mmol,

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1.5 equiv) to afford product **5b** which crystallized into white flakes from toluene (0.17 g, 81%). Mp =108.8−109.3 °C. ^{1}H NMR: δ 8.73 (1H, s), 8.16 (1H, d, J = 7.3 Hz), 7.93 (3H, m), 7.63 (1H, t, J = 7.3 Hz), 7.56 (1H, t, J = 7.3 Hz), 5.68 (1H, ddd, J = 9.2, 2.4, 2.4 Hz), 2.40−1.75 (7H, m), 1.25 (3H, s), 1.14 (3H, s), 1.04 (1H, d, J = 10.2 Hz). ^{13}C NMR: δ 165.9, 135.9, 132.5, 130.6, 129.1, 128.5, 127.8, 127.5, 126.8, 126.3, 125.0, 76.1, 45.2, 40.6, 37.3, 27.4, 26.9, 24.3, 22.9, 22.8. IR ν_{max}: 2918, 1708, 1276, 777, 761 cm^{-1}. HRMS (ESI): calcd $C_{20}H_{22}O_2$ [M + Na]$^+$ 317.15120, found [M + Na]$^+$ 317.15125.

*α-Nopinyl 3-Nitrobenzoate (**5c**).* Following general procedure B, α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 3-nitrobenzoyl chloride (0.14 g, 0.75 mmol) for 2 h to afford product **5c** as a yellow solid (0.16 g, 76%). Mp = 80.1−80.5 °C. ^{1}H NMR: δ 8.84 (1H, s), 8.40 (1H, dd, J = 8.0, 2.3 Hz), 8.35 (1H, d, J = 8.0 Hz), 7.65 (1H, t, J = 8.0 Hz), 5.56 (1H, ddd, J = 9.8, 3.3, 3.3 Hz), 2.51−1.78 (7H, m), 1.26 (3H, s), 1.19 (3H, s,), 1.11 (1H, d, J = 10.3 Hz). ^{13}C NMR: δ 163.4, 147.9, 134.7, 132.4, 129.3, 126.7, 124.0, 77.0, 44.9, 40.4, 37.2, 27.1, 26.6, 24.1, 22.6, 22.5. IR ν_{max}: 2921, 1714, 1536, 1346, 1294, 1259, 717 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{19}NO_4$ [M + Na]$^+$ 312.12063, found [M + Na]$^+$ 312.12083.

*α-Nopinyl 4-Nitrobenzoate (**5d**).* Following general procedure B, α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 4-nitrobenzoyl chloride (0.14 g, 0.75 mmol) for 2 h to afford product **5d** as yellow solid (0.15 g, 73%). Mp = 80.1−80.5 °C. ^{1}H NMR: δ 8.29 (2H, d, J = 8.8 Hz), 8.19 (2H, d, J = 8.8 Hz), 5.55 (1H, ddd, J = 9.8, 3.6, 3.3 Hz), 2.51−1.78 (7H, m), 1.26 (3H, s), 1.17 (3H, s), 1.11 (1H, d, J = 10.3 Hz). ^{13}C NMR: δ 164.0, 150.3, 136.3, 130.5, 123.4, 77.4, 45.2, 40.6, 37.4, 27.4, 26.9, 24.3, 22.9, 22.7. IR ν_{max}: 2924, 1712, 1523, 1345, 1288, 717 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{19}NO_4$ [M + H]$^+$ 290.13868, found [M + H]$^+$ 290.13871.

*α-Nopinyl 3,5-Dinitrobenzoate (**5e**).* Following general procedure B, α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 3,5-dinitrobenzoyl chloride (0.17 g, 0.75 mmol) for 2 h to afford product **5e** as a yellow solid (0.19 g, 80%). Mp = 100.0−101.8 °C. ^{1}H NMR: δ 9.21 (1H, d, J = 2.1 Hz), 9.14 (2H, d, J = 2.1 Hz), 5.62 (1H, ddd, J = 10.0, 3.5, 3.3 Hz), 2.52−1.81 (7H, m), 1.28 (3H, s), 1.20 (3H, s), 1.13 (1H, d, J = 10.3 Hz). ^{13}C NMR: δ 161.9, 148.5, 134.6, 129.2, 122.0, 78.7, 45.1, 40.6, 37.5, 27.3, 26.8, 24.2, 22.9, 22.6. IR ν_{max}: 2923, 1719, 1541, 1344, 1286, 719 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{18}N_2O_6$ [M + Na]$^+$ 357.10571, found [M + Na]$^+$ 357.10598.

*α-Nopinyl 3,4-Dinitrobenzoate (**5f**).* Following general procedure B, α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 3,4-dinitrobenzoyl chloride (0.17 g, 0.75 mmol) for 2 h to afford product **5f** as yellow solid (0.19 g, 76%). Mp = 122.0−123.3 °C. ^{1}H NMR: δ 8.53 (1H, d, J = 1.7 Hz), 8.38 (1H, dd, J = 8.4, 1.7 Hz), 7.97 (1H, d, J = 8.4 Hz), 5.57 (1H, ddd, J = 9.8, 3.4, 3.3 Hz), 2.50−1.77 (7H, m), 1.25 (3H, s), 1.14 (3H, s), 1.10 (1H, d, J = 10.3 Hz). ^{13}C NMR: δ 162.1, 144.9, 142.5, 135.8, 134.3, 126.1, 125.2, 78.7, 45.1, 40.6, 37.5, 27.4, 26.8, 24.2, 23.0, 22.7. IR ν_{max}: 2919, 1710, 1539, 1367, 1289, 732 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{18}N_2O_6$ [M + Na]$^+$ 357.10571, found [M + Na]$^+$ 357.10595.

*α-Nopinyl 2-nitrobenzoate (**5g**).* Following general procedure B, α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous DCM (1 mL) and pyridine was treated with 2-nitrobenzoyl chloride (0.14 g, 0.75 mmol) for 2 h to afford product **5g** as yellow solid (0.18 g, 87%). Mp = 81.0−81.6 °C. ^{1}H NMR: δ 7.89 (1H, dd, J = 7.8, 1.2 Hz), 7.73 (1H, dd, J = 7.8, 1.8 Hz), 7.66 (1H, dt, J = 1.2 Hz), 7.61 (1H, dt, J = 1.8 Hz), 5.51 (1H, ddd, J = 9.8, 3.5, 3.4 Hz), 2.44−1.80 (7H, m), 1.21 (3H, s), 1.04 (1H, d, J = 10.3 Hz), 0.96 (3H, s). ^{13}C NMR: δ 164.2, 148.0, 132.4, 131.2, 129.4, 127.9, 123.3, 77.7, 44.5, 40.2, 36.9, 27.3, 26.5, 24.0, 21.9, 21.7. IR ν_{max}: 2924, 1721, 1533, 1350, 1290, 736 cm^{-1}. HRMS (ESI): Calc. $C_{16}H_{19}NO_4$ [M + Na]$^+$ 312.12063, found [M + Na]$^+$ 312.12070.

*α-Nopinyl 2,4-Dinitrobenzoate (**5h**).* Following general procedure B, α-nopinol (**5**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 2,4-dinitrobenzoyl chloride (0.17 g, 0.75 mmol) for 2 h to afford product **5h** as yellow solid (0.20 g, 84%). Mp = 110.5−112.2 °C. ^{1}H NMR: δ 8.77 (1H, d, J = 2.1 Hz), 8.52 (1H, dd, J = 8.4, 2.1 Hz), 7.92 (1H, d, J = 8.4 Hz), 5.56 (1H, ddd, J = 10.0, 3.4, 3.3 Hz), 2.48−1.80 (7H, m), 1.22 (3H, s), 1.05 (1H, d, J = 10.5 Hz), 0.94 (3H). ^{13}C NMR: δ 163.1, 148.6, 147.9, 133.3, 131.1, 127.3, 119.3, 79.4, 44.7, 40.4, 37.1, 27.5, 26.6, 24.2, 22.1, 21.8. IR ν_{max}: 2912, 1724, 1529, 1349, 1295, 732 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{18}N_2O_6$ [M + Na]$^+$ 357.10571, found [M + Na]$^+$ 357.10593.

*β-Nopinyl 4-Nitrophenoxide (**6a**).* Following general procedure A, potassium hydride (0.03 g, 0.71 mmol) was added to β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous THF (2 mL). 4-Fluoronitrobenzene (0.08 g, 0.75 mmol) was then added to this mixture and stirred for 2 h to afford product **6a** which crystallized into brown rectangular blocks from DCM (0.15 g, 81%). Mp = 75.2−77.0 °C. ^{1}H NMR: δ 8.14 (2H, d, J = 9.4 Hz), 6.87 (2H, d, J = 9.4 Hz), 4.82 (1H, ddd, J = 6.93, 6.93, 1.8 Hz), 2.26−1.78 (7H, m), 1.62 (1H, d, J = 9.6 Hz), 1.28 (3H, s), 0.93 (3H, s). ^{13}C NMR: δ 163.3, 140.9, 125.8, 115.2, 77.1, 44.4, 40.2, 39.2, 29.6, 26.4, 23.2, 22.8, 20.1. IR ν_{max}: 2917, 1590, 1495, 1300, 1266 cm^{-1}. HRMS (ESI): calcd $C_{15}H_{19}NO_3$ [M + H]$^+$ 262.14377, found [M + H]$^+$ 262.14377.

*β-Nopinyl 2-Naphthoate (**6b**).* Following general procedure B, β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous DCM (1 mL) and pyridine was treated with 2-naphthoyl chloride (0.142 g, 1.75 mmol, 1.5 equiv) to afford product **6b** which crystallized into white flakes from toluene (0.16 g, 76%). Mp = 88.9−90.4 °C. ^{1}H NMR: δ 8.60 (1H, s), 8.08 (1H, d, J = 10.8 Hz), 7.95 (1H, d, J = 8.0 Hz), 7.85 (2H, d, J = 8.4 Hz), 7.55 (2H, m), 5.54 (1H, bt, J = 7.6 Hz), 2.44−1.82 (7H, m), 1.74 (1H, d, J = 8.8 Hz), 1.31 (3H, s), 0.97 (3H, s). ^{13}C NMR: δ 166.2, 135.3, 132.3, 130.6, 129.1, 128.6, 127.9, 127.8, 127.6, 126.3, 125.1, 74.4, 45.0, 40.2, 39.4, 26.3, 23.3, 23.2, 22.3, 20.0. IR ν_{max}: 2922, 1705, 1277, 779, 762 cm^{-1}. HRMS (ESI): calcd $C_{20}H_{22}O_2$ [M + H]$^+$ 295.16926, found [M + H]$^+$ 295.16935.

*β-Nopinyl 3-Nitrobenzoate (**6c**).* Following general procedure B, β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 3-nitrobenzoyl chloride (0.14 g, 0.75 mmol) for 2 h to afford product **6c** as a yellow solid (0.18 g, 87%). Mp = 70.0−71.0 °C. ^{1}H NMR: δ 8.65 (1H, d, J = 1.6 Hz), 8.28 (1H, d, J = 7.9 Hz), 8.25 (1H, t, J = 7.9 Hz), 7.57 (1H, t, J = 7.9 Hz), 5.37 (1H, br t, J = 6.7, 6.1, 1.5 Hz), 2.26−1.71 (7H, m), 1.58 (1H, d, J = 10.3 Hz), 1.19 (3H), 0.84 (3H, s). ^{13}C NMR: δ 163.7, 147.9, 134.9, 132.4, 129.3, 126.8, 124.0, 75.5, 44.7, 40.0, 39.3, 26.2, 23.1, 23.0, 22.0, 19.9. IR ν_{max}: 2927, 1716, 1524, 1347, 1264, 717 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{19}NO_4$ [M + Na]$^+$ 312.12063, found [M + Na]$^+$ 312.12073.

*β-Nopinyl 4-Nitrobenzoate (**6d**).* Following general procedure B, β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 4-nitrobenzoyl chloride (0.14 g, 0.75 mmol) for 2 h to afford product **6d** as a yellow solid (0.18 g, 87%). Mp = 104.3−106.0 °C. ^{1}H NMR: δ 8.26 (2H, d, J = 8.9 Hz), 8.18 (2H, d, J = 8.9), 5.47 (1H, m), 2.34−1.77 (7H, m), 1.64 (1H, d, J = 9.6 Hz), 1.28 (3H, s), 0.94 (3H). ^{13}C NMR: δ 164.1, 150.2, 136.2, 130.4, 123.3, 75.7, 44.9, 40.2, 39.5, 26.3, 23.2, 23.1, 22.2, 20.0. IR ν_{max}: 2919, 1710, 1522, 1346, 1285, 716 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{19}NO_4$ [M + Na]$^+$ 312.12063, found [M + Na]$^+$ 312.12077.

*β-Nopinyl 3,5-Dinitrobenzoate (**6e**).* Following general procedure B, β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 3,5-dinitrobenzoyl chloride (0.17 g, 0.75 mmol) for 2 h to afford product **6e** as a yellow solid (0.20 g, 84%). Mp = 93.0−94.7 °C. ^{1}H NMR: δ 9.06 (1H, s), 8.98 (2H, s), 5.42 (1H, m), 2.28−1.74 (7H, m), 1.60 (1H, d, J = 8.0 Hz), 1.21 (3H, s), 0.86 (3H, s). ^{13}C NMR: δ 161.8, 148.3, 134.3, 129.0, 121.8, 76.9, 44.6, 40.0, 39.4, 26.1, 23.0, 22.9, 21.9, 19.8. IR ν_{max}: 2926, 1723, 1543, 1343, 1280, 721 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{18}N_2O_6$ [M + Na]$^+$ 357.10571, found [M + Na]$^+$ 357.10605.

*β-Nopinyl 3,4-Dinitrobenzoate (**6f**).* Following general procedure B, β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 3,4-dinitrobenzoyl chloride (0.17 g, 0.75 mmol) for 2 h to afford product **6f** as yellow solid (0.17 g, 71%). Mp = 109.3−111.0 °C. ^{1}H NMR: δ 8.43 (1H, s), 8.34 (1H, d, J = 8.2 Hz), 7.92 (1H, d, J = 8.2 Hz), 5.41 (1H, m), 2.27−1.74 (7H, m), 1.57 (1H, d, J = 8.8 Hz), 1.20 (3H, s), 0.85 (3H, s). ^{13}C NMR: δ 162.0, 144.6, 142.2, 135.6, 134.3, 125.8, 125.1, 76.8, 44.6, 40.0, 39.4, 26.1, 23.0, 22.9, 21.9, 19.8. IR ν_{max}: 2913, 1710, 1538, 1366, 1289, 742 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{18}N_2O_6$ [M + Na]$^+$ 357.10571, found [M + Na]$^+$ 357.10580.

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*β-Nopinyl 2-Nitrobenzoate (**6g**).* Following general procedure B, β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous DCM (1 mL) and pyridine was treated with 2-nitrobenzoyl chloride (0.14 g, 0.75 mmol) for 2 h to afford product **6g** as a yellow solid (0.17 g, 83%). Mp = 77.0−78.6 °C. ^{1}H NMR: δ 7.85 (1H, dd, *J* = 7.6, 1.6 Hz, 7.72 (1H, dd, *J* = 7.6, 1.9 Hz, 7.64 (1H, dt, *J* = 1.6 Hz), 7.59 (1H, dt, *J* = 1.9 Hz), 5.44 (1H, m), 2.31−1.71 (7H, m), 1.50 (1H, d, *J* = 9.6 Hz) 1.25 (3H, s), 0.89 (3H, s). ^{13}C NMR: δ 164.7, 148.2, 132.5, 131.4, 129.7, 127.7, 123.5, 76.4, 44.3, 40.0, 39.3, 26.2, 23.0, 22.9, 21.4, 19.9. IR ν_{max}: 2927, 1714, 1530, 1359, 1293, 735 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{19}NO_4$ [M + Na]$^+$ 312.12063, found [M + Na]$^+$ 312.12079.

*β-Nopinyl 2,4-Dinitrobenzoate (**6h**).* Following general procedure B, β-nopinol (**6**) (0.1 g, 0.71 mmol) in anhydrous Et_2O (1 mL) and pyridine was treated with 2,4-dinitrobenzoyl chloride (0.17 g, 0.75 mmol) for 2 h to afford product **6h** as yellow solid (0.19 g, 79%). Mp = 142.0−143.3 °C. ^{1}H NMR: δ 8.75 (1H, s), 8.51 (1H, d, *J* = 8.4 Hz), 7.93 (1H, dd, *J* = 8.4, 1.8 Hz), 5.49 (1H, m), 2.32−1.76 (8H, m), 1.49 (1H, d, *J* = 11.9 Hz), 1.28 (3H, s), 0.92 (3H, s). ^{13}C NMR: δ 163.1, 148.7, 148.2, 133.2, 131.3, 127.2, 119.3, 77.9, 44.4, 40.1, 39.5, 26.3, 23.1, 23.0, 21.5, 20.0. IR ν_{max}: 2924, 1715, 1538, 1352, 1290, 729 cm^{-1}. HRMS (ESI): calcd $C_{16}H_{18}N_2O_6$ [M + Na]$^+$ 357.10571, found [M + Na]$^+$ 357.10583.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{13}C NMR spectra for compounds **5a−h** and **6a−h**. Crystallographic information files (CIF) are available and have been deposited with the Cambridge Crystallographic Data Centre and assigned CCDC codes 916415−916422, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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