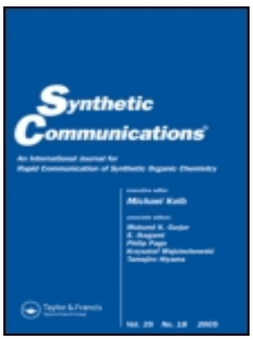

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REGIOSELECTIVE MONOESTERIFICATION STUDY OF THE DIOL IN 1-C-(4,6-O-BENZYLIDENE-β-D-GLUCOPYRANOSYL) ACETONE

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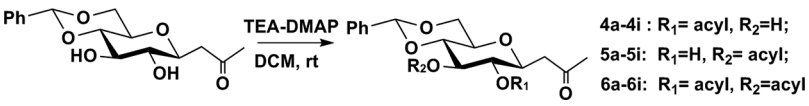
GRAPHICAL ABSTRACT



Abstract *1-C-(4,6-O-Benzylidene-β-D-glucopyranosyl) acetone has been studied in a catalytic system consisting of triethylamine-p-dimethylaminopyridine (TEA-DMAP) in the presence of a number of esterification reagents in dichloromethane. It was found that all-protected and monoprotected products form simultaneously. However, the regioselectivity tends to favor the 3-substituted derivative. Structural parameters have been determined by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H correlation spectroscopy, and elemental analysis. Furthermore, a possible mechanism for the formation of intramolecular hydrogen-bond networks between the carbonyl group and 2-OH was described. The energy changes of the transition state in this reaction, as determined by a molecular modelling study, provided further evidence to assign the relative reactivities of each individual hydroxyl group.*

Keywords C-Glycosides; NMR; regioselective protection

INTRODUCTION

In recent years, C-glycosides have received considerable attention owing to their extraordinary biological properties and stability towards acidic media or enzymatic hydrolysis.[1] Furthermore, as central building blocks of a variety of natural products, including tunicamycin,[2] sTn,[3] sialic acid,[4] etc., these functional groups provide important features in chemical synthesis.[5] The enzymatic synthesis of carbohydrate derivatives proves to be more effective than chemical approaches,[6] particularly in terms of achieving a suitable regioselectivity and stereoselectivity. Unfortunately, practical applications are scarce due to a limited access of suitable enzymes. In synthetic carbohydrate chemistry also, the protection and deprotection

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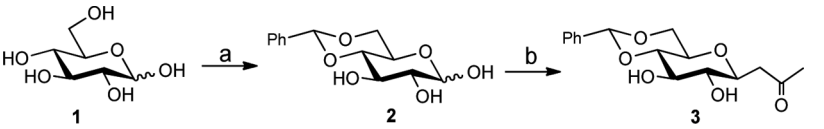


Scheme 1. (a) PhCHO, $ZnCl_2$, 63%; (b) acetylacetone, $NaHCO_3$, H_2O, 90°C, 92%.

reaction of hydroxyl groups prove to be rather challenging to carry out. Therefore, advanced methods for the synthesis of C-glycosides mimics and oligosaccharides are required to improve synthetic efficacy. Oligosaccharides with 1→2 and/or 1→3 linkages exhibit superior bioactivities[7] and can be found in a variety of natural compounds, for example, in ginsenoside,[8] MBr1/Globo-H,[9] Lewis^y-KLH,[10] etc. This is why the efficient regioselective protection of the two secondary 2,3-dihydroxyl groups remains a major synthetic goal in carbohydrate chemistry.

The electronegativity of anomeric atoms, such as N, O, and C, leads to changes in the electron density of the hexagonal sugar ring system, affecting the selectivity of esterification reactions of each hydroxyl group. A variety of catalysts have been studied in an effort to improve the selectivity in O- or S-glycosides, including PTC (phase-transfer catalyst),[11] Al_2O_3,[12] fresh Ag_2O,[13], $MoCl_5$,[14] etc. However, we selected triethylamine-p-dimethylaminopyridine (TEA-DMAP) as the catalytic system, mostly due to its high accessibility and availability. NMR spectral analysis and molecular modelling study were conducted to provide a reasonable explanation for the monoprotection results obtained. In this report, we described an efficient and convenient strategy featuring a regioselective and regiocontrolled manipulation of the hydroxyl groups on glycosides without the need for conventional multistep protection/deprotection reactions (Scheme 1).

RESULTS AND DISCUSSION

Preparation of 1-C-(4,6-O-Benzylidene-β-D-glucopyranosyl) Acetone

A general procedure for compound **3** usually involves the synthesis of methyl-1-C-(β-D-glucopyranosyl)-2-one as the first step with the benzyl reaction being the second step.

However, conducting this synthetic route proves to be challenging due to the poor solubility of methyl-1-C-(β-D-glucopyranosyl)-2-one in benzaldehyde and some product loss being observed in the reaction workup. Furthermore, due to the fact that some benzaldehyde remains upon washing with petroleum ether, the product species does not commonly precipitate in ice water. Even though dimethoxyphenylmethane[15] as a benzylation reagent offers a good yield, its use proves to be less economical. Therefore, in an effort to improve the yield and simplify the reaction workup, the synthetic route was reversed.[16] First, 4,6-O-benzal-glucose was prepared, which was then transformed 1-C-(4,6-O-benzylidene-β-D-glucopyranosyl) acetone via Knoevenagel condensation.[17] The total yield of these two combined steps was found to exceed 55%, considerable more than using the conventional method described previously. After one-time recrystallization in ethanol, the product was obtained in ≥95% purity.

Regioselective Esterification of 1-C-(4,6-O-Benzylidene-β-D-glucopyranosyl) Acetone

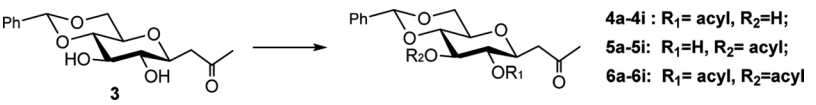
Because of varying steric demands and different electronic effects of each esterification reagent, alkyl chloride and aryl chloride have been selected to be the reagents for this synthetic step (cf. Table 1). Dimethylaminopyridine (DMAP) and 4-chlorobenzoyl chloride in the presence of TEA (triethylamine) were added to a solution of 1-C-(4,6-O-benzylidene-β-D-glucopyranosyl) acetone (**3**) in dichloromethane. The reaction mixture was stirred at room temperature for a total of 6 h, resulting in the formation of 2- and 3-monosubstituted as well as 2,3-disubstituted products at a ratio of 1:9.31:7.24. As shown in Table 1, the product yield for the 3-substituted species increases when the esterification reagents **a** to **e** were used. This latter finding indicates that high steric hindrance is indeed a key factor for the outcome of this synthetic step. The electronic effect has been evaluated by using reagents **e**–**i.** It was found that upon decreasing the electron density on the benzene ring, the product yield for the 3-substituted analog increased accordingly. However, upon using **h** and **i** as esterification reagents, the product yields for both the 3- and the 2,3-substituted derivatives decreased. This latter finding stands in sharp contrast to the results obtained in the presence of reagents **e**–**g**. Otherside, the product yield for the 3-substituted analog was found to be larger than for the 2,3-substituted derivative. The results obtained taken in concert indicate that the use of reactants exhibiting strong electron-withdrawing effects and/or significant steric hindrance may lead to an increase in regioselectivity for the formation of the 3-substituted ester as product.

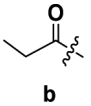
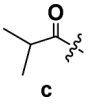
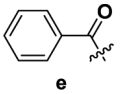
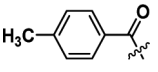
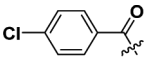
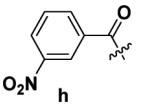
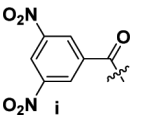
The selection of the right solvent proves to be another crucial parameter in the success of the reactions described. In general, a suitable solvent provides a reaction environment in which raw materials disperse adequately. Good solubility will accelerate the speed of a reaction; however, this feature may be a disadvantage for the regioselectivity of a reaction. Three classic solvents have been selected with varying polarity, namely CH_3CN, tetrahydrofuran (THF), and CH_2Cl_2. Compound **3** proves to be less soluble in CH_2Cl_2 compared to CH_3CN and THF, which ultimately results in a slow reaction process but high selectivity. Consequently, TEA-DMAP was chosen as the catalyst system of choice in the reactions detailed in this report.

Proton Affinity Calculation, Activation Energy Estimation, and Spectroscopic Analysis of the OH- Groups in the Hydrogen-Bond Networks

The regioselectivity effects of the esterification reagents, solvents, temperature, and catalysts have been described. However, compound **3** itself also affects the regioselectivity. The mechanism for the formation of compound **3** in the first step involves the acyl chloride esterification reagent in combination with DMAP, which results in the formation of a carboxylate as counteranion. The interaction of a hydroxyl group with a carbonyl group then generates an unstable adduct. The second step involves the formation of a high-energy intermediate generating the final product after deprotonation and cleavage of the leaving group. Upon inspection of the reaction mechanism, one can see that the key parameters leading to the reaction

Table 1. Regioselectivity of the esterification of secondary 2,3-dihydroxyl groups



Entry	Acyl	Solvent	Cat.	**4** (%)	**5** (%)	**6** (%)[a]	Ratio[b] **4**:**5**:**6**
1	 **a**	DCM	DMAP	32.28	67.72	—	1.00:2.05:0.00
		THF	DMAP	25.68	45.29	29.03	1.00:1.76:1.13
		CH_3CN	DMAP	38.10	55.46	6.43	1.00:1.46:0.17
2	 **b**	DCM	DMAP	32.66	44.99	22.35	1.00:1.38:0.68
3	 **c**	DCM	DMAP	29.77	61.97	8.27	1.00:2.08:0.28
4	 **d**	DCM	DMAP	25.35	71.85	2.80	1.00:2.83:0.12
5	 **e**	DCM	DMAP	9.78	54.55	35.68	1.00:5.58:3.65
6	 **f**	DCM	DMAP	19.31	56.95	23.75	1.00:2.95:1.23
7	 **g**	DCM	DMAP	5.70	53.05	41.24	1.00:9.31:7.24
8	 **h**	DCM	DMAP	17.36	58.33	24.31	1.00:3.36:1.40
9	 **i**	DCM	DMAP	13.50	70.30	16.20	1.00:5.21:1.20

[a]Based on reacted material, 80–98% conversion, counted by chromatography.

[b]Reaction conditions: Compound **3** 1.07 mmol (1 eq); esterification reagent: 1.177 mmol (1.1 eq), DCM 50 mL, TEA 1.77 (1.5 eq), DMAP 6.4‰.

results prove to be proton affinity[18] of each OH group and the activation energy of the two steps.

It has been reported previously that a semiempirical method (PM3) offers a suitable tool for obtaining experimental proton affinities of primary alcohols. In this study, we have adopted the PM6 method[19] to evaluate the proton affinity of each OH group in compound **3**.

Proton affinities[20] have been calculated according to Eq. (1):

$$Proton\ Affinity\ (R-OH) = \Delta H_f(H^+) + \Delta H_f(R-OH) - \Delta H_f\left(R-OH_2^+\right) \quad (1)$$

In this equation, ΔH_f represents the calculated heat of formation. The experimental $\Delta H_f(H^+)$ is found to be 1536 KJ mol^{-1}. The calculated results (PA-2-OH = 1191.95 KJ/mol, PA-3-OH = 1362.58 KJ/mol) show that the 3-OH is more likely be protonated. Furthermore, the relative contribution of activation energy in the two steps needs to be considered as well.[21]

To provide a reasonable representation, we designed a schematic energy diagram for the DMAP-catalyzed esterification step (cf. Fig. 1). The total energy of the 2-substituted product as well as the 3-substituted product was obtained by a DFT method with the Gaussian 03 package at B3LYP/6-31g* level. The results obtained indicate that the 3-substituted product proves to be more stable with its total energy being lower than the 2-substituted product (i.e., $\Delta E_{4g\text{-}5g} = 9.45$ KJ/mol). Moreover, since the pyridinium ion proves to be an excellent leaving group, very little difference between the activation energy of the second step of the 2- and 3-substituted products can be found, i.e., $\Delta E2_2 \approx \Delta E3_2$. Therefore, the rate-determining step for the DMAP-catalyzed esterification of carbohydrates is the first step. According to the synthesis results shown in Table 1, the main reaction product found is the 3-substituted derivative. Therefore, the yield for the 3-substituted intermediate should be greater than the yield for the 2-substituted intermediate. As a result, the activation energy of $E3_1$ proves to be lower than $E2_1$(i.e., $E2_1 > E3_1$).

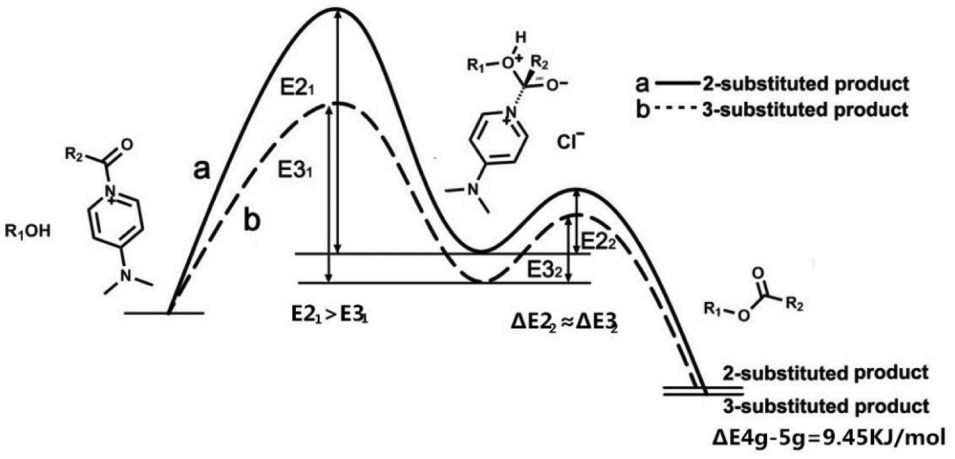


Figure 1. Proposed energy diagram for the DMAP-catalyzed esterification.

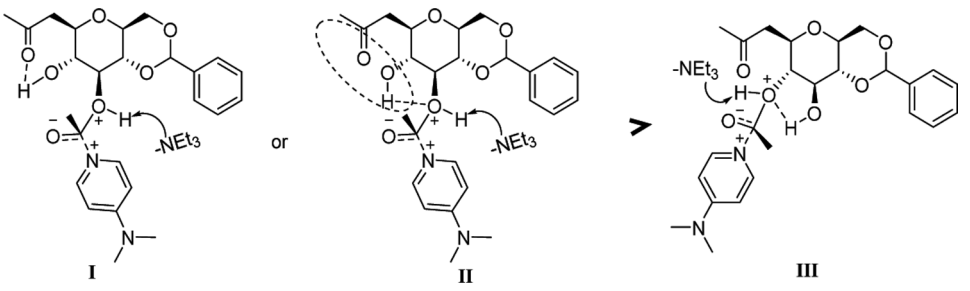


Figure 2. Schematic representation of a delocalized positive charge in hydrogen-bond networks.

Moreover, the hydrogen-bond networks (cf. Figure 2) exhibit further effects on the regioselectivity with the positive charge in the transition state being delocalized. The 2-OH group as a hydrogen donor can interact with the oxygen atom in the 3-OH group as well as the carbonyl oxygen. The 3-OH group as a hydrogen donor, however, can only form a hydrogen-bond network with the 2-OH group. The interactions in these hydrogen-bond networks can be verified by spectroscopic analyses, e.g., via ^{1}H NMR.

In compound **3** the proton shift of the 2-OH is found to be larger than 3-OH, with network **I** being present by comparing the shifts between the 2- and the 3-substituted product. Affected by these networks, the proton shifts of the corresponding hydrogens move to a low field. Compound **3** is able to form a network between the 2-OH and the carbonyl oxygen. Hence, the ^{1}H NMR shift of the proton in 2-OH can be found at low field. After esterification reaction, the 3-substituted product can expose 2-OH and form a hydrogen bond with the carbonyl oxygen, whereas the 2-substituted product can only generate 3-OH, which has little effect on the surrounding hydrogens. As shown in Table 2, the proton in free 2-OH features a larger chemical shift than the proton in free 3-OH. As a result, the first network (**I, II**) proves to be more efficient in the delocalization of the hydroxyl group proton than the second (**III**).

NMR Spectral Analysis of 2- or 3-Substituted Products

Upon comparison of the spectrum of **3** with the spectrum of **6a** (cf. Figure 3), two peaks (i.e., $\delta = 3.40$ and $\delta = 3.76$) were found to disappear in the spectrum of **3** but appear at $\delta = 4.95$ and $\delta = 5.35$ in the spectrum of **6a**. The chemical shifts of H-2 and H-3 were found to move to a lower field, indicating that the two hydroxyl groups

Table 2. Representative chemical shifts of free hydroxyl groups

Compound	δ3-OH	Compound	δ2-OH
3(3-OH)	3.0	**3**(2-OH)	3.1
5a	2.7	**4a**	3.2
5b	2.7	**4b**	3.1
5c	2.9	**4c**	3.1
5e	3.1	**4e**	3.5
5f	3.0	**4f**	3.4
5g	2.7	**4g**	3.4

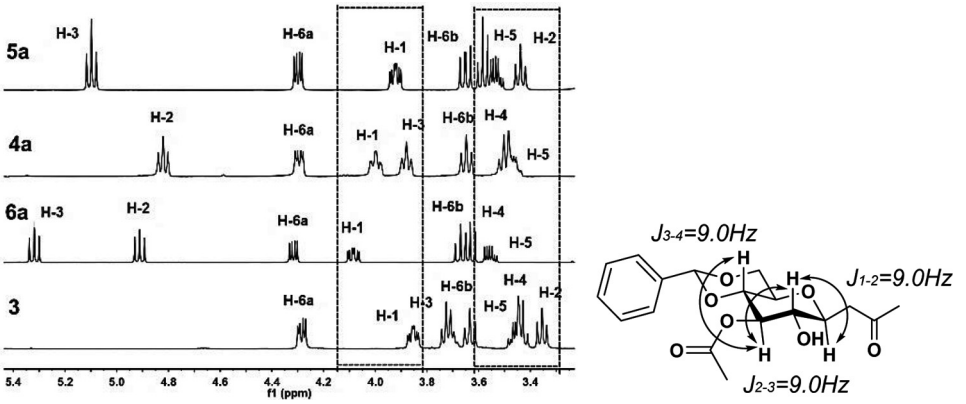


Figure 3. ^{1}H NMR spectra of **3, 4a, 5a**, and **6a** in $CDCl_3$ and a corresponding coupling figure of **5a**.

were fully protected by acetyl groups. From the ^{1}H NMR spectra of **4a** and **5a** (cf. Figure 3), it was found that the individual signals at $\delta = 4.85$ and $\delta = 5.10$ give the same coupling constant, i.e., $J = 9.0$ Hz and triplets. This indicated **4a** or **5a** must be one of the 2- and 3-monosubstituted products. The question of which is which can be determined by using a ^{1}H-^{1}H correlation spectroscopy (COSY) spectrum (cf. Figure 4). As shown in the two-dimensional (2D) spectrum, using **5a** as an example, the upfield coupling correlation between H-1′a and H-1′b ($\delta = 2.68$ and

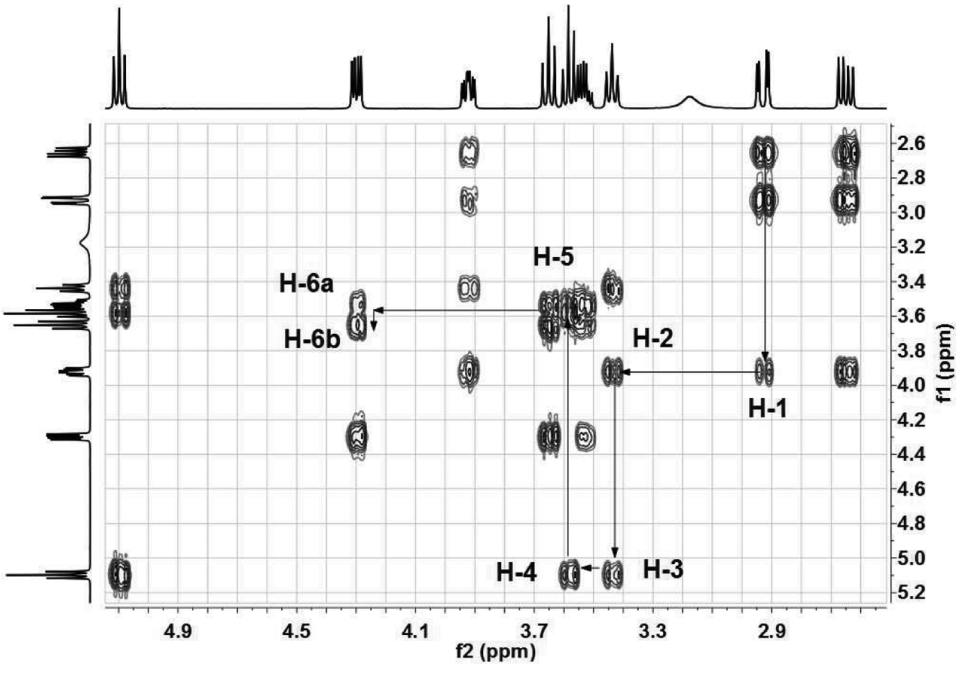


Figure 4. ^{1}H-^{1}H COSY spectra of **5a**.

2.92) can be determined. Similarly, all the correlation of H-1′a,b ($\delta = 2.68$ and 2.92) and H-1 ($\delta = 4.30$), H-1($\delta = 4.30$) and H-2 ($\delta = 3.45$), H-2 ($\delta = 3.45$) and H-3 ($\delta = 5.10$), H-3 ($\delta = 5.10$) and H-4 ($\delta = 3.59$), H-4 ($\delta = 3.59$) and H-5 ($\delta = 3.56$), and H-5 ($\delta = 3.56$) and H-6a,b ($\delta = 3.65$, 4.30) have also been referenced in Fig. 4.

CONCLUSION

To summarize, we systematically demonstrated experiments directed towards the regioselective protection of the two structurally similar secondary 2,3-dihydroxyl groups in 1-C-(4,6-O-benzylidene-β-D-glucopyranosyl) acetone. The results obtained from ^{1}H NMR spectroscopic and molecular computation analysis show that strong electron-withdrawing effects and the steric demand of the esterification reagents provide a general regioselective product trend towards the 3-substituted ester. In addition, the inspection of the activation energy ($E3_1 < E2_1$) offers a simple way to explain the formation of a 3-substituted intermediate. Using TEA-DMAP as a catalytic system may be considered as an attractive alternative to existing methodologies for the regioselective protection of C-glycosides, particularly protection reactions of the 2,3-dihydroxyl groups.

EXPERIMENTAL

All chemicals were analytical pure and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using silica-gel-coated TLC plates. Detection was performed by UV absorption (254 nm) where applicable by spraying with 50% sulfuric acid in ethanol followed by charring at 150 °C. Melting points (mp) were determined on a WRS-1B digital melting-point apparatus (Shanghai Shenguang Instrument Co., Ltd). ^{1}H, ^{13}C, and ^{1}H-^{1}H COSY NMR spectra were recorded on a Bruker-500 (500/125 MHz) spectrometer and Bruker-300 (300/75 MHz). Electrospray ionization–liquid chromatography–mass spectrometry (ESI-LCMS) spectra were obtained on a Shimadzu LCMS-2010EV mass spectrometer.

General Procedure for the DMAP-Catalyzed Esterification

A solution of acid chloride (1.18 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of 1-C-(4,6-O-benzylidene-β-D-glucopyranosyl) acetone **3** (0.33 g, 1.07 mmol), DMAP (6.4 mg), and TEA (0.22 mL, 1.605 mmol) in CH_2Cl_2(50 mL) and stirred at room temperature for 6 h. The resulting mixture was washed first with saturated $NaHCO_3$ solution, further with saturated sodium chloride solution, and finally dried over $MgSO_4$. After filtration, the crude mixture was evaporated to dryness under reduced pressure. The residue was further purified by flash column chromatography (PE/EA, 2:1) to afford the product.

ACKNOWLEDGMENT

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SUPPLEMENTAL MATERIAL

^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY spectra, and molecular computation data for this article can be accessed on the publisher's website.

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