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Regio- and stereochemistry of Michael addition of methanol to Thiele's ester

David E. Minter,[1] William B. Smith,[1]* Alan P. Marchand,[2] Jagan Reddy Etukala[2] and Rasapalli Sivappa[2]

[1]Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129-8860, USA
[2]Department of Chemistry University of North Texas, Denton, Texas 76203-5070, USA

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ABSTRACT: Acid-promoted esterification of Thiele's acid with methanol was found to afford three products. In addition to the expected major product (i.e. the corresponding dimethyl ester, **2a**), two minor products are obtained, one of which, **3**, results from subsequent Michael addition of methanol to the norbornene C═C double bond in **2a**. Analysis of its one- and two-dimensional NMR spectra indicates that this minor product possesses structure **3a** in which the (C-5)—OCH_3 and (C-6)—CO_2CH_3 bonds are *exo* and *endo*, respectively. This conclusion is reinforced by the results of thermodynamics calculations and associated chemical shift calculations. In addition, theoretical analysis of competing transition states for Michael addition of methanol to **2a** suggests that *exo* approach of methanol towards the (C-5)═(C-6) double bond in the substrate is preferred kinetically over the corresponding *endo* reaction pathway.

KEYWORDS: polycyclic aliphatic compounds; Michael reactions; NMR, theoretical studies

INTRODUCTION

A century ago, Thiele reported that carbonation of sodium cyclopentadiene affords a dicyclopentadienedicarboxylic acid, $C_{14}H_{16}O_4$ (**1**, Scheme 1), which subsequently became widely known as 'Thiele's acid'.[1] Esterification of this compound with methanol affords the corresponding dimethyl ester, **2a**, whose structure has been established unequivocally via chemical[2] and spectroscopic[3] methods. In recent years, we have utilized Thiele's acid as a precursor to functionalized pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{5,8}]decanes and related compounds.[4]

Recently, we observed that the formation of **2a** via acid-promoted esterification of **1** is accompanied by the formation of two minor products in low yield. One of these is a monoester, which possesses either structure **2b** or **2c** (Scheme 1). Elucidation of the structure of this compound was not pursued in the present study. The ^{1}H NMR spectrum of the other minor product, **3**, indicates that it contains three OCH_3 groups (δ 3.26, 3.64 and 3.74 ppm), a result which suggests that addition of methanol to one of the two C═C double bonds in **1** and/or **2** may have occurred during esterification. This conclusion is reinforced by the observation that the product, **3**, contains only one vinyl proton absorption (δ 6.63 ppm, area 1H).

It seems likely that the formation of **3** might have proceeded via conjugate addition of methanol to one of the two C═C double bonds in protonated Thiele's ester (i.e. via Michael addition). A related observation has been reported in the esterification of **1** using dimethyl sulfate.[5] However, the proposed product is invalid since the correct structure for Thiele's ester was unknown at the time. Thus, compound **3** possesses either gross structure **3a** or **3b** (Scheme 1), with the stereochemistry of each of the individual C—OCH_3 and C—CO_2CH_3 bonds remaining to be determined in either case.

Here, we describe the results of ^{1}H and ^{13}C NMR studies that permit the assignment of the detailed structure of compound **3** as being **3a** rather than **3b**. Analysis of the NMR spectra of **3a** permits the assignment of the stereochemistry of each of the individual C—OCH_3 and C—CO_2CH_3 bonds to be made. In addition, the mechanism of formation of **3a** from **2a** has been probed by application of quantum chemical calculations, the results of which are described in detail below.

COMPUTATIONAL METHODS

Density functional calculations (B3LYP/6–31G*) were carried out with Gaussian 98.[6] The structures and energies (Table 1) of the possible Michael addition products were calculated with the molecular mechanics MMX

**Correspondence to:* W. B. Smith, Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129-8860, USA.
E-mail: w.b.smith@tcu.edu
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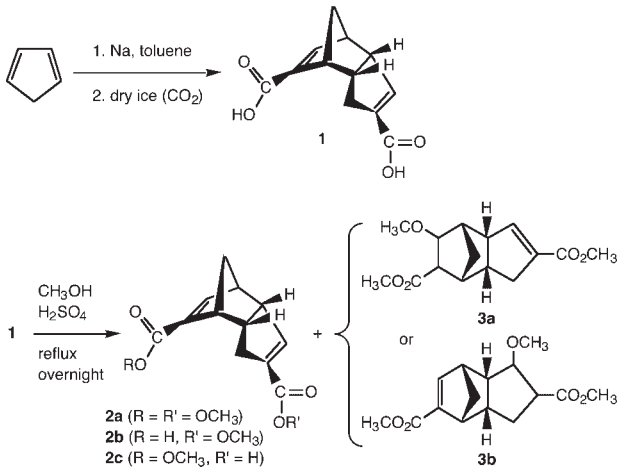


Scheme 1

force field (PCMODEL) (the MMX force field is a modified version of the MM2 force field; Serena Software, Bloomington, IN, USA). Earlier work has established the suitability of this method for geometries adequate for NMR shielding calculations.[7]

In modeling the acid-catalyzed addition of methanol, Thiele's ester was replaced by methyl 2-norbornene carboxylate in the interest of conserving CPU time. At the B3LYP/6–31 G* level, the QST3 method[8] provided satisfactory transition-state structures (TSs) for both the *exo* and *endo* additions to the double bond. In order to avoid contamination of the computational results by basis set superposition error (BSSE),[9] the total energy of the combined reactants approaching one another in the manner shown in **4** (Fig. 1) was optimized. The energy thus determined was 1.9 kcal mol^{-1} (1 kcal = 4.184 kJ) below that of the sum of the individual components.

Furthermore, the calculated C═C and C—CO_2CH_3 bond lengths were found to be the same as the corresponding bond lengths in the isolated cation structure. Since these bond lengths change with the approach of the methanol molecule toward C-5 in the substrate, this result suggests that there is little or no interaction between reactants in the initial reaction geometry depicted as **4** (Fig. 1). Frequency calculations were carried out and the energies for pertinent species were ascertained at 338 K, the boiling-point of methanol. Solvent corrections to the energies were carried out by the polarized continuum model.[10] The solvent dielectric constant was approximated from the values for methanol ($\varepsilon = 32.6$ D) and sulfuric acid ($\varepsilon = 100.0$ D) on the assumption of a linear relationship between ε and the weight fractions of the components. The result was $\varepsilon = 44.0$ D.

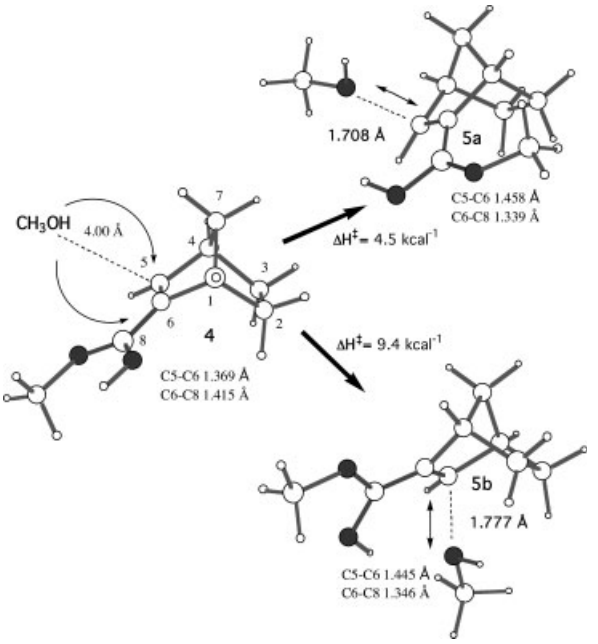
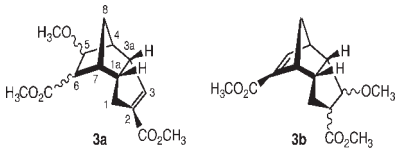


Figure 1. Initial orientation of reactants, methanol and methyl 2-norbornenecarboxylate (4). The transition state formed via *exo* attack of methanol upon the substrate is depicted in **5a**; the corresponding transition state formed via *endo* attack of methanol upon the substrate is depicted in **5b**

Table 1. MMX heats of formation for the eight possible products that potentially can result via Michael addition of methanol to **2a**



Structure	ΔH_f (kcal mol^{-1})	Structure	ΔH_f (kcal mol^{-1})
5-*exo*-6-*exo*-**3a**	−188.1	2-*exo*-3-*exo*-**3b**	−160.7
5-*exo*-6-*endo*-**3a**	−183.3	2-*exo*-3-*endo*-**3b**	−171.5
5-*endo*-6-*exo*-**3a**	−191.0	2-*endo*-3-*exo*-**3b**	−169.6
5-*endo*-6-*endo*-**3a**	−178.7	2-*endo*-3-*endo*-**3b**	−162.6

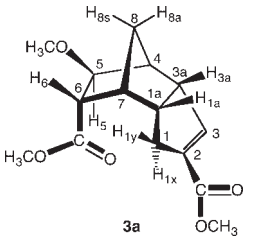
Results of thermodynamic calculations

Michael addition of methanol to Thiele's ester (**2a**) potentially can produce as many as eight β-methoxy ester products. These esters are represented in Table 1 along with their respective MMX-calculated heats of formation (ΔH_f) in kcal mol^{-1}.

By assuming that the acid-catalyzed Michael addition is a reversible process, it is clear from the data in Table 1 that the addition across the C(5)—C(6) double bond leads to the thermodynamically preferred set of isomers. Furthermore, it is evident from these computational results that 5-*endo*-6-*endo*-**3a** can be removed from further consideration, as can the entire **3b** series.

NMR analysis of minor reaction product 3

NMR spectral characterization of **3** (numbering system shown in Scheme 2) begins with a DEPT spectrum to locate the two methylene carbons at δ 30.8 and 40.1. The former is clearly C-1, since the bridging methylene carbons in substituted norbornanes are substantially further downfield.[11] A three-bond correlation between C-1 and the proton at δ 6.63 (H-3) in the HMBC spectrum and the complementary correlation between C-3 at δ 142.4 and the geminal protons at δ 2.28 (H-1x) and 2.42 (H-1y) establish the allylic system in this ring. HMBC correlations for the conjugated carbonyl carbon at δ 165.1 with both H-3 and the methyl protons at δ 3.74 confirm the chemical shifts for the carbomethoxy substituent.



Scheme 2

Analysis of the COSY spectrum allows the assignments of H-3a at δ 3.30 through its vicinal coupling with H-3 and of H-1a at δ 2.70 through its vicinal couplings with H-1x and H-1y. These assignments are supported by HMBC correlations between the carbon at δ 136.4 (C-2) and both H-1a and H-3a. The chemical shifts for C-1a (δ 41.3), C-3a (δ 51.46) and C_2—CO_2CH_3 (δ 51.42) follow from the HMQC spectrum. Comparing the carbon chemical shifts for the cyclopentene ring and the attached carbomethoxy group in **3a** with the corresponding carbon chemical shifts in Thiele's ester[3] reveals an agreement within 2 ppm at every position. Clearly, the attack by methanol occurs at C-5 rather than C-3 of Thiele's ester.

The bridging methylene carbon at δ 40.1 and the attached protons H-8s and H-8a are easily identified using the HMQC spectrum. Three-bond correlations of the proton at δ 1.79 with both C-1a and C-3a (but not C-5 or C-6) identify this absorption as H-8s, as observed previously in the long-range HETCOR spectrum of Thiele's ester.[3] On the same basis, three-bond correlations of the proton at δ 1.46 (H-8a) with the carbons absorbing at δ 80.2 and 53.8 serve to identify C-5 and C-6, respectively, with the former at lower field owing to the deshielding effect of the attached methoxy substituent.

Assignments of H-5 at δ 3.75 and H-6 at δ 2.58 follow from analysis of the HMQC spectrum. HMBC correlations for the non-conjugated carbonyl carbon at δ 172.8 with both H-5 and the methyl protons at δ 3.64 confirm the carbomethoxy group attached at C-6. The ether function attached at C-5 is assigned from the HMBC correlation of H-5 with the methyl carbon at δ 56.1 and the complementary correlation of the methyl protons at δ 3.26 with C-5.

Table 2. Proton and carbon chemical shifts for a 5% (v/v) solution, $CDCl_3$ solvent, in ppm vs internal tetramethylsilane

Proton position	Chemical shift (multiplicity)	Carbon position	Chemical shift
1a	2.70 (ddddd)	1a	41.3
1x	2.28 (dddd)	1	30.8
1y	2.42 (dddd)	2	136.4
3	6.63 (multiplet)	3	142.4
3a	3.30 (multiplet)	3a	51.46
4	2.61 (broad d)	4	44.9
5	3.75 (dd)	5	80.2
6	2.58 (broad t)	6	53.8
7	2.78 (multiplet)	7	43.6
8a	1.46 (dddd)	8	40.1
8s	1.79 (ddd)	C_2—CO_2CH_3	165.1
C_2—CO_2CH_3	3.74 (s)	C_2—CO_2CH_3	51.42
C_6—CO_2CH_3	3.64 (s)	C_6—CO_2CH_3	172.8
C_5—OCH_3	3.26 (s)	C_6—CO_2CH_3	51.56
		C_5—OCH_3	56.1

The only remaining unidentified positions are the bridgehead carbons and protons. These are distinguished by a vicinal coupling between H-1a and the proton at δ 2.78 (H-7) and also a vicinal coupling between H-3a and the proton at δ 2.61 (H-4). The associated carbons absorb at δ 43.6 (C-7) and 44.9 (C-4). The assignments are supported by three-bond HMBC correlations of H-7 with C-5, C-4 and C-3a and of H-4 with C-6, C-7 and C-1a.

Stereochemistry at the C5—C6 bond is evidenced clearly by the presence of 'W-coupling'[12] between H-5 and H-8a and the absence of a 'W-coupling' of H-5 with H-3a. These observations require that H-5 be situated *endo*. Similarly, the *exo* stereochemistry of H-6 is established by its 'W-coupling' with H-1a and the absence of a 'W-coupling' with H-8a. Additional support is provided by the HMBC spectrum, which exhibits a three-bond cross peak for C-8 and H-5 but not for C-8 and H-6. The *trans* relationship between H-5 and H-6 is also evident from the magnitude of the vicinal coupling constant, i.e. 3.4 Hz. Hence the methoxy group at C-5 is *exo* and the carbomethoxy group at C-6 is *endo*. Tables 2 and 3 give a

Table 3. Proton–proton coupling constants

Coupling	$\lvert J\rvert$ (Hz)	Coupling	$\lvert J\rvert$ (Hz)
1a–1x	2.9	3a–4	5.8
1a–1y	10.3	4–8a	1.3
1a–3a	10.3	4–8s	1.6
1a–6	0.9	5–6	3.4
1a–7	4.3	5–8a	1.7
1x–1y	18.3	6–7	4.4
1x–3	1.7	7–8a	1.3
1x–3a	3.5	7–8s	1.6
1y–3	2.6	8a–8s	10.0
1y–3a	2.6		

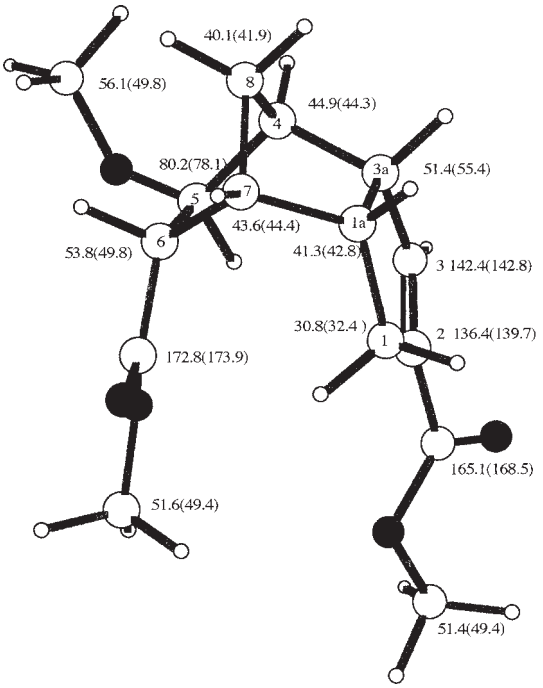


Figure 2. Experimental and (calculated) C-13 chemical shifts for 5-*exo*-6-*endo*-**3a**

summary of the chemical shifts and coupling constants discussed above.

Confirming the above results, the three structures of lowest energy in Table 1 were used to calculate the isotopic magnetic shielding (GIAO method[13]) determined at the BPW91/6–311++G**[8c]//MMX level of theory. The same calculation was carried out for Thiele's ester. The values obtained for Thiele's ester were plotted against the experimental carbon chemical shift values[3] following the procedure of Forsyth and Sebag.[14] Examination of the linear least-squares plot revealed a correlation coefficient of 1.000. Comparison of the calculated carbon chemical shifts for the 5-*exo*-6-*exo*-**3a** and 5-*endo*-6-*exo*-**3a** isomers with the experimental values for the observed reaction product (**3**) gave average deviations of ± 3.7 and ± 2.9 ppm, respectively, and correlation coefficients of 0.9955 and 0.901, respectively. Both plots showed several carbons well removed from the least-squares correlation line. In contrast, the average chemical shift deviation for the 5-*exo*-6-*endo*-**3a** gave a correlation coefficient of 0.9990 and an average deviation of ± 2.0 ppm, confirming the experimental analysis as correct. A comparison of the experimental and calculated chemical shifts is given in Fig. 2.

RESULTS AND DISCUSSION

The starting point for the TS calculations is shown as **4** in Fig. 1; the TS for *exo* attack is given as **5a** and for *endo* attack as **5b**. The sense of the imaginary vibrations is shown as double-headed arrows in Fig. 1 and correspond to the expected bond-making process. The energies for all pertinent structures corrected to the dielectric constant of methanol–sulfuric acid solvent mixture are given in Table 4.

Table 4. B3LYP/6–31G* energies corrected to the solvent dielectric constant and temperature of the solvent

Compound	B3LYP/6–31G* energy (hartree)
Methyl 2-norbornenecarboxylate reactants (**4**, Fig. 1)	−616.474824
Transition state for *exo* approach by methanol (**5a**, Fig. 1)	−616.467647
Transition state for *endo* approach by methanol (**5b**, Fig. 1)	−616.459820
5-*exo*-6-*endo*-**3a** (Michael addition product)	−616.097964

The overall reaction was assumed to form the β-methoxy ester **3**. The calculated activation enthalpies corrected for temperature and solvent effects for the formation of 5-*exo*-6-*endo*-**3a** and 5-*endo*-6-*exo*-**3a** are 4.5 and 9.4 kcal mol^{-1}, respectively. The calculated energy difference, 4.9 kcal mol^{-1}, is consistent with the structure for the product formed via Michael addition of methanol to **2a**, as arrived at by detailed consideration of the NMR spectra of the isolated product (see above).

CONCLUSION

In addition to Thiele's ester (**2a**), acid-promoted esterification of Thiele's acid with methanol has been found to afford a minor reaction product, **3**, which results from subsequent Michael addition of methanol to the norbornene C═C double bond in **2a**. Analysis of the one- and two-dimensional NMR spectra of this minor product suggests that its structure is **3a**, i.e. the isomer in which the (C-5)—OCH_3 and (C-6)—CO_2CO_3 bonds are *exo* and *endo*, respectively. This conclusion receives strong support from the results of ^{13}C chemical shift calculations and also from an evaluation of competing transition states for Michael addition of methanol to methyl 2-norbornencarboxylate.

EXPERIMENTAL

Melting-points are uncorrected. High-resolution mass spectral data reported here were obtained by Professor J. S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin, by using a ZAB-E double-sector high-resolution mass spectrometer (Micromass, Manchester, UK) that was operated in the chemical ionization (CI) mode. Elemental microanalytical data were determined at M-H-W Laboratories, Phoenix, AZ, USA.

Carbonation of sodium cyclopentadienide.[1,15] Sodium sand was prepared by refluxing a suspension of Na (28.0 g, 1.2 mol) in toluene under argon for 1.5 h. The reaction vessel was cooled rapidly to 0 °C via immersion in an ice–water bath. Toluene was decanted under argon and was replaced with dry THF (250 ml). To the reaction vessel maintained at 0 °C was added dropwise with stirring under argon freshly cracked cyclopentadiene[16] (80.0 g, 1.3 mol) over 1 h. After addition of cyclopentadiene had been completed, the external ice–water bath was removed and the reaction mixture was allowed to warm gradually to ambient temperature while stirring overnight. The reaction mixture then was poured rapidly over crushed dry-ice (500 g, 11.3 mol), and the resulting mixture was allowed to stand at ambient temperature for 3 h. The reaction mixture was diluted with water (150 ml) and the resulting mixture was acidified by addition of 6 N H_2SO_4 (180 ml). The precipitated reaction product (crude Thiele's acid)[1,15] was collected by suction filtration and then air-dried. The crude product, a tan solid (65.0 g, 58%), was used as obtained, without additional purification or characterization.

Esterification of the crude reaction product obtained via carbonation of sodium cyclopentadienide. A solution of crude Thiele's acid (20.0 g, 102 mmol), prepared as described above, in MeOH (100 ml) was placed in a 250 ml round-bottomed flask. This solution was heated to 50 °C, then concentrated H_2SO_4 (8 ml) was added dropwise. After the addition of H_2SO_4 had been completed, the resulting mixture was refluxed overnight. The reaction mixture was concentrated *in vacuo*, and the residue was neutralized via careful addition of saturated aqueous $NaHCO_3$ (50 ml). The resulting aqueous suspension was extracted with EtOAc (2 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 25% EtOAc–hexane. Workup of the first chromatographic fraction thereby obtained afforded pure Thiele's ester (**2a**, 8.0 g, 46%) as a colorless microcrystalline solid: m.p. 85 °C (lit.[1b,17] m.p. 85 °C); IR (KBr) 2980 (s), 2953 (s), 2872 (m), 2672 (w), 2573 (w), 1714 (s), 1437 (s), 1277 (s), 1250 (m), 1082 (s), 733 cm^{-1} (s). The ^1H and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra reported previously for Thiele's ester.[3]

Continued elution of the chromatographic column afforded a second fraction. Workup of this fraction afforded **3a** (1.0 g, 4%) as a colorless microcrystalline solid: m.p. 106–107 °C; IR (KBr) 2953 (m), 2361 (w), 1720 (s), 1629 (w), 1437 (m), 1273 (s), 1094 cm^{-1} (s). Proton and ^{13}C NMR data for **3a** are given in Tables 1 and 2. Exact mass (CI HRMS): calcd for $C_{15}H_{20}O_5$, $[M_r+H]^+$ *m/z* 281.1389; found, $[M_r+H]^+$ *m/z* 281.1391.

Continued elution of the chromatographic column afforded a third fraction. Workup of this fraction afforded **2** (i.e. either **2b** or **2c**, 200 mg, 1%) as a colorless microcrystalline solid: m.p. 120–121 °C; IR (KBr) 2980 (m), 2953 (m), 2872 (sh, m), 1714 (vs), 1699 (vs), 1437 (s), 1277 (vs), 1082 (s), 733 cm^{-1} (s); ^1H NMR (CDCl3), δ 1.40 (*AB*, J_{AB} = 11.2 Hz, 1 H), 1.65 (A*B*, J_{AB} = 11.2 Hz, 1 H), 1.90–2.10 (m, 1 H), 2.40–2.60 (m, 1 H), 2.90–3.10 (m, 1 H), 3.10–3.20 (m, 1 H), 3.30–3.40 (br s, 1 H), 3.40–3.60 (m, 1 H), 3.70 (s, 3 H), 6.45–6.55 (m, 1 H), 6.80–6.90 (m, 1 H); ^{13}C NMR ($CDCl_3$), δ 33.1 (t), 41.5 (d), 47.1 (d), 47.8 (d), 51.3 (t), 52.0 (q), 54.9 (d), 138.1 (s), 139.3 (s), 145.8 (d), 147.7 (d), 165.9 (s), 170.3 (s). Exact mass (CI HRMS): calcd for $C_{13}H_{14}O_4$, $[M_r+H]^+$ *m/z* 235.0970; found, $[M_r+H]^+$ *m/z* 235.0968.

NMR spectra. NMR spectra were acquired by using a 5% solution in $CDCl_3$ at 25 °C with a Varian INOVA 400 spectrometer operating at 399.968 MHz for ^1H and 100.581 MHz for ^{13}C. Chemical shifts were referenced to 0.1% internal TMS. In the ^1H NMR experiments, the spectral width was 3200 Hz, number of data points 38 400 with zero-filling to 64 K, acquisition time 6.0 s, relaxation delay 5.0 s and number of transients = 8. In the ^{13}C NMR experiments, the spectral width was 25 000 Hz, number of data points 60 000 with zero-filling to 64 K, acquisition time 1.2 s, relaxation delay 2.0 s and number of transients 10 000. In the COSY experiment, the spectral range was 3200 Hz in both directions, acquisition time 0.32 s, relaxation delay 3.0 s. A total of 533 increments were collected with 32 transients per increment and processed as a 2 K × 2 K matrix. In the HMQC[18] experiment, the spectral ranges were 3200 Hz (^1H axis) and 15 000 Hz (^{13}C axis), acquisition time 0.32 s, relaxation delay 0.9 s. A total of 2 × 373 increments were collected with 16 transients per increment and processed as a 2 K × 2 K matrix. In the gradient HMBC[19] experiment, the spectral ranges were 3200 Hz (^1H axis) and 15 000 (^{13}C axis), acquisition time 0.32 s, relaxation delay 1.4 s. A total of 373 increments were collected with 16 transients per increment and processed as a 2 K × 2 K matrix.

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