Structure of a minor reaction product formed via base promoted hydrolysis of Thiele's ester

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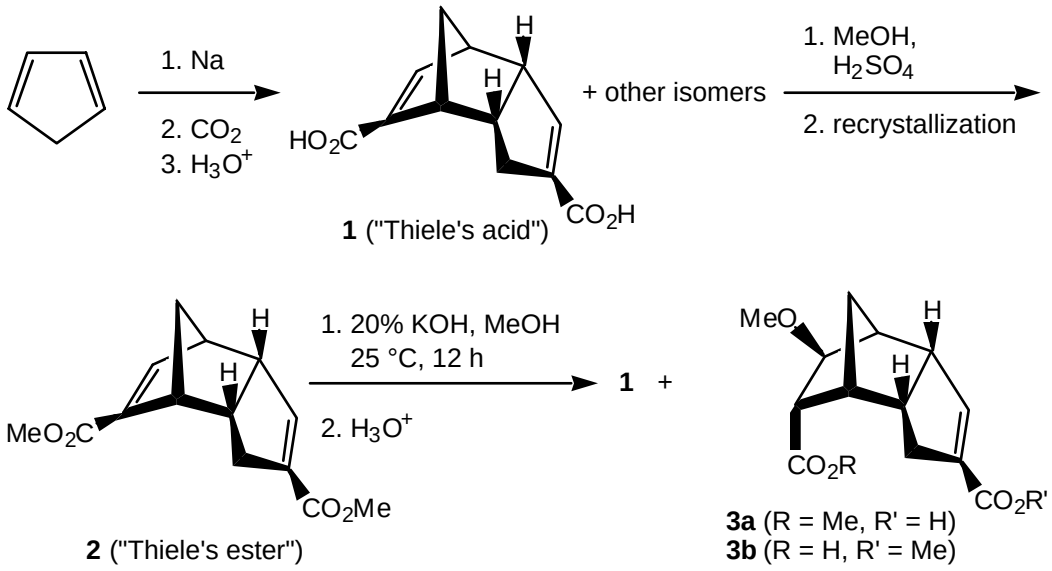
Abstract
Base promoted hydrolysis of dimethyl 3aα,4α,7α,7aα-tetrahydro-4,7-methano-l*H*-indene-2,5-dicarboxylate (i.e., "Thiele's ester", **2**), performed by using KOH-MeOH, afforded after aqueous acidic workup the corresponding diacid (i.e., "Thiele's acid", **1**) along with a minor reaction product, **3**. Compound **3** has been shown to possess structure **3a** via application of single crystal X-ray crystallographic techniques.

Keywords: Michael addition, selective ester hydrolysis, X-ray crystal structure determination

Introduction

Carbonation of sodium cyclopentadienide leads to the formation of 3aα,4α,7α,7aα-tetrahydro-4,7-methano-l*H*-indene-2,6-dicarboxylic acid[1] [i.e., "Thiele's acid", **1**, 60%] along with several isomeric $C_{12}H_{12}O_4$ minor products.[2] Recently, our attention has turned to Thiele's acid as a potentially useful intermediate in the synthesis of unusual polycarbocyclic systems.[2,3]

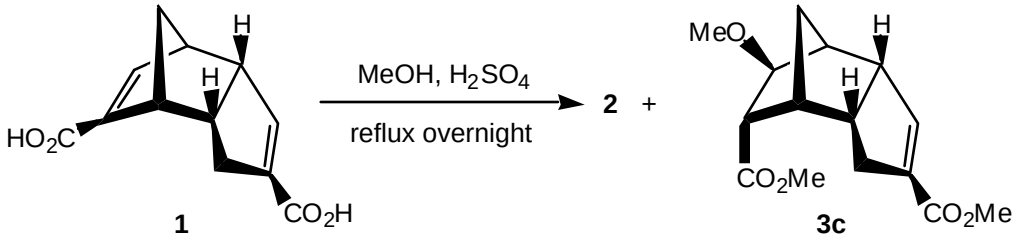
In connection with ongoing research projects, it was necessary for us to prepare isomerically pure Thiele's acid in quantity. To this end, the crude mixture of carboxylic acids obtained via carbonation of sodium cyclopentadienide was esterified by using MeOH-H_2SO_4. Pure Thiele's ester, **2** (Scheme 1), mp 85 °C,[1] could be isolated in good yield via fractional recrystallization of the mixture of esterification products from 10% EtOAc-hexane mixed solvent.



Scheme 1

Subsequently, purified Thiele's ester was subjected to base promoted hydrolysis by using KOH-MeOH followed by aqueous acidic workup. As expected, Thiele's acid was obtained as the major reaction product. Pure Thiele's acid was obtained in an overall yield of 47% via application of the reaction sequence shown in Scheme 1. In addition, this material was accompanied by a second, minor product, **3**, which was obtained in 10% yield. Inspection of the ^{1}H and ^{13}C NMR spectra of **3** suggested that base promoted hydrolysis of **2** might have been accompanied by Michael addition of MeO^{-} to one of the two nonequivalent α,β-unsaturated ester moieties in **2**.

Apropos of the present study, we recently elucidated the structure of a minor reaction product, **3c** (Scheme 2), formed during acid promoted esterification of Thiele's acid.[4] The similarity between ^{1}H and ^{13}C NMR spectra of **3** and **3c** suggested that these two compounds are structurally very similar. However, on the basis of NMR spectral analysis alone, a clear choice could not be made between structures **3a** and **3b** for the minor product, **3**, formed via reaction of **2** with KOH-MeOH. Accordingly, we turned to single crystal X-ray crystallographic analysis to provide unequivocal resolution to this question.



Scheme 2

Results and Discussion

X-Ray crystal structure of the minor reaction product formed via base promoted hydrolysis of 2. A thermal ellipsoid plot of the minor reaction product, **3**, is shown in Figure 1; the corresponding packing diagram, which shows intermolecular interactions, is presented in Figure 2. Therein, it can be seen that the minor reaction product possesses structure **3a** rather than **3b**. Crystal and refinement data for **3a** are presented in Table 1.

As with most carboxylic acids, the molecules form strongly hydrogen bonded dimers, [see Figure 3; therein, O(5)-H(14)···O(4A), O(5)-H(4) = 1.02(4) Å, H(14)···O(4A) = 1.62(4) Å, O(5)···O(4A) = 2.631(4) Å, and O(5)-H(14)···O(4A) = 172(4)^{o}]. The carboxylic acid hydrogen atom was found in the difference map and was refined. The strength of the hydrogen bond is also reflected in the almost equivalent C-O distances [C(14)-O(4) = 1.236(3) Å and C(14)-O(5) = 1.290(3) Å]. The two carboxylic acid groups in the hydrogen bonded dimer are related by a center of symmetry. The cyclopentene ring is planar; in addition, the carboxylic acid group, C(14), and the ester group, C(11) are essentially coplanar (Figure 1).

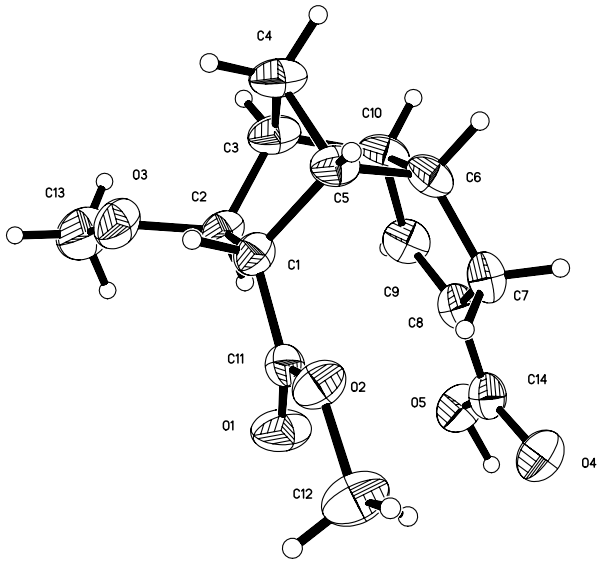


Figure 1. Thermal ellipsoid plot of **3a**.

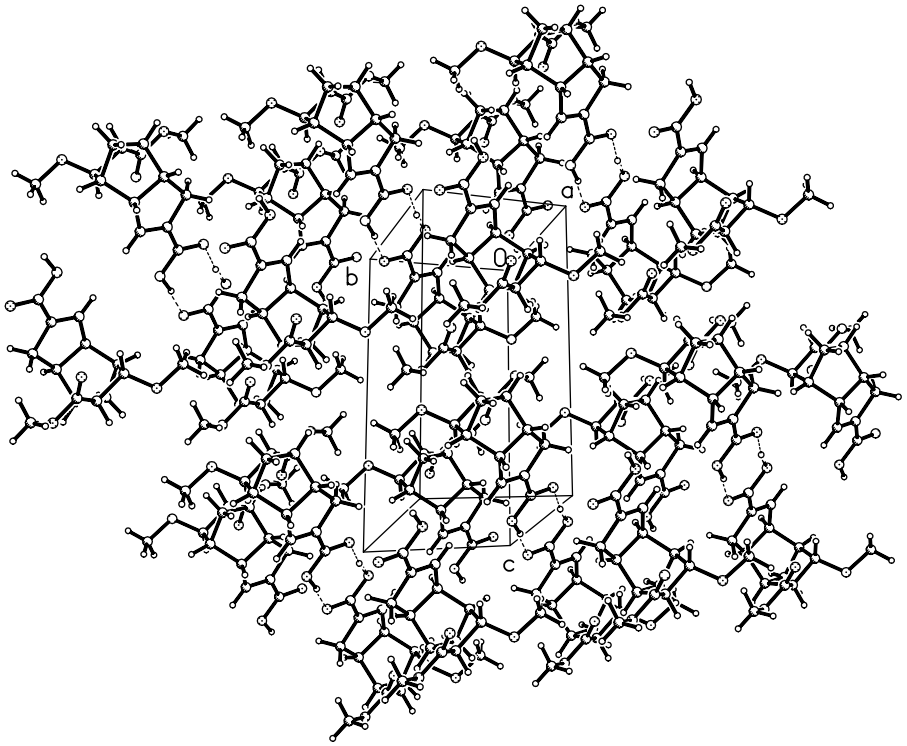


Figure 2. Crystal packing diagram for **3a**.

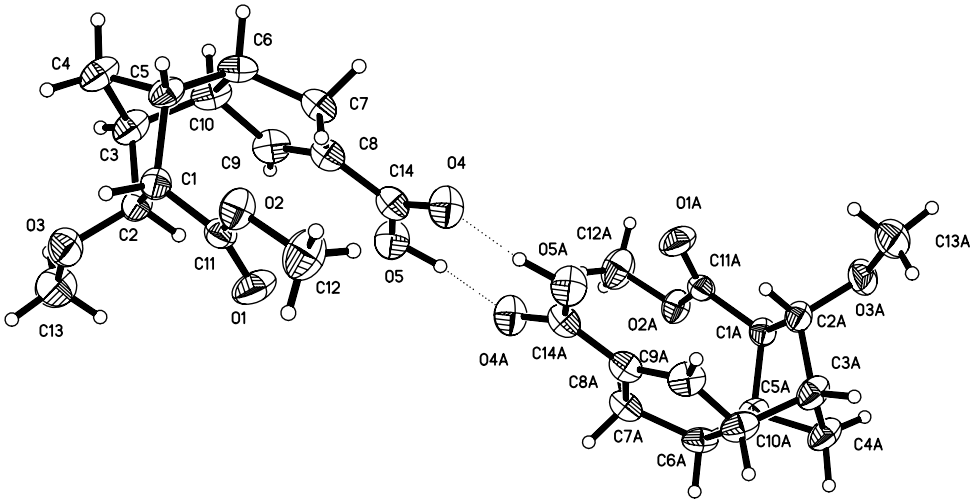


Figure 3. Thermal ellipsoid plot of the hydrogen bonded dimer of **3a**.

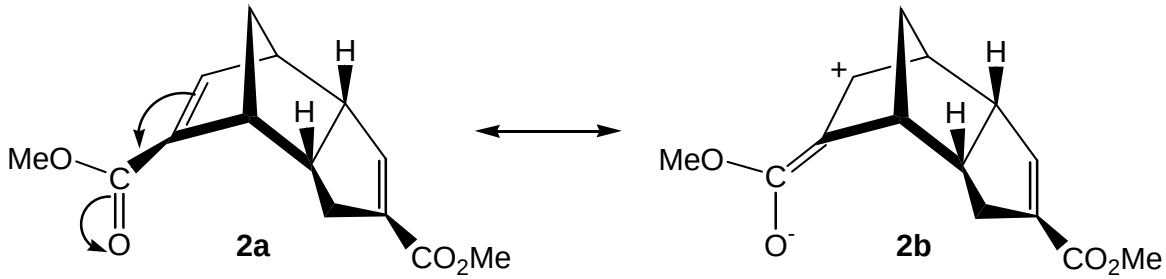
Table 1. Crystal data and structure refinement for **3a**

Empirical formula	$C_{14}H_{18}O_5$	
Formula weight	266.28	
Temperature	300(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.784(7) Å	α= 73.037(16)°.
	b = 8.319(8) Å	β= 86.368(16)°.
	c = 13.237(13) Å	γ = 67.809(15)°.
Volume	660,7(11) $Å^3$	
Z	2	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	284	
Crystal size	0.60 x 0.36 x 0.33 mm^3	
Theta range for data collection	2.76 to 25.00°.	
Index ranges	-8<=h<=8, -9<=k<=9, -15<=l<=15	
Reflections collected	4723	
Independent reflections	2299 [R(int) = 0.128]	
Completeness to theta = 25.00°	99.3 %	
Absorption correction	Empirical	
Max. and min. transmission	0.973 and 0.704	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2299 / 0 / 179	
Goodness-of-fit on F^2	1.095	
Final R indices [I>2sigma(I)]	R1 = 0.0458, wR2 = 0.1326	
R indices (all data)	R1 = 0.0545, wR2 = 0.1409	
Extinction coefficient	0.018(6)	
Largest diff. peak and hole	0.594 and 0.169 e·$Å^{-3}$	

Mechanistic rationalization. Thiele's ester contains two α,β-unsaturated ester moieties, either or both of which might undergo Michael addition by methoxide ion. One of these moieties contains a norbornene C=C double bond, whereas the C=C double bond in the remaining α,β-unsaturated ester moiety resides in a cyclopentene ring. In our hands, Michael addition of MeO^- occurred exclusively at the β-position in the norbornene C=C double bond to afford **3a**. It is likely that relief of additional steric strain present in the norbornene C=C *vis-à-vis* that associated with the cyclopentene C=C provides a driving force for nucleophilic attack at the former position. The fact that attack by MeO^- occurs preferentially via the *exo* face of the norbornene

C=C bond is consistent with earlier observations[5] with regard to the course of conjugate addition of nucleophiles to methyl 2-norborna-2,5-dienecarboxylate.

Furthermore, the additional strain present in the norbornene C=C is expected to destabilize the ground state resonance form, **2a** (Scheme 3), relative to the higher energy, charge-separated canonical form, **2b** (Scheme 3), thereby minimizing norbornene C=C double bond character in the resonance hybrid. This effect is expected to render the carbon atom β- to the C=O group in the norbornene α,β-unsaturated ester moiety more highly electrophilic (due to increased δ^+ charge at the β-carbon atom in the resonance hybrid) than would be the case in the less highly strained α,β-unsaturated ester system situated within the cyclopentene ring in Thiele's ester. As a consequence, the norbornene C=C is rendered more highly reactive toward nucleophilic attack by MeO^-, a conclusion that is consistent with our experimental observations.



Scheme 3

Finally, the somewhat increased importance of the resonance contribution of the charge-separated canonical form in the norbornene α,β-unsaturated ester moiety, i.e., **2b**, is expected to reduce the C=O double bond character in the associated ester group, thereby rendering this CO_2Me group more resistant to base promoted hydrolysis than the corresponding ester group in the cyclopentene α,β-unsaturated ester moiety. The conclusion that the cyclopentene CO_2Me group in Thiele's ester thus is expected to be the more highly susceptible of the two ester functionalities toward base promoted ester hydrolysis is consistent with the experimentally observed preferential formation of **3a**.

Experimental Section

General Procedures. Melting points are uncorrected. High-resolution mass spectral data reported herein were obtained 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, England) that was operated in the chemical ionization mode.

Base promoted hydrolysis of Thiele's ester. A mixture of **2** (9.60 g 38.7 mmol) and 20% aqueous KOH (6.48 g, 116 mmol), in 50% aqueous MeOH (60 mL) was stirred at ambient temperature during 12 h. The reaction mixture was concentrated *in vacuo* to remove excess methanol, and the resulting aqueous suspension was extracted with EtOAc (25 mL). The aqueous layer was acidified by careful, dropwise addition with stirring of 10% aqueous HCl, whereupon a white precipitate formed. The precipitate was isolated by suction filtration and then was air dried to afford **1** (7.43 g, 85%) as a colorless microcrystalline solid: mp 211 °C (lit. mp 212 °C).[1] The IR, ^{1}H NMR, and ^{13}C NMR spectrum of the material thereby obtained were essentially identical with the corresponding published spectral data for authentic **1**.[6]

The filtrate was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOAc, thereby affording pure 5-methoxycarbonyl-6-methoxy-3aβ,4α,5β,6α,7α,7aβ-hexahydro-4,7-methanoindene-2-carboxylic acid (**3a**, 1.0 g, 10%) as a colorless microcrystalline solid: mp 169-170 °C; IR (KBr) 3411 (br, m), 2972 (br, s) 2613 (m), 1737 (vs), 1676 (vs), 1348 (s) 1318 (m), 1277 (m), 1094 (s), 714 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.45 (*A*B, J_{AB} = 11.2 Hz, 1 H), 1.75 (A*B*, J_{AB} = 11.2 Hz, 1 H), 2.14-2.58 (m, 2 H), 2.59-2.89 (m, 4 H), 3.22 (s, 3 H), 3.28 (m, 1 H), 3.63 (s, 3 H) 3.72 (m., 1 H) 6.73 (d, *J* = 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.2 (t), 39.8 (t), 41.2 (d), 43.4 (d), 44.7 (d), 51.4 (d), 51.5 (d), 53.6 (q), 55.8 (q), 80.0 (d) 136.0 (s), 144.7 (d), 169.4 (s), 172.7 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{14}H_{19}O_5$, *m/z* 267.1232. Found (high-resolution chemical ionization mass spectrometry): *m/z* 267.1237.

X-Ray crystal structure of 3a. All X-ray data were collected on a Bruker SMART^{TM} 1000 CCD-based diffractometer. A total of 1,800 frames were collected at 10 sec per frame and integrated via the *SAINT* software package[7] using a narrow frame algorithm. The structure was solved by using the *SHELXTL* program package.[8] The data were analyzed and corrected for absorption by using the *SADABS*[7] program.

Acknowledgments

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Supplementary Information

The X-ray data has been deposited with the Cambridge Crystallographic Data Centre and has been allocated deposition number 220111. A copy may be obtained by writing to CCDC, University Chemistry Laboratory, Lensfeld Road, Cambridge, CB2 1EW, United Kingdom.

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8. *SHELXTL* Version 5.1 Bruker Analytical X-ray Systems, Inc. Copyright 1998.