Resolution of Thiele's Acid

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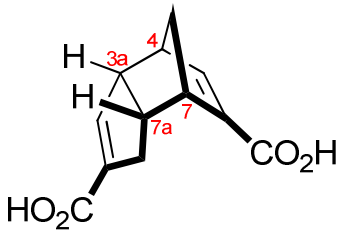
Abstract:



(3a*R*,4*R*,7*S*,7a*R*)

Thiele's acid has been resolved for the first time by diastereomeric salt formation with brucine. Determination of absolute stereochemistry was accomplished by X-ray crystallography of the corresponding diester. We anticipate that access to optically resolved Thiele's acid will stimulate its use in a diverse range of applications requiring chiral molecular clefts.

Keywords:

Thiele's acid, resolution, molecular cleft, X-ray structure, diastereomeric salt formation.

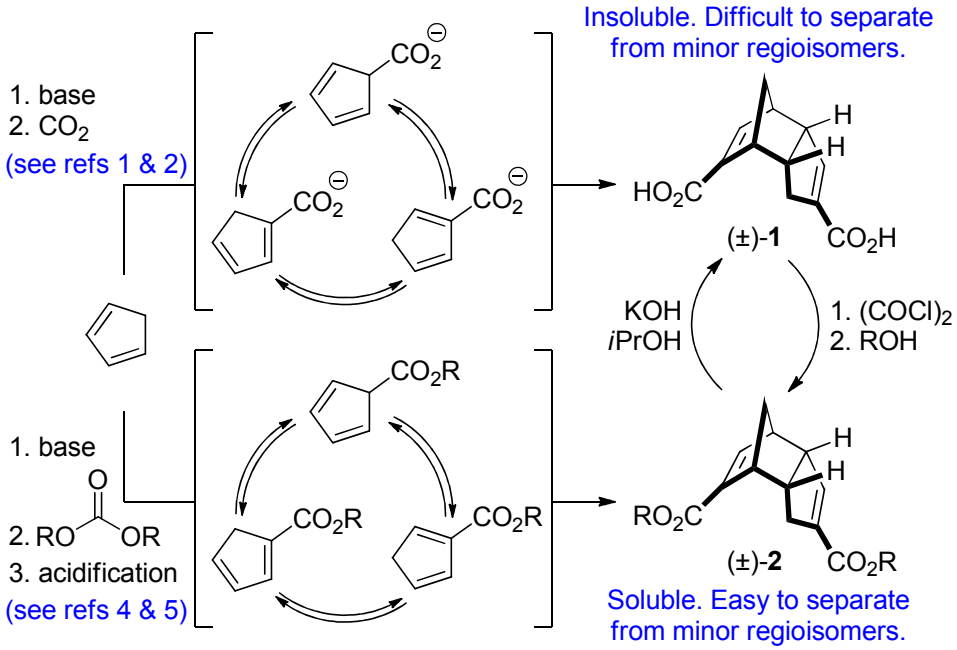
Dedication:

This authors dedicate this article to Professor Reg Mitchell, who first taught the PI how to interpret an NMR spectrum, and to Professor Tom Fyles, who taught undergraduates to properly interpret stereochemistry from Fischer projections by saying: "Just think of Reg Mitchell in his pink bow tie."

Introduction:

Thiele's acid, **1**, is the principal Diels-Alder dimer of cyclopentadiene carboxylate. Its synthesis from metalated cyclopentadiene and carbon dioxide has been known for over a century,[1,2] although applications for **1** have been limited by the fact that the insoluble diacid can be somewhat difficult to purify away from minor regioisomeric co-products.[3]

Out of a desire to broaden the scope of Thiele's acid chemistry, and inspired by an earlier publication from Dive and co-workers,[4] we recently developed an improved preparation of Thiele's esters **2** (Scheme 1).[5] The soluble ester derivative can be isolated as a single regioisomer, on multigram scale, following chromatographic purification. Furthermore, the ability to use a broad range of commercially available carbonates as the electrophile facilitates access to an equally broad range of functionalized Thiele's ester products. When the free acid is desired for use, the ester precursor can be easily hydrolyzed provided that one employs a hindered alcohol solvent to minimize unwanted conjugate additions[6,7] to the strained alkene.[5]



Scheme 1. Synthetic approaches to Thiele's acid and esters.

From a structural perspective, Thiele's acid is a *molecular cleft:* a rigid molecule containing a chemically inert framework that projects functionality outward from its central core at a well-controlled angle.[8] In this regard, **1** may be compared to the widely studied compound Tröger's base (Figure 1A),[9,10,11] and should be similarly useful for a broad range of applications in supramolecular, biological and materials chemistry.

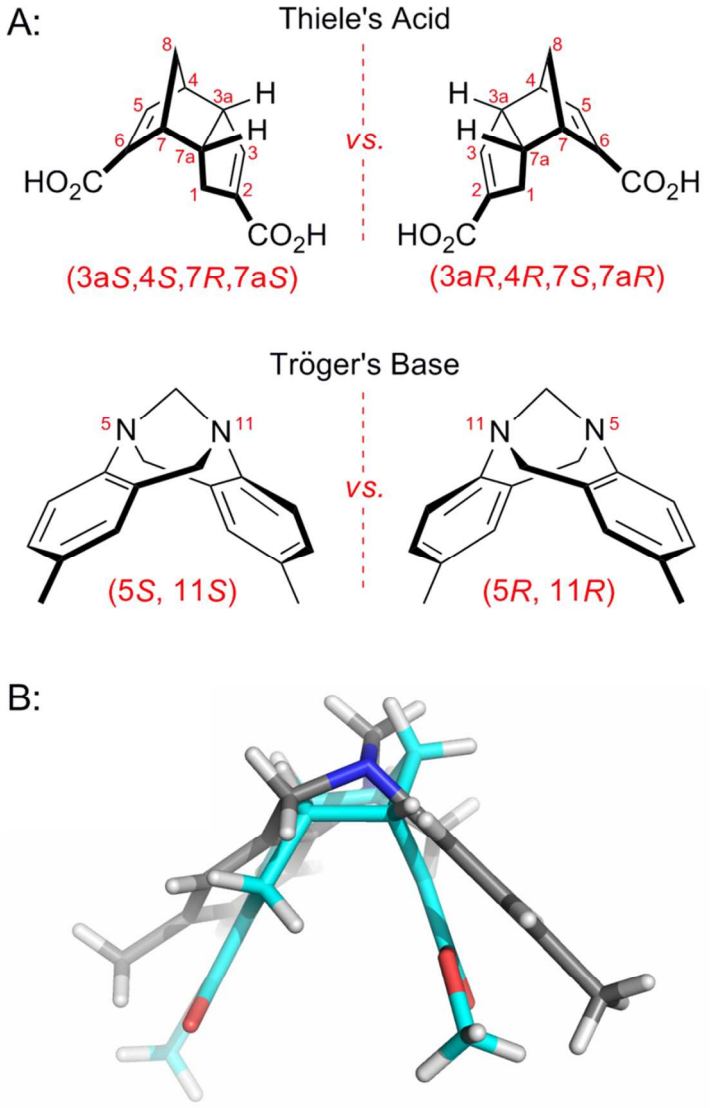


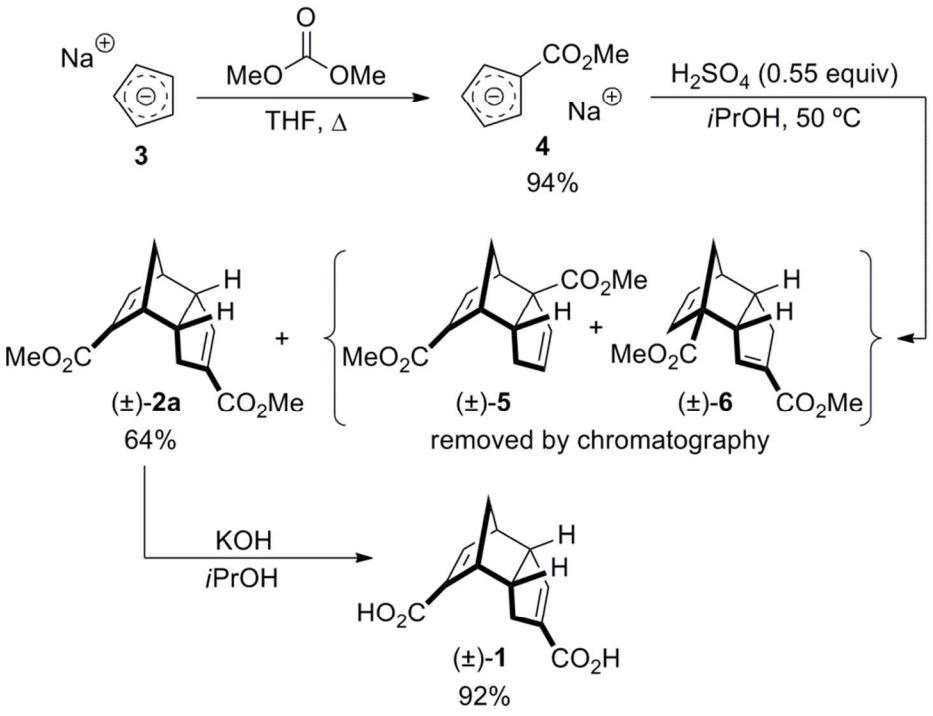
Figure 1. Comparison of Thiele's acid to Tröger's base. **A:** Structures and stereochemical assignment for each compound. **B:** Overlay of Tröger's base (gray) and Thiele's acid methyl ester (cyan), revealing a narrower cleft angle for the latter compound.

In fact, Thiele's acid supports a considerably narrower cleft angle than does Tröger's base (Figure 1B), which may make it complementary for applications that require modified projection vectors. Moreover, previous work from our lab resulted in a suite of "Thiele-like" scaffolds that have a range of cleft angles spanning from Thiele's acid itself all the way to 180° reverse turns that could potentially be used in the design of β-hairpin mimics.[5]

Naturally, many applications that could be envisioned for these molecular clefts (particulary for biological chemistry) would require enantiopure material. But while racemic Tröger's base (and analogues thereof) has been successfully resolved into its constituent enantiomers using several different methods,[12,13,14,15,16,17,18,19] the resolution of Thiele's acid has never been reported. We sought to remedy this deficiency by developing a resolution of **1** via diastereomeric salt formation, and report here the results of our studies.

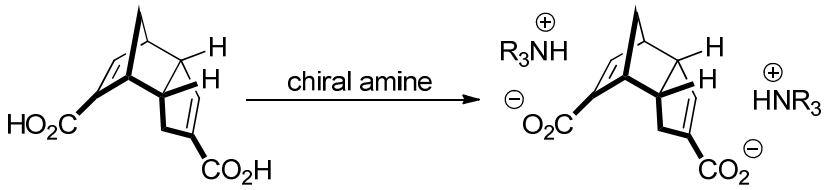
Results and Discussion:

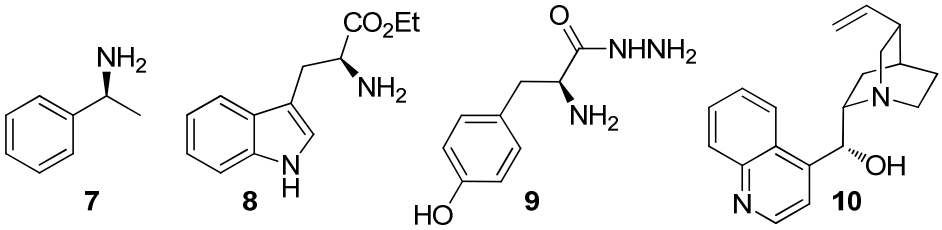
Pure racemic Thiele's acid was prepared using our previously developed methodology (Scheme 2).[5] With (±)-**1** in hand, we began attempts to form a crystaline diastereomeric salt, using a variety of chrial amines. As illustrated in Chart 1, (*S*)-(–)-methylbenzylamine (**7**), L-tryptophan ethyl ester (**8**), L-tyrosine hydrazide (**9**), and (–)-cinchonidine (**10**) all failed to produce diastereomerically enriched crystals, despite our evaluating a range of crystallization solvents. Fortunately, however, the bis-brucine salt of **1** formed readily and could be at least partially enriched by crystallization from alcoholic solvents. Methanol proved superior to ethanol and isopropanol for this purpose.



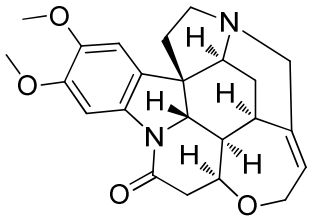
Scheme 2. Synthesis of racemic Thiele's acid.

Chart 1. Formation of Diastereomeric Salts from Thiele's Acid.





No selectivity in a wide range of solvents:
EtOH, acetone, water, EtOAc, iPrOH, MeOH



crystalization solvent	dr
ethanol	–[a]
isopropanol	1.5 : 1
methanol	3.6 : 1
methanol[b]	>18 : 1

[a] No crystals were observed from ethanol.
[b] After three successive recrystallizations from methanol.

Measurement by NMR methods of the diastereomeric ratio in the crystallized salt formed from **1** and brucine (**11**) was more challenging than expected. After evaluating several different unary and binary solvent combinations, we eventually found that an 8.3:1 mixture of benzene-d_6 and $CDCl_3$ provided sufficient resolution of the H-5 proton on the Thiele acid scaffold to permit accurate integration (Figure 2). Using this method, we determined that the solid **1**•**11**$_2$ salt precipitated from methanol had a diastereomeric ratio (dr) of approximately 3.6:1. Three further recrystallizations from methanol improved the dr to >18:1. Starting from 1.1 g of racemic acid (5

mmol), we were thereby able to obtain a respectable yield of 1.9 g (37%) diastereomerically pure salt.

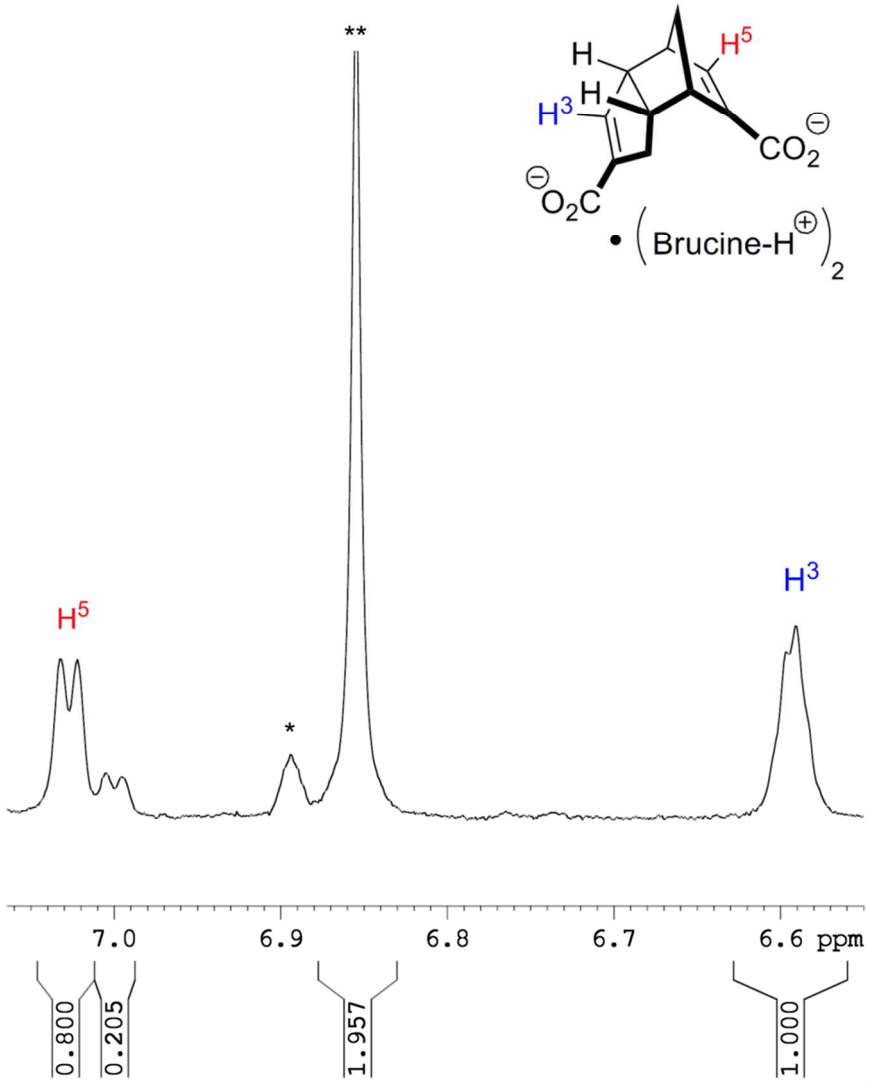
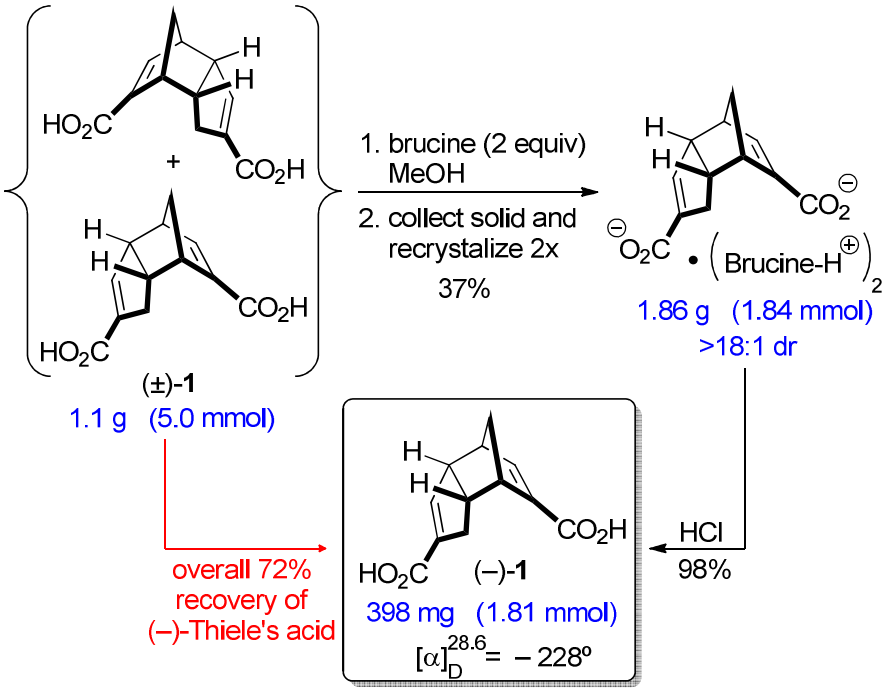


Figure 2. ^{1}H NMR spectrum of the bis-brucine salt of **1** after the first recrystalization from methanol, recorded in 8.3:1 C_6D_6:$CDCl_3$. Signals corresponding to the two vinyl C-H protons are labeled. The peaks indicated by the single and double asterisks correspond to a ^{13}C satellite from benzene and an aromatic C-H from brucine, respectively.

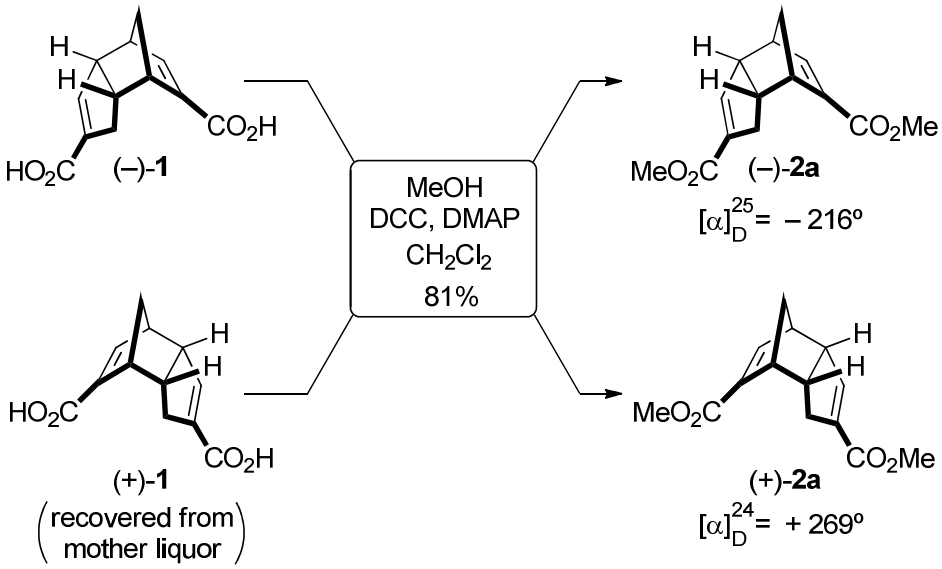
The purified salt was acidified to remove the brucine, and the desired diacid was extracted into ethyl acetate. The organic solution was dried and evaporated, affording a near-quantitative recovery of (–)-**1** (Scheme 3). The overall yield of (–)-Thiele's acid from the initial racemic mixture was 72%.



Scheme 3. Resolution of Thiele's acid.

Attempts to determine *which* enantiomer of **1** had been produced (either using X-ray crystallography or VCD/ECD) were thwarted by the poor solubility of the compound. We were aware, however, of a prior report describing an X-ray structure of the racemic methyl ester derivative.[20] Hypothesizing that we could likewise obtain an X-ray quality crystal of the ester as a means of solving its absolute stereochemistry, we converted (–)-**1** to (–)-**2a** (Scheme 4). Gratifyingly, crystals produced from (–)-**2a** diffracted well, and high quality X-ray dffraction

data were obtained. A copper microfocus source was used in order to reliably determine the absolute stereochemistry despite the absence of heavy atoms in the crystal.



Scheme 4. Esterification of resolved Thiele's acids.

Because (–)-**2a** crystallized in a chiral space group, Flack *x* and Hooft *y* parameters [0.04(8) and 0.03(7), respectively] were obtained for the structure, confirming the correct absolute stereochemistry to be that shown in Figure 3.[21] These data thus allowed us to unambiguously assign the structure of (–)-**2a** and (–)-**1** as (3a*R*,4*R*,7*S*,7a*R*).[22,23]

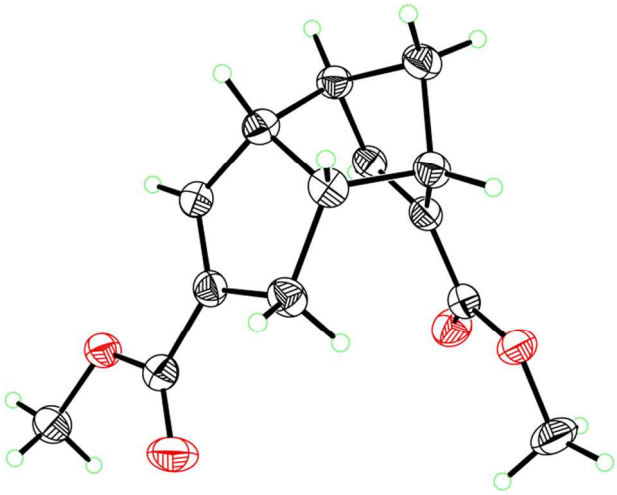


Figure 3. X-ray structure for **(–)-2a**. Thermal elipsoids are shown at 50% probability.

To demonstrate access to the opposite enantiomeric series, the mother liquor containing the bis-brucine salt of (+)-**1** was concentrated to a brown oil. This was acidified to provide the crude free acid, which was then subjected to identical esterification conditions to those employed above. Ester (+)-**2a** was thereby obtained without incident. The spectra for (–)-**2a** and (+)-**2a** were identical, and the magnitudes of their optical rotations were equal within experimental error (Scheme 4).

Conclusions:

In summary, we have achieved the optical resolution of Thiele's acid for the first time, and have correlated the absolute stereochemistry for each enantiomer to the sign of the optical rotation. We hope and anticipate that the availability of these new chiral building blocks will stimulate their use by other research groups.

Experimental:

All reactions were performed in single-neck, flame-dried, round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Liquid reagents were transferred via glass microsyringe. Solvents were transferred via syringe with a stainless steel needle. Organic solutions were concentrated at 40 °C by rotary evaporation under vacuum. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with silica gel (0.20 mm, 60 Å pore-size, 230-400 mesh, Macherey-Nagel) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Flash-column chromatography was performed over silica gel 60 (63-200 μM, Caledon). Commercial solvents and reagents were used as received, except that dichloromethane was dried before use by passage through alumina in a commercial solvent purification system (SPS).

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz and 500 MHz at ambient temperature. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane, and are referenced to residual protium in the NMR solvent. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 75 MHz at ambient temperature. Carbon chemical shifts are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent. Melting points were obtained using a Mel-Temp II apparatus, and are uncorrected.

General Procedure for the Preparation of Racemic Thiele's Ester.[5] A flame-dried round bottomed flask fitted with an oven-dried condensor was charged with sodium cyclopentadienylide solution (Sigma-Aldrich cat. no. 304026, 2 M in THF, 1.0 equiv). To this solution was added dimethyl carbonate in THF, at room temperature with stirring. The reaction

mixture was heated to reflux for six h, then cooled to room temperature and concentrated *in vacuo*. The resulting solid was suspended in ether and collected by vacuum filtration. The collected solid was washed with ether until the washings became colorless and then dried *in vacuo* to give intermediate salt (**4**) as a tan-brown air sensitive solid. In a separate step, the partially-purified salt (1 equiv) was added to a fresh round bottomed flask, where it was combined with *i*PrOH (to 0.33 M) and sulfuric acid (0.55 equiv) at room temperature with stirring. Acidification was marked by a brown to orange color change. The solution was heated to 50 °C overnight. The reaction mixture was concentrated *in vacuo* and the resulting oil was dissolved in toluene, and loaded onto a silica gel column. Elution with hexanes-ethyl acetate provided the desired Thiele's ester, (±)-**2a**. Spectral data were identical to those reported previously,[5] while yields were consistently in the range of 60–65%.

General Procedure for the Preparation of Racemic Thiele's Acid.[5] To a solution of Thiele's ester in *i*PrOH was added 10% KOH solution (10 mL / g of Thiele's ester) dropwise. After 5 h, *i*PrOH was removed *in vacuo*. The mixture was acidified to pH=1 by the addition of 2M HCl, then extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford Thiele's acid, (±)-**1**, as a white powder without further purification. Spectral data were identical to those reported previously,[5] while yields were consistently >90%.

Resolution of Thiele's acid. A 100 mL round bottomed flask was charged with racemic Thiele's acid (**1**, 1.10 g, 5.00 mmol) and methanol (20 mL). The suspension was warmed to 80 °C to provide a clear solution. To this hot solution was added brucine (**11**, 3.94 g, 10.0 mmol).

An additional 10 mL of methanol was added to facilitate complete dissolution. The resulting solution was filtered to remove a small amount of residual insolubles, and then cooled in a freezer at 0 °C. Brown crystals of crude **1•11**$_2$ were formed within 2 h. NMR analysis of the crude salt revealed a ~3.6:1 ratio of diastereomers. This ratio varied only slightly across multiple trials. The crude salt was filtered from the mother liquor, added to 25 mL of methanol, and warmed until all of the solid dissolved. The solution was then cooled in the freezer. Crystals of purified **1•11**$_2$ were formed within 2 h. This recrystallization was repeated twice more, and the final, thrice recrystallized solid was obtained by suction filtration to provide 1.86 g (1.84 mmol, 37%) of **1•11**$_2$ as a pale brown solid after drying *in vacuo*. MP = 147 °C (dec).

^{1}H NMR (500 MHz, $CDCl_3$: C_6D_6 = 1:8.3) δ 8.22 (s, 2H), 7.07 (d, *J* = 2.9 Hz, 0.95H, **Major**), 7.02 (d, *J* = 2.9 Hz, 0.05H, **Minor**), 6.90 (s, 2H), 6.63 (s, 1H), 5.40 (s, 2H), 4.16 (s, 2H), 3.74 (dd, *J* = 14.0, 7.1 Hz, 2H), 3.69 (d, *J* = 14.4, 2H), 3.58-3.64 (m, 8H), 3.53-3.57 (m, 8H), 3.47 (dd, *J* = 13.5, 6.0 Hz, 2H), 3.12-3.22 (m, 3H), 3.01-3.09 (m, 2H), 2.81 (s, 1H), 2.66-2.77 (m, 3H), 2.61 (dd, *J* = 17.5, 2.2 Hz, 2H), 2.35-2.46 (m, 4H), 2.32 (s, 2H), 2.09 (d, *J* = 14.7 Hz, 2H), 1.89 (dt, *J* = 13.0, 7.9 Hz, 2H), 1.60 (d, *J* = 8.1 Hz, 1H), 1.42 (dd, *J* = 12.8, 5.9 Hz, 2H), 1.10 (d, *J* = 8.4 Hz, 1H), 0.97 (d, *J* = 14.4 Hz, 2H), 0.49 (d, *J* = 10.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$:C_6D_6 = 1:8.3) δ 171.3, 169.9, 168.7, 150.8, 147.3, 144.6, 142.4, 141.4, 137.9, 136.9, 130.3, 122.3, 107.3, 101.9, 77.7, 64.2, 60.1, 59.9, 54.6, 52.2, 52.1, 50.4, 50.3, 48.9, 47.7, 47.6, 42.6, 41.8, 41.6, 34.1, 31.1, 26.0; IR (cm^{-1}, film) 3400, 2939, 1641, 1602, 1555, 1501, 1448, 1398, 1198, 987, 847; HRMS (ESI) calcd for [**1•11**+H]$^+$ $C_{35}H_{39}N_2O_8$ 615.2706, found 615.2702.

The isolated salt was added to 30 mL of 10% aqueous HCl, and extracted with 60 mL of ethyl acetate three times. The combined organic layers were dried over $MgSO_4$. After removal of the solvent *in vacuo*, (–)-Thiele's acid was isolated as a light brown solid (398 mg, 1.81 mmol, 98% from the intermediate salt; 72% recovery of (–)-**1** from the initial racemic mixture). Spectral data were consistent with the racemic compound that has been described previously in the literature.[5] $[\alpha]_D^{28.6}$ = –228 deg mL dm^{-1} g^{-1} (c = 0.25, 1 M KOH solution). MP = 180–182 °C.

Esterification of Optically Active Thiele's acids. To a solution of (–)-**1** (220 mg; 1.00 mmol) in CH_2Cl_2 (20 mL) was added DMAP (24 mg, 0.2 mmol) and MeOH (0.4 mL, 10 mmol). DCC (460 mg, 2.2 mmol) was then added at 0 °C. The mixture was allowed to warm to room temperature, and was stirred overnight. The next day, the product mixture was washed with 1M HCl and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (hexanes-ethyl acetate, 4:1) afforded (–)-Thiele's ester **2a** as a white solid (200 mg, 81%). Spectral data were consistent with the racemic compound that has been described previously in the literature.[5] $[\alpha]_D^{25}$ = –216 deg mL dm^{-1} g^{-1} (c = 0.25, ethanol solution). MP = 87–89 °C.

(+)-Thiele's ester **2a** was prepared by the same procedure, beginning from crude (+)-**1** recovered from the crystalization mother liquor. Spectral data were identical, but a lower melting point (51–53 °C) was attributed to the presence of minor impurities. $[\alpha]_D^{24}$ = +269 deg mL dm^{-1} g^{-1} (c = 0.25, ethanol solution).

Supplementary Material:

Supplementary material is available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/xx.xxxx/cjc-2016-xxxx. These data include NMR spectra for both Thiele's acid and the corresponding brucine salt, as well as X-ray data for (–)-**2a**.[21]

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