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The Structural Determination, Total Synthesis and Endochronicity of Thiotimoline

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Abstract: The natural product thiotimoline was isolated from the bark of *Rosaceae Karlsbadensis rufo* and its structure was unambiguously determined by time-resolved X-ray crystallomancy and spectroscopy. A total synthesis of thiotimoline was conducted following a convergent strategy. The pivotal transformations in this synthesis were a tandem Suzuki-Miyaura/Schinkenfaust radical cross-spifflication, a Szymankowszczyzna allylic inquisition and a [3+2+3+2] Puccini-Gershwin echocyclisation in Aƅ major. An unnatural isomer of thiotimoline was also synthesised, and a theory of kairality and chronomers is presented and discussed.

Thiotimoline (**1**) was discovered in 1930 by researchers cataloguing the phytochemicals of the *Rosaceae* genus.[1] The molecule went largely unremarked for almost two decades until Isaac Asimov and co-workers reported peculiarities in its solubility profile.[2] Specifically, it was observed that when thiotimoline was combined with water, it dissolved up to 1.1 seconds *before* the water was added. This remarkable property was termed "endochronicity" by Asimov, who developed an instrument (the endochronometer) to quantify this effect. He went on to conduct multiple studies on thiotimoline and its applications in chemistry, psychology and meteorology.[3–5]

Asimov conducted his exploratory studies in the late 1940's, when the spectroscopic sciences had not attained their present heights of sophistication. Thus, the minutiae of thiotimoline's chemical structure were unknown to him. By probing the physical and reactive properties of thiotimoline, Asimov was able to deduce the presence of "at least 14 hydroxy groups, two amino groups and a sulphonic acid" as well as a potential nitro group.[6] In 1949, the Tinúviel lab tentatively assigned a structure (Fig. 1A, **2**) to thiotimoline on the basis of IR spectroscopy (Fig. 1B).[7] This assignment was disputed both at the time and since, and the authors themselves remarked that "the quality of our data leaves much to be desired".

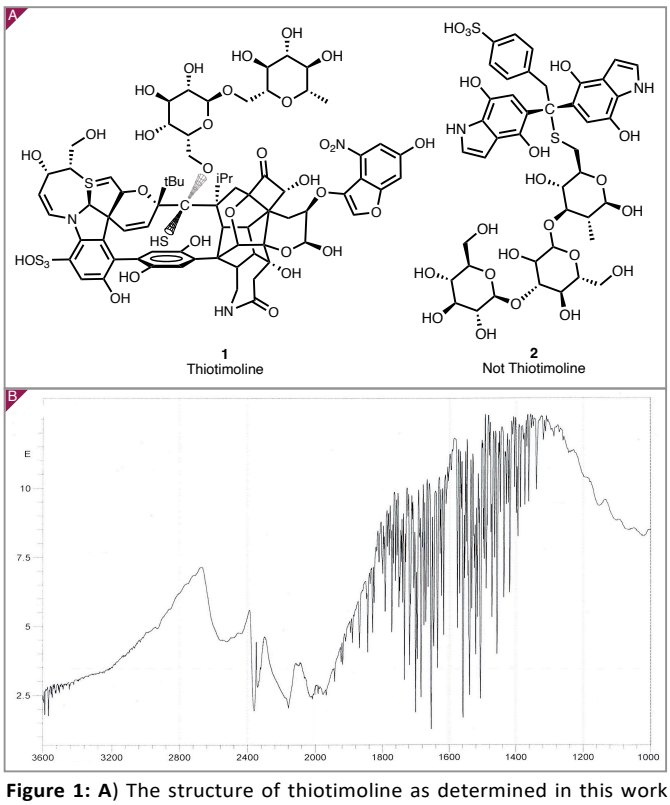
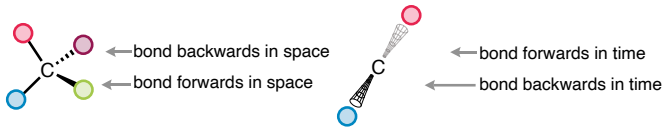


Figure 1: A) The structure of thiotimoline as determined in this work (**1**), and the incorrect structure proposed by Tinúviel in 1949. **B**) The IR data used by Tinúviel to assign the structure of **2**.

Despite the obscurity surrounding the intricacies of thiotimoline's structure, Asimov was able to formulate a theory to rationalise its endochronicity. He proposed that at least one carbon within thiotimoline was subject to such profound steric hinderance that two of its bonds were forced into the temporal plane.[4] Such a chronomeric carbon would, he believed, possess a pair of bonds within the spatial dimensions, one bond pointing into the future, and another pointing into the past. As no convention exists to depict such chronospatial bonds, we have taken the liberty of defining one:



Research on thiotimoline has languished since 1960, at least in part because the relevant material has become difficult to obtain. Asimov's original report stated "Since no method of laboratory synthesis of the substance has been devised, it may be practically obtained only through tedious isolation from its natural source, the bark of the shrub *Rosaceae Karlsbadensis rufo*".[3] This plant (Fig. 2) is native to alpine valleys surrounding the West Failian town of Karlsbaden, but its populations have diminished drastically since the 1940's. This decline has been attributed to climatic disturbances, habitat loss and foliar pathogens, and surviving enclaves of *K. rufo* are rigorously protected. Multiple kilograms of bark are required for the extraction of thiotimoline in useful quantities, the collection of which is typically lethal to the plant in question. *K. rufo* has resisted cultivation outside of its native environs, further detracting from its sustainability as a source of thiotimoline.

We have assessed that meaningful progress in the field of chronochemistry requires both the full structural characterisation of thiotimoline, and a practical synthesis thereof. Our research group has a long-standing interest in the synthesis and isolation of supernatural products, so it is to these tasks that we have addressed ourselves in this miscommunication.[8a-d]

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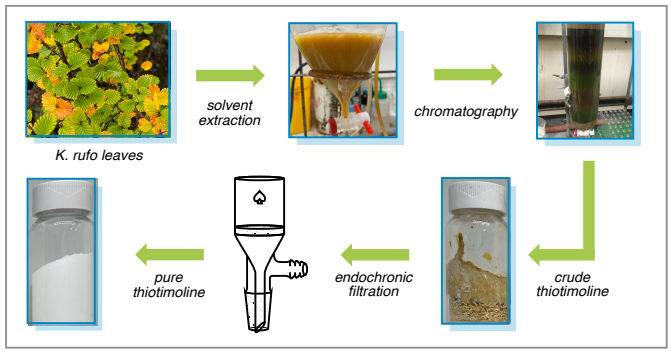
Figure 2: A scientific illustration of *Rosaceae Karlsbadensis rufo.* Karlsbadensis refers to the West Failian town of Karlsbaden, near which the plant was first documented. The species name is a tribute to Rufus Bruce Brown, the Australian botanist who discovered it.

Experiments and Results

Logically, it was deemed essential to determine the structure of thiotimoline before attempting to synthesise it. The reverse scenario has rarely been met with success (for example, consider Henry Perkin's failed syntheses of quinine). To obtain an authentic sample of **1**, we conducted an isolation of thiotimoline from 80 kg of *K. rufo* leaves. Though the compound is less abundant in the leaves than in the bark, the former may be collected in bulk without drastic detriment to the plant.

Asimov's description proved accurate, for the extraction is indeed a tedious process. The leaves were dried, macerated, and extracted with ethyl acetate/H_2O, a process that produced fearsome emulsions (Scheme 1). The extract was exhaustively chromatographed on silica to give crude thiotimoline, which was further purified by the technique of endochronic filtration, as described by Asimov.[4]



Scheme 1: Protocol for the extraction of thiotimoline (**1**) from the leaves of *K. rufo*.

We analysed our extracted thiotimoline by endochronometry and obtained a time-of-solution (T_s) of -1.10 seconds, a comparable measurement to those disclosed in Asimov's original report. It should be noted that all organic trace impurities must be removed from the water used to conduct endochronometry. This can be accomplished by refluxing the water with Caro's acid, followed by distillation. With the purity of our sample thus established, we subjected it to a range of modern analytical techniques.

The endochronicity of thiotimoline is readily apparent under spectroscopic conditions. We first observed this effect when we attempted to record NMR spectra of our extract. After some initially confusing spectra were obtained, we examined the relevant free induction decay (FID) data and noticed a peculiarity. Figure 3A displays the ^{1}H FID we obtained after a single 90˚ excitation of **1**. As expected, the 90˚ pulse prompts an immediate decay curve lasting several milliseconds. The peculiar element is a second excitation-decay sequence which occurs 1.12 seconds *before* the pulse, and a third 1.12 seconds after it. We suggest that these extra sequences correspond to the excitations of the portions of thiotimoline present in the future and past respectively. Regrettably, spectra of **1** exhibited very significant signal broadening, precluding the inference of useful structural information. The reason for the broadening is not currently understood, but it is presumed to be associated with the molecule's endochronicity.

Through a presumably similar mechanism, time-of-flight mass-spectrometry (TOF-MS) also gave unusual results when used to analyse thiotimoline. As a result of a 1.12 second lag time, an ion was registered with a molar weight of 3.9 solar masses.

X-ray crystallomancy proved to be far more productive in the structural elucidation of **1**. Crystals of thiotimoline were grown by vacuum sublimation and subjected to collimated X-rays.[9] The data we obtained was bafflingly disordered, with almost every atom displaying partial occupancy. We attributed this disorder to the same endochronicity that had thwarted our NMR and MS analyses. However, we surmised that by pulsing the X-ray source and collecting data before, during and after each pulse, we might obtain resolved data on each of thiotimoline's three temporal domains. We tested this theory by exposing crystals of **1** to 50 µs bursts of X-rays and recording data simultaneously, and at 1.12 second intervals before and after each pulse. Even with a synchrotron as the radiation source, 116 days of continuous data collection were required to obtain results of publishable quality.

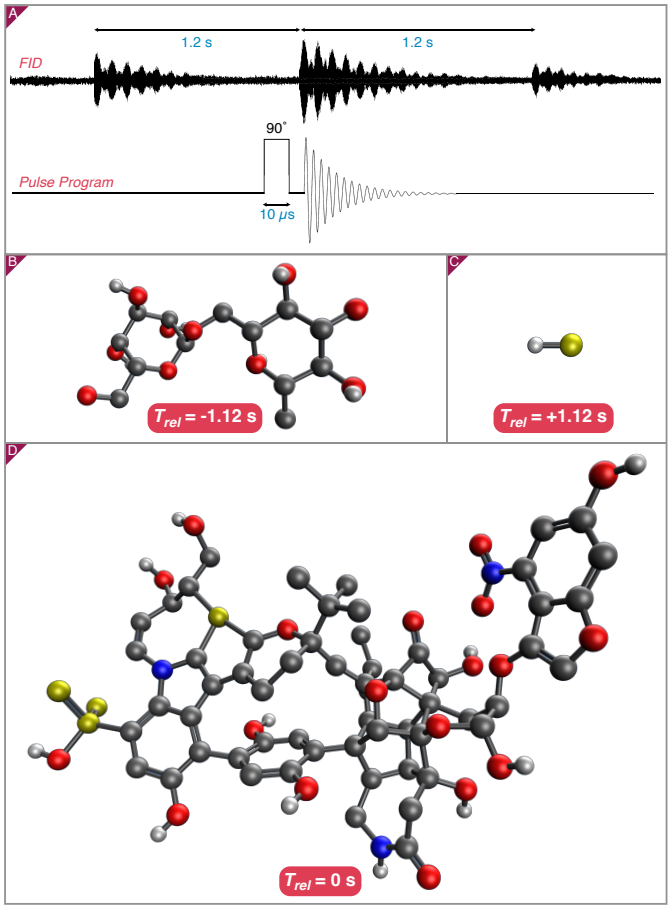


Figure 3: A) FID and pulse-program for a single-scan ^{1}H NMR experiment on **1**. X-axis not to scale. **B–D**) Time-resolved pulsed-X-ray crystal structures of thiotimoline, recorded at 1.12-second intervals. Selected hydrogens, solvent and $OPPh_3$ removed for clarity, ellipsoids at 100% sphericity.

Gratifyingly, our strategy succeeded, and we obtained three fully-resolved structures. The data acquired 1.12 seconds before each X-ray pulse revealed a structure consistent with the disaccharide (+)-fucnose (Fig. 3B), while X-ray data collected 1.12 seconds after each pulse revealed the presence of protonated atom of sulphur (Fig. 3C). Data collected concomitantly with X-ray exposure revealed an entirely different structure: the core of thiotimoline. The hydrocarbon framework of thiotimoline represents a hitherto-unknown class of natural product. **1** constitutes a complex, polyhydroxylated hydrocarbon scaffold supporting a number of uncommon functionalities. Prominent among them are a C_{sp}^4–type pentavalent carbon, and a thiothiosulphonic acid. At the time of Asimov's original studies, such moieties were unknown, thus it is unsurprising that the structure of thiotimoline eluded him. Interested readers should consult Fielding and Barratt's

comprehensive review "The Moiety Boosh" for a history of unconventional functional groups.[10]

The most intriguing element of **1** is a central divalent carbon atom with an apparently linear geometry. Flanked by bulky, C_{sp}^3–hybridised carbons, it is neither alkyne nor allene. It can only be the chronomeric carbon proposed by Asimov over 70 years ago. We propose that the fucnosyl and thiol fragments observed in our time-resolved X-ray experiments are bound to this carbon through bonds spanning forwards and backwards in time, respectively. This hypothesis is supported by thiotimoline's reactivity: the hydrophilic disaccharide is projected forwards into time, allowing the molecule to dissolve in water before the bulk of the sample even makes contact with it. Conversely, the thiol is projected into the past.

Asimov's predictions of thiotimoline's structure have proved remarkably accurate (Table 1). Such prescient foresight was ever a hallmark of Asimov's work. Most impressive among his predictions was the divination of the endochronic carbon's nature, without recourse to modern NMR or X-ray techniques.

Asimov's Prediction	X-ray Confirmed
14 hydroxyls	*15 hydroxyls*
2 amino groups	*1 arylamine, 1 amide*
1 sulphonic acid	*1 thiothiosulphonic acid*
0–1 nitro	*1 nitro*
partially aromatic hydrocarbon	*1 biphenyl, 1 benzofuran*
-	*1 ketone*
-	*1 sulfcarbide*
-	*1 mercaptan*
1 chronomeric carbon	*1 chronomeric carbon*
-	*1 pentavalent carbon*

Table 1: Asimov's predications of thiotimoline's structural elements, compared to those observed by X-ray crystallomancy.

Synthesis

With the structure of thiotimoline secured, we turned our attention to its synthesis. Undoubtably, the foremost challenge in such an endeavour was contriving a method of forcing parts of a molecule into the temporal plane through steric repulsion. As Asimov conjectured in 1948, the endochronic carbon is ensconced in the centre of the molecule, sheltered by the stalwart bulk tert-butyl and isopropyl groups. Functionalisation of this carbon after the placement of these groups is impracticable, as density-dysfunctional calculations have implied that not even methylcaesium could penetrate such a steric shield, much less a cumbersome disaccharide (*vide supportus*).

To overcome the extravagant energetic barrier inherent to such a transformation, we deemed it essential to incorporate a thermodynamic driving force into the crucial time-space displacement reaction. The expulsion of N_2 was the obvious candidate for this purpose, which led us to select the Schinkenfaust radical cross-spifflication for the pivotal disconnection (Fig. 4A).

This reaction was developed by Schinkenfaust and Krankenwurst for the preparation of epihemithioacetals in the conventional three spatial dimentions.[11] It was our hypothesis that if sufficient steric bulk were present on the spectating groups, two of them might be propelled into the temporal dimension by the 112 kcal/mol of enthalpy generated by the collapse of intermediate **IV**. With this strategy in mind, we set about preparing the required precursors **3**, **4** and **5**.

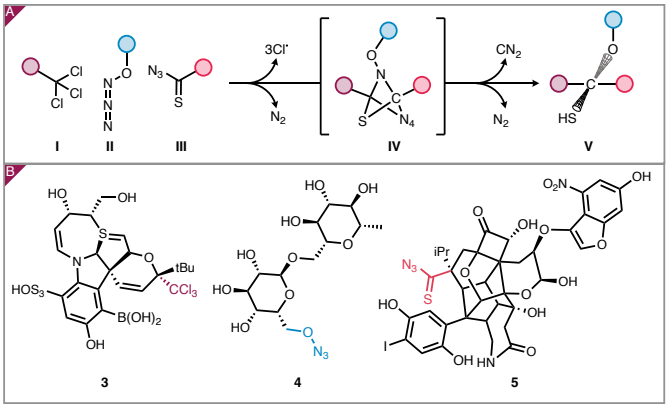


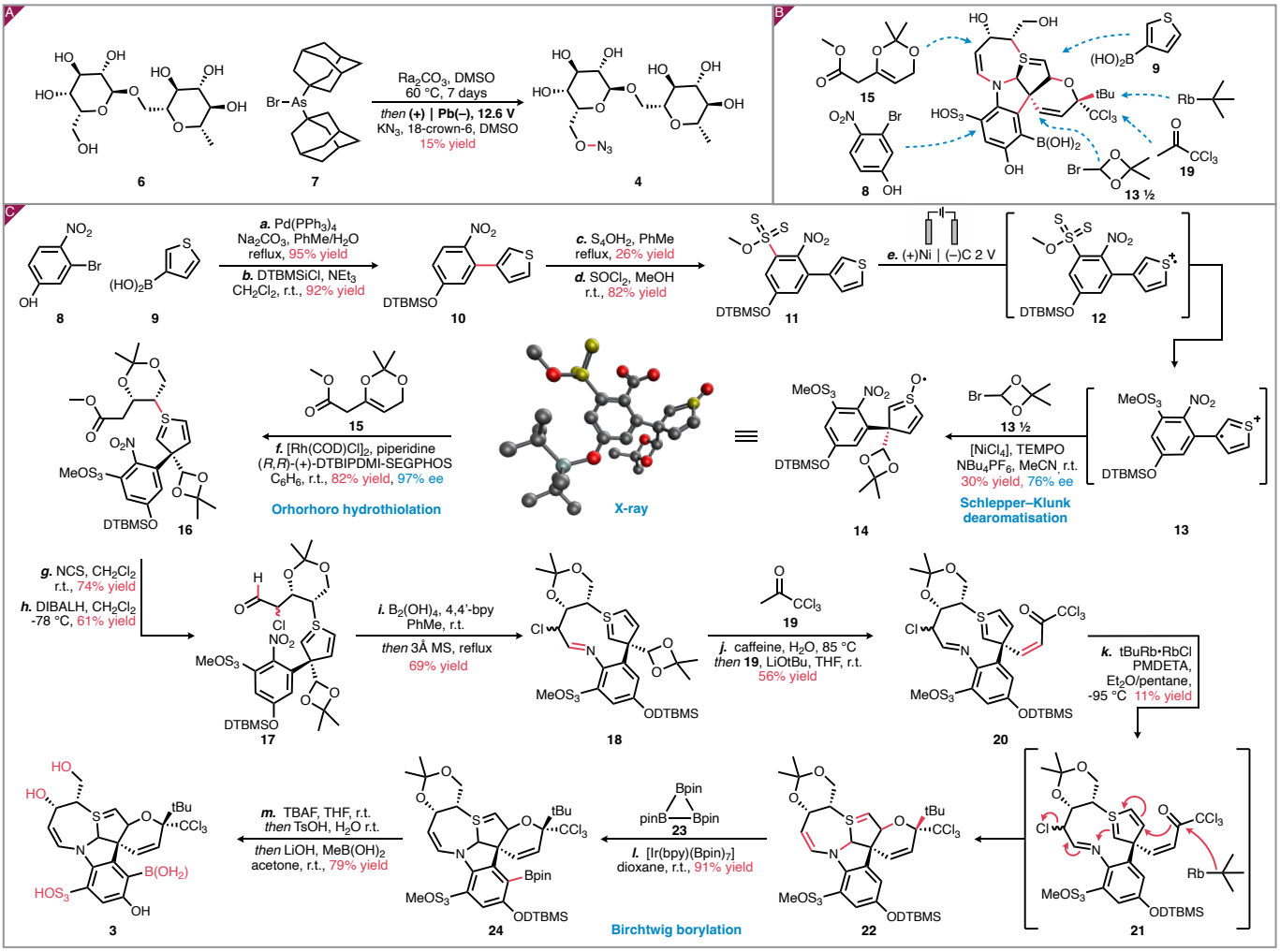
Figure 4: A) Simplified mechanism for the Schinkenfaust radical cross-spifflication. **B**) Three fragments that through a tandem Suzuki-Miyaura cross-coupling/radical spifflication might join to form thiotimoline.

We began with the preparation of (+)-*O*-azidofucnose **4**. The *de novo* synthesis of saccharides is "a laborious pursuit, brimming with adversity and tedium yet lacking the glamour and cache of alkaloid chemistry". So reads the opening line of Xazavian Kersplunkit's authoritative tome on the subject: "The Dance of the Protecting Groups".[12] As such, any route to **4** beginning from an intact disaccharide was deemed desirable, regardless of yield. Previously, our group has pioneered a protocol for the functionalisation of primary alcohols in the presence of multiple secondary alcohols.[13] We adapted this methodology to affect the azidation of (+)-fucnose (**6**) (Scheme 2A). This was accomplished by reacting **6** with fat arsine **7**, followed by electrochemical oxidation and displacement of the resultant arsinium cation with potassium azide. The product (**4**) decomposes rapidly and with some force at ambient temperature, thus it was deemed expeditious to generate it *in situ* immediately before subjecting it to the Schinkenfaust reaction.

The Western Chemisphere

We next considered the synthesis of **3**, the western chemisphere of thiotimoline. This fragment contains the thiothiosulphonic acid, the sulfcarbide and six stereocentres. Scheme 2B details our selected disconnections, the full retrosynthetic analysis is left as an exercise for the reader. This sequence began with the Suzuki-Miyaura cross-coupling of 3-bromo-4-nitrophenol (**8**) and 2-thiopheneboronic acid (**9**). To deter *ortho*-functionalisation of the aryl ring, the bulky di-*tert*-butylmethylsilyl group was selected from the pantheon of silanes to protect the cross-coupled product (**10**). Thus, subsequent electrophilic thiothiosulphonylation of **10** with thiothiothiosulphuric acid was directed predominantly to the *meta* position. Technically, the predominant product was tar, but the next most dominant product was the desired one, which was esterified with methanol to give **11**.

An enantioselective Schlepper-Klunk dearomatisation was used install a protected aldehyde at the *3'* position of the thiophene. This remarkable reaction proceeds by a 1-electron oxidation of thiophene **12** at a chiral nickel electrode, followed by migration of the resultant radical (**13**), which is annexed by an alkylnickel^{III} intermediate. Obstructive elimination proceeds rapidly therefrom to deliver dioxetane **14**, which was obtained in moderate ee and disheartening yield. X-ray crystallomancy confirmed the desired stereochemical configuration was present at the quaternary carbon.

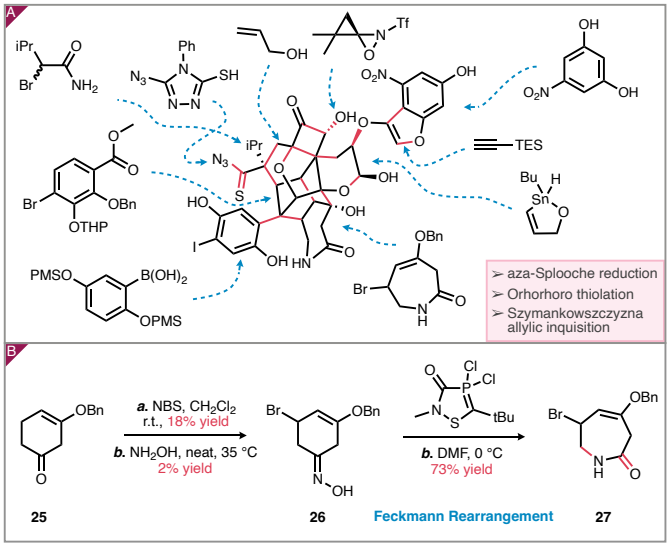


Scheme 2: A) Selective O-azidation of (+)-fucnose with a fat arsine. **B)** Retrosynthetic approach to the western chemisphere of thiotimoline. **C)** Synthesis of the western chemisphere, with a Crangleburt-Finkledink nucleophilic cascade (20–22) as the pivotal step.

The next two stereocentres were set with an Orhorhoro-type enantioselective olefin deoxohydrothiolation. This reaction delivered **16** in good yield at a modest 70 mol% catalyst loading. Thence, α-chlorination and DIBALH reduction gave aldehyde **17**. Reduction of the nitro group prompted spontaneous cyclisation to imine **18**, which was selectively deprotected with caffeine and subjected to an aldol condensation with trichloroacetone (**19**). The resultant enone (**20**) was primed for a Crangleburt-Finkledink nucleophilic cascade. This transformation proved extremely challenging when tBuLi was employed as the nucleophile. We surmised that competing attack on the imine was leading to unproductive side-reactions and tested other nucleophiles to address the issue. Sodium and potassium analogues gave similar results, while tBuCs ignited the starting material. *Tert*-butylrubidium proved to be an acceptable compromise. The product (**22**) was borylated with B_3pin_3 under Birchtwig's conditions and globally deprotected to give **3** in 0.07% yield over 13 steps.

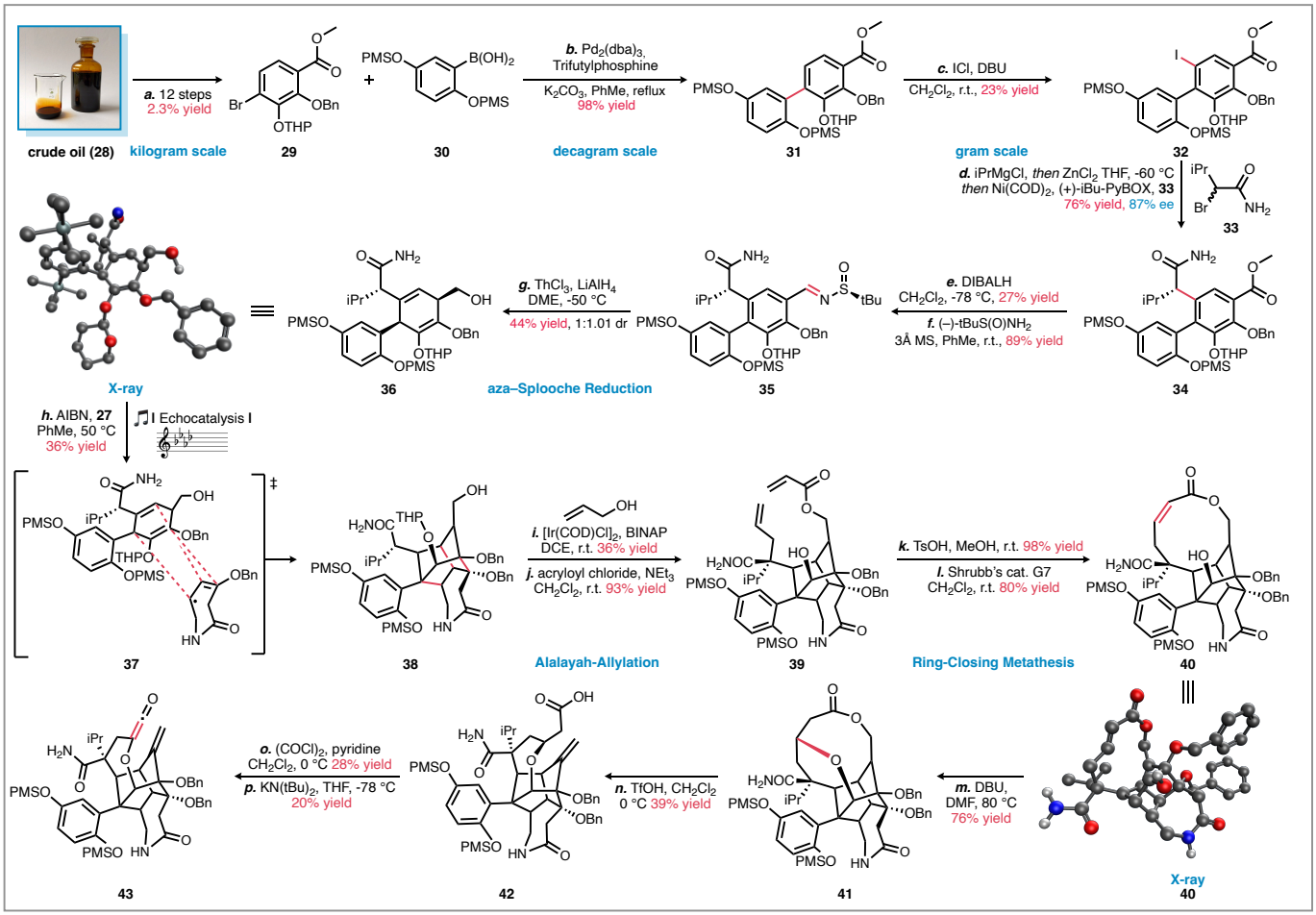
The Eastern Chemisphere

Finally, we confronted the synthesis of fragment **5**. Once again, we have elected to leave the detailed retrosynthesis to the reader. In brief, we envisioned a [3+2+3+2] Puccini-Gershwin echocyclisation could be used to construct the core carbocyclic framework from a biaryl precursor (Scheme 3A). To that end, we prepared diminuendophile **27** from ketone **25** by bromination and condensation with hydroxylamine followed by a Feckmann rearrangement (Scheme 3B).



Scheme 3: A) Retrosynthetic fragments of thiotimoline's eastern chemisphere. **B)** Preparation of fragment 27 by a Feckmann reaction.

To preclude any persnickety snark from the reviewers regarding the "total" nature of this synthesis, we elected to begin our preparation of **3** from crude oil. A simple 12-step sequence of literature reactions delivered ester **29** on kilogram scale. The venerable Suzuki-Miyaura reaction served to couple **29** with boronic acid **30** in exaltant yield. Pentamethylsilyl (PMS) groups were employed to prevent hydroquinone **31** from participating in deleterious side-reactions.



Scheme 4: Construction of the first halt of thiotimoline's eastern chemisphere.

Iodination with ICl was followed by an enantioconvergent Negishi cross-coupling with racemic α-bromoamide **33**.[14] A selective reduction of ester **34** proved challenging, and significant over-reaction and amide reduction diminished the yield of the desired aldehyde. This aldehyde was condensed with one of Ellman's chiral sulfinamides in the hope of imparting some enantioselectivity on the subsequent aza-Splooche reduction. Alas, this attempt met with abject failure, as alcohol **36** was obtained as a 1:1.01 mixture of diastereomers.

In accordance with standard practice for echocatalytic reactions,[15] we performed cyclic echometry on **27** and **36** to determine their resonant frequencies. The C=C and C-Br bond of **27** were found to resonate in E♭ and B♭ respectivly, while the olefins of **36** harmonise in C♮ and E♭. Thus, to affect the conjunction of **27** and **36**, our [3+2+3+2] Puccini-Gershwin echocyclisation was conducted in A♭ major. Wagner's Ring cycle was found to be an appropriate echocatalytic agent, and the product was obtained in middling yield.

Swift progress was made thenceforth. Alalayah allylation of **38** followed by acylation with acryloyl chloride gave diene **39**, the orthogonally-protected alcohol of which was revealed by tetrahydropyran hydrolysis. Cyclisation by ring-closing metathesis with Shrubb's catalyst G7 yielded pelargolactone **40**. An intramolecular Michael addition proceeded smoothly to form **41**, which underwent one-pot hydrolysis/elimination with triflic acid to give **42**. The corresponding acid chloride was generated with oxalyl chloride and eliminated with $KN(tBu)_2$ to generate ketene **43**, alongside copious carbonised residue/amorphous precipitate (CRAP). This compound was highly unstable and decomposed rapidly in light and at ambient temperature.

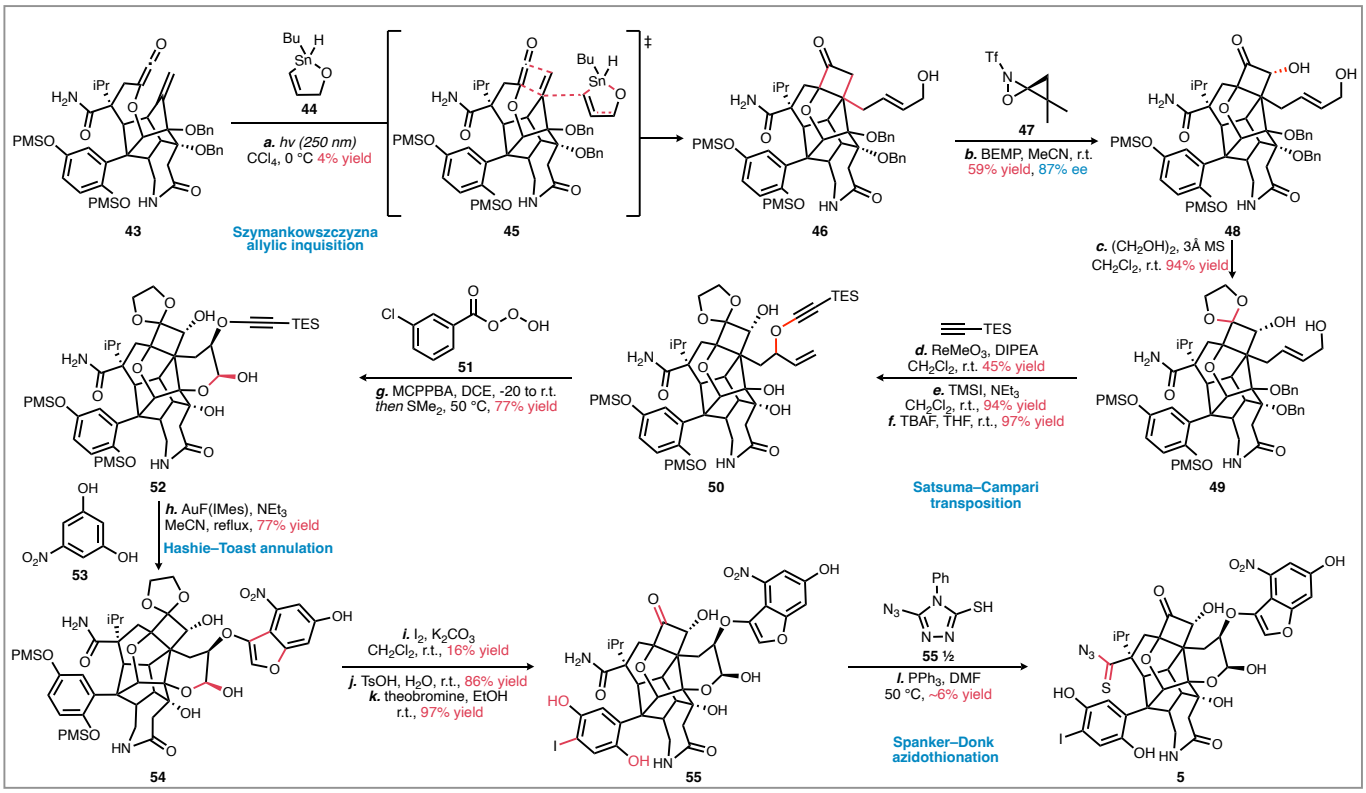
The generation of pentavalent carbons has been acknowledged as a challenging pursuit since their discovery. We harnessed the high-energy nature of ketene **43** to mitigate the inaccessibility of such carbons by employing it in a Szymankowszczyzna allylic inquisition (Scheme 5).[16] This reaction was promoted by UV irradiation of **43** in CCl_4, in the presence of cycloxystananene **44**. As the ketene undergoes a [2+2] cycloaddition, a tin-derived carbon radical populates the olefinic π* omnibonding orbital (**45**), forming an allylated $C_{sp}{}^4$ carbon (**46**).

Schmaltzof's chiral oxaziride was employed to affect the α-hydroxylation of ketone **47**,[17] and the resultant acyloin (**48**) was protected as an acetal (**49**). A modified Satsuma–Campari transpositon was used to rearrange the allylic alcohol and trap it as an oxyacetalide, followed by debenzylation to give **50**. Meta-chloroperperoxybenzoic acid (**51**) served as a mild ozone source to cleave the resultant terminal olefin, and the aldehyde thus formed smoothly cyclised to hemiacetal **52**.

The final sequence in the preparation of fragment **5** began with a gold-catalysed Hashie-Toast annulation of the oxyacetyide with nitroresorcinol **53**. Subsequent aryl iodination proceeded with abysmal selectivity, while acetal hydrolysis (TsOH) and PMS deprotection (ethanolic theobromine) were straightforward. Finally, a Spanker-Donk azidothionation with Donk's azide (**55 ½**) generated the desired azidothione (**5**). The sheer instability of **5** precluded its comprihensice purification and characterisation, and it was necessary to use the crude material immediately in the subsequent Schinkenfaust reaction.

The Schinkenfaust Radical Cross-Spifflication

As with any complex transformation, careful tuning of reaction conditions is essential for a successful radical spifflication. The complexity of our reaction was compounded by our



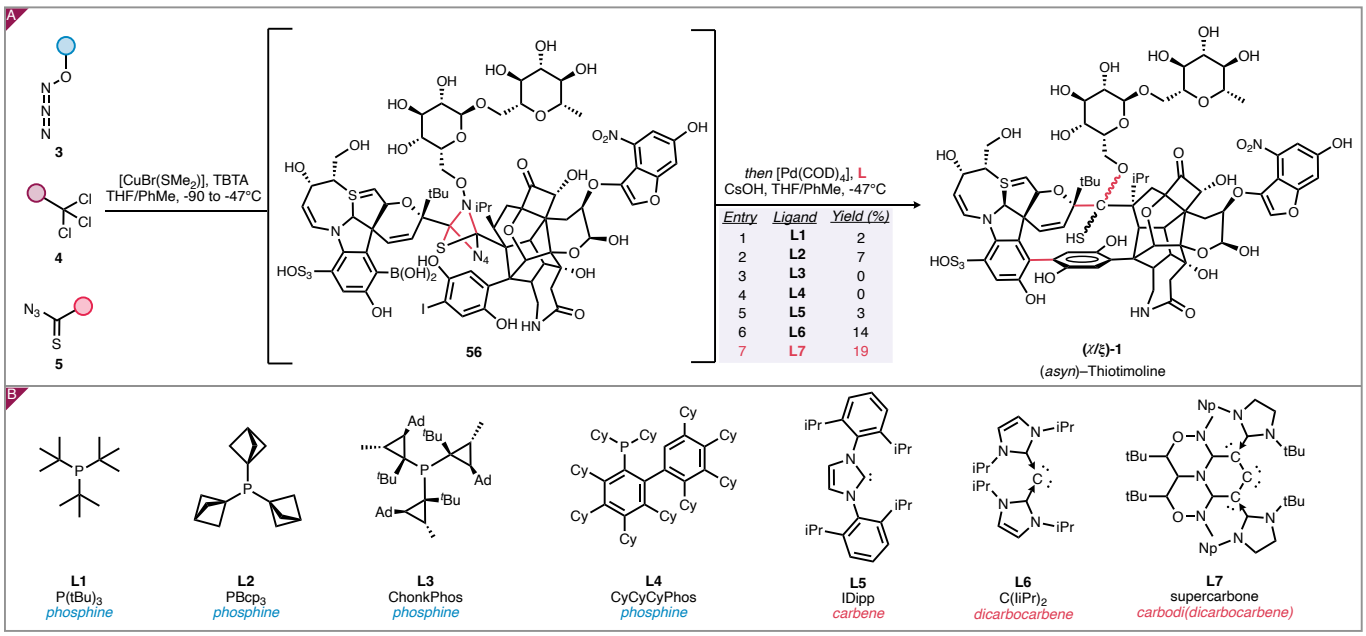
Scheme 5: Completion of thiotimoline's eastern chemisphere, including the formation of the pentavalent carbon by allylic inquisition.

requirement for intermediate **56** to persist in solution long enough for an intramolecular Suzuki-Miyaura reaction to occur. Conversely, we required conditions for a Suzuki reaction that would take a place at a temperature low enough to stabilise intermediate **56**.

We observed that the starting materials (**3**, **4** and **5**) were consumed when combined in 13:9 THF/PhMe at temperatures higher than -85 ˚C, as determined by ESIMS. A new ion was observed at *m/z* = 1879, which corresponds to intermediate **56**. When the reaction was warmed above -46 ˚C, this ion was in turn consumed, and an ion of *m/z* = 1799 replaced it as the predominant component of the mixture. This ion matches the product of a radical cross-spifflication without cross-coupling. It was thus determined that intermediate **56** persists between -85 and -46 ˚C, and we sought conditions that would affect a Suzuki-Miyaura cross-coupling at such temperatures.

An automated, high-throughput sceening approach was adopted to evaluate reaction conditions for the final cross-coupling. This necessitated the preparation of **4** and **5** more than twenty times to provide sufficient starting material. Comprehensive optimisation data is presented in pages 35–598 of the positronic supporting information. The culmination of this work was the set of reaction conditions presented in Scheme 6.

$Pd(COD)_4$ was selected as the palladium source, as it is exceptionally labile, even at low temperature. In combination with a bulky, electron-rich monodentate ligand and caesium hydroxide, this catalysts system formed small amounts of



Scheme 6: A) Unity of thiotimoline's eastern and western chemispheres by tandem Schinkenfaust radical cross-spifflication/Suzuki-Miyaura cross-coupling. **B)** A selection of ligands screened in the aforementioned reaction.

thiotimoline **1** (as detected by MS). Phosphine ligands **L1** and **L2** were competent, while the bulkier ChonkPhos (**L3**) and CyCyCyPhos (**L4**) were ineffective. NHCs such as IDipp (**L5**) did catalyse the desired reaction, albeit in atrocious yield. We hypothesised that a more electron dense ligand was needed to facilitate oxidative addition at such a low temperature, and turned to a dicarbocarbene. Indeed, **L6** furnished a comparatively pleasing 14% yield of **1**. Finally, we employed carbodi(dicarbocarbene) **L7** (the most electron-rich ligand we could think of) and obtained a 19% yield of thiotimoline.

With optimised spifflication/cross-coupling conditions in hand, we conducted a large (50 mg) scale reaction and attempted to isolate thiotimoline from the reaction mixture. This proved to be easier than expected. A reverse-phase TLC of the reaction mixture was run in 10% MeCN/H_2O, and a spot was observed *above* the solvent line with an R_f of 1.2 (Fig. 5A). Such an unusual retention factor could only be the characteristic of an endochronic molecule, and indeed a sample of pure thiotimoline isolated from the natural source produced an identical R_f. Thus informed, we subjected the crude reaction mixture to flash column chromatography on C18-silica and obtained 9.5 mg of a white crystalline solid, which eluted before the solvent did. One milligram of this compound dissolved in water in -1.12 seconds, and it was spectroscopically identical to the thiotimoline isolated from *K. rufo.*

These TLC's contained a second startling element: a spot with an apparent R_f of -0.2. The movement of a compound against the flow of solvent in a chromatographic context has, to the best of our knowledge, never been observed before. Naturally, we wished to isolate this material so that it's composition might be determined. This was accomplished by filling the headspace of the column with eluent, and allowing half to flow through the silica. The remaining eluent was decanted and concentrated under reduced pressure, to give a further 9.5 grams of white solid. When 1 mg of this material was placed in 1 mL water, there was no observable reaction for 1.12 seconds. Then almost instantly, the material dissolved, with an alacrity akin to an iodine clock.

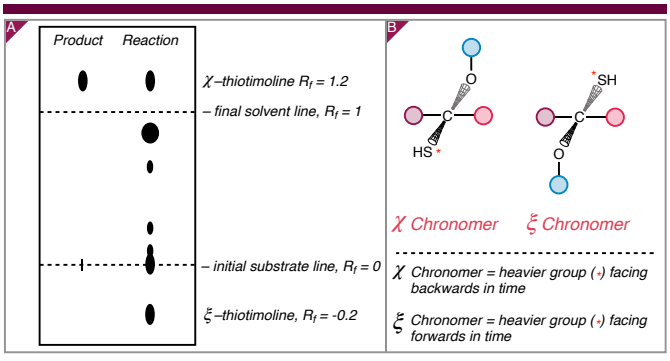


Figure 5: A) A reverse-phase TLC of our impure, synthetic thiotimoline (right) against a sample extracted from *K. rufo*. **B)** The natural (left) and unnatural (right) chronomers of thiotimoline, produced by our reaction as an asynchronous mixture.

On the basis of this observation and subsequent spectroscopic analysis, we contend that this substance is an unnatural isomer of thiotimoline. Put simply, this compound has the opposite configuration of substituents at the chronomeric carbon. The thiol is projected 1.12 seconds into the future, and the fucnose lags 1.12 seconds into the past. Hence, the negative R_f and positive time of solution.

We believe these results imply the existence of a type of isomerism thus far unknown to science. That is, two molecules whose structures differ only by the distribution of two or more substituents in the temporal plane (Fig. 5B). We suggest the term "kairality" be used to describe this type of isomerism, a word we have derived from the ancient Greek "Kairos" meaning "time" or "the opportune moment". Furthermore, we propose a system to classify such isomers, which we have termed "chronomers". The priority of the two chronomeric substituents should be determined in accordance with the principles of Cahn, Ingold and Prelog. Thenceforth, the chronomer bearing the higher-priority substituent projected into the future is designated the ξ-chronomer, and its counterpart the χ-chronomer. Under these rules, the compound extracted from *K. rufo* is χ -thiotimoline, while that generated by our radical cross-spifflication is an asynchronous mixture.

Discussion

The results presented above have definitively answered questions that have puzzled and intrigued chemists for more than 70 years, by providing a structural basis for understanding molecular endochronicity. As is so frequently the case in research, answering these question prompts the posing of others. Our first question is this: might it be possible to prepare molecules other than thiotimoline that display endochrinicity? Our synthesis is far too lengthy and inefficient to provide practical amounts of thiotimoline for any future applications, but this drawback would be negated entirely if a smaller and simpler analogue could be prepared.

Another quandary as yet unanswered is the nature of thiotimoline's biosynthesis. As evidenced by our extraction, *K. rufo* produces only one of two possible chronomers of thiotimoline. Ergo, the plant possesses some mechanism of selectively generating a carbon centre with a defined chronochemical configuration. We can only speculate as to the nature of this mechanism, as the molecular biology of *K. rufo* is entirely unexplored. Perhaps an enzyme involved in the biosynthesis of **1** also contains chronomeric carbons in its active site, which project a hydrophilic pocket or steric bulk into the future, thus biasing the geometric outcome of a crucial reaction.

The applications of molecular endochronicity have been pondered since its discovery. Isaac Asimov described the use of thiotimoline in the determination of NaCl concentration, in willometry, and micropsychiatry. He further speculated on its use in endochronic batteries, meteorological instruments and even weapons of mass destruction. All such applications would become more feasible with the availability of mass-produced thiotimoline analogues. Our aspirations, however, lie within the field of synthetic chemistry. Specifically, we are intrigued by the concept of a "chronal auxiliary". That is, the appendage of a chronomeric unit or "chronophore" to another molecule in order to facilitate its separation/purification from a complex mixture. In a manner similar to a chiral auxiliary, a compound tagged with a chronophore could be readily purified chromatographically if it's resultant R_f was larger than 1 or less than 0. Investigation into this principle of "flash column chronotography" are currently underway in our laboratory, concurrent with attempts to produce novel endochronic compounds.

Conclusion

The structure of thiotimoline has been unambiguously assigned, which represents the solution to a mystery over 90 years old. We have probed the nature of the chronospatial bonds that make thiotimoline so distinctive by physical and spectroscopic means. Furthermore, we have conducted the first total

synthesis of thiotimoline, and uncovered a novel form of molecular isomerism: kairality, for which we have devised both theory and notation. We hope this work will serve to reinvigorate the field of chronochemisty and pave the way for future studies on the theory of endochronicity and the synthesis of novel endochronic molecules.

Experimental details, spectra and optimisation data are contained in the positronic supported information, which is available in the basement of the planning office, in a locked filing cabinet in a disused lavatory, next to a sign reading "beware of the leopard".

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Author Contributions

H.W. and G.S. determined the structure of **1**. M.C. prepared figure **2**. G.S. conducted the experiments and prepared the manuscript.

Conflicts of Interest

The authors declare the conflict between their interest in whimsical science and the demands of the real world.

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