Hz, 1.0, 5-anthryl C–H), 7.90 (apparent t, unresolved d of d, 1.0, 3-anthryl C–H), 7.77–7.48 (m, 10.7, C_6H_5, 6- and 7-anthryl C–H, H ortho to S), 7.42 (d, J = 8.4 Hz, 2.0, H meta to S), 7.11 (d, J = 8.1 Hz, 1.0, 8-anthryl C–H), 6.96 (d, J = 8.6 Hz, H ortho to $-OCH_3$), 3.77 (s, 6.0, OCH_3), 2.54 (s, 3.0, CCH_3).

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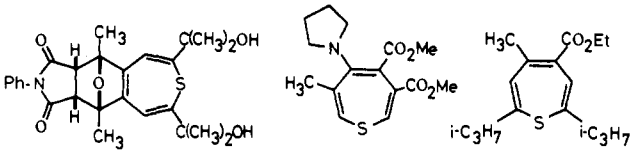
Synthesis of 2,7-Di-*tert*-butyl-4-ethoxycarbonyl-5-methylthiepin. A Remarkably Stable and Simple Monocyclic Thiepin[1]

Sir:

Heterocyclic 8-π electron systems, heteropins, have long been a subject of interest. In contrast to azepines and oxepins, which have been studied extensively,[2] little is known about thiepins because of their thermal instability owing to ready sulfur extrusion.[3] An accepted mechanism for this involves valence isomerization of the thiepin ring into its corresponding thianorcaradiene isomer.[4]

Molecular models of a thiepin possessing two bulky groups at the 2 and 7 positions indicate that these groups force the nonbonding interaction in corresponding thianorcaradiene structure to be large, and hence the thiepin form will be favored. This concept has been revealed by the successful isolation of a stable but complex thiepin (**1**),[5] whereas the compound having no bulky groups at these positions such as **2** never has been isolated though it can be generated and detected.[6]



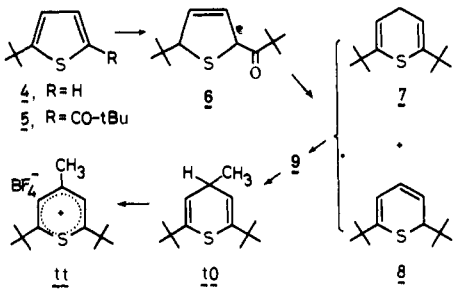
1 **2** **3**

We have previously shown that the thiepin **3** undergoes ready sulfur extrusion ultimately to give the corresponding benzene derivative even at −70 °C.[7] We report here a first example of a simple thiepin stabilized by two bulky *tert*-butyl groups.[8]

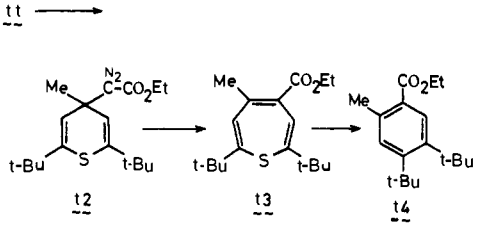
The synthesis of the key intermediate, 2,6-di-*tert*-butyl-4-methylthiopyrylium salt (**11**), is illustrated in Scheme I. The Friedel-Crafts reaction of 2-*tert*-butylthiophene (**4**)[9] with pivaloyl chloride ($SnCl_4$, in benzene at room temperature) gave crystalline 2-*tert*-butyl-5-pivaloylthiophene (**5**)[10] in 94% yield. Birch reduction of **5** (Li/NH_3, *t*-BuOH, −78 °C, 10 min) gave 88% 2-*tert*-butyl-5-pivaloyl-2,5-dihydrothiophene (**6**)[10] contaminated with small amounts (<5%) of the corresponding 2,3- and 4,5-dihydrothiophenes. Compound **6** was converted into **7** and **8** according to a novel strategy,[11] by treatment with a large excess of zinc dust and trimethylchlorosilane and quenching with 1 N sodium hydroxide. A 1:8 mixture of **7** and **8** was obtained in 86% yield[10] and was separated by column chromatography on silica gel with hexane. Hydride abstraction of the mixture of **7** and **8** ($Ph_3C^+BF_4^-/CH_3CN$) afforded the thiopyrylium salt (**9**)[10] in 68% yield. Methylation of **9** (CH_3Li in ether, −78 °C) gave the thiopyran **10**[10] which was finally converted into 2,6-di-*tert*-butyl-4-methylthiopyrylium tetrafluoroborate (**11**)[10] by the usual method. The 2,6-di-*tert*-butylthiopyrylium salt thus obtained was not readily accessible via previously available methodologies.[12]

The di-*tert*-butylthiopyrylium salt **11** was transformed into a thiepin ring system via the sequence of reactions shown in Scheme II. The thiopyrylium salt **11** was treated with ethyl lithiodiazoacetate[1,7,13] (in ether and THF, −120 °C) to give diazo compound **12**[10] (yellow needles, mp 32–33 °C, 90% yield). Treatment of **12** with π-allylpalladium chloride dimer (5 mol %, $CHCl_3$, 0 °C, 1 h) gave thiepin **13** (yellow prisms, mp 23.5–24.5 °C (from methanol), 99% yield). The structure of **13** ($C_{18}H_{28}O_2S$) was supported by elemental analysis for C, H, and S and spectroscopic data. The ^1H NMR spectrum shows signals of the *tert*-butyl groups at δ 1.22 and 1.23 (each s, 9 H), ring methyl protons doublet coupled with H-3 at 2.11 (d, J = 0.9 Hz), quartet of H-3 at 6.50 (J = 0.9 Hz), and singlet of H-6 at 6.14 along with the ethoxycarbonyl protons at 1.32 (t, 3 H, J = 7.1 Hz) and 4.23 (q, 2 H). ^{13}C NMR spectrum of **13** is also consistent with the structure.[14] Thiepin **13** exhibits UV maxima (in cyclohexane) at 234 nm (log ϵ 4.11) and 356 (2.95) with low-intensity tailing up to 510 nm.[15] The IR spectrum of **13** (KBr) shows typical absorption for an α,β-unsaturated ester carbonyl group at 1715 cm^{-1}.

Scheme I



Scheme II



In spite of its monocyclic thiepin structure, **13** shows remarkable thermal stability and can be handled under atmospheric conditions with no detectable decomposition. Its half-life at 131 °C in toluene-d_8 is 7.1 h.[16] On prolonged heating in toluene at 140 °C in a sealed tube **13** was converted in nearly quantitative yields into sulfur and ethyl 4,5-di-*tert*-butyl-2-methylbenzoate (**14**), colorless needles, mp 21–22 °C (from methanol). Anal. ($C_{18}H_{28}O_2$) C, H. The ^1H NMR of the compound **14** shows signals at δ 1.53 (s, 18 H), 2.43 (s, 3 H), 7.25 (s, 1 H), and 8.04 (s, 1 H), and the ethyl ester protons at 1.37 (t) and 4.27 (q, J = 7.0 Hz). The relatively downfield chemical shift of the *tert*-butyl groups is due to the ortho arrangement of the two *tert*-butyl groups in the benzene ring.[17] A comparison of **13** and **3** shows that substitution of *tert*-butyl groups for isopropyl groups on 2 and 7 positions of the thiepin ring produces high thermal stability.[18] Presumably, formation of the thianorcaradiene intermediate does not arise owing to increased steric hindrance.

The thiepin is isoelectronic with the cycloheptatrienide ion and, if planar, may actually be antiaromatic. Paratropicity[19] of thiepins associated with 8-π and 12-π electrons has been proposed for some complex thiepins.[5,20] In the NMR spectrum, the methyl proton of **13** is at δ 2.11, similar to that of the methyl group cis to methoxycarbonyl in methyl 3,3-dimethyl acrylate (δ 2.12).[21] Furthermore, the chemical shift of H-6 (δ 6.41) is in fair agreement with the value (δ 6.24) calculated by using the substituent shielding coefficient Z[22] for olefinic protons. In addition, available X-ray crystallographic results of some thiepins[23] suggested that **13** must exist in a boat conformation. From these results we consider the thiepin **13** to be

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an atropic[19] molecule. We are currently investigating the detailed chemistry, including a X-ray crystallography, of this simple monocyclic thiepin.

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Supplementary Material Available: The spectroscopic data for **7-12** (2 pages). Ordering information is given on any current masthead page.

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(12) Cf. "Organic Compounds of Sulphur, Selenium, and Tellurium", Reid, D. H., Ed.; The Chemical Society: London, 1973; Vol. 2 (Specialist Periodical Reports). Quite recently, we found that the thiopyrylium salt **11** can also be prepared from 4-methylthiopyrylium salt via a sequence of reactions (i, t-BuMgCl; ii, $Ph_3C^+BF_4^-$; iii, t-BuLi; iv, $Ph_3C^+BF_4^-$).
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(14) ^{13}C NMR ($CDCl_3$): δ 14.2 ($-OCH_2CH_3$), 60.5 ($-OCH_2CH_3$), 168.2 ($-COOC_2H_5$), 30.5 ($-C(CH_3)_3$), 39.6, 39.9 ($-C(CH_3)_3$), 22.6 (C_4-CH_3), 126.8, 130.9 (C_3, C_6), 132.1, 146.2, 151.4, 155.8 (C_2, C_4, C_5, C_7).
(15) Thiepin **1** also showed tailing to 500 nm in the visible; see ref 5.
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(18) A referee has suggested that, in addition to the stabilization of **13** by steric effects, it may be that the ethoxycarbonyl group also plays an important role by diminishing the antiaromaticity. Cf.: Hess, B. A. Jr.; Schaad, L. J.; Reinhoudt, D. N. *Tetrahedron* **1977,** *33,* 2683; also ref 6. However, we have recently confirmed that, in contrast to theoretical prediction and some experiments, the thiepin system is stabilized by an electron-donating methyl group and destabilized by an electron-withdrawing ethoxycarbonyl group. Cf.: Murata, I.; Tatsuoka, T. *Tetrahedron Lett.* **1975,** 2697. Nishino, K.; Nakasuji, K.; Murata, I. *Ibid.* **1978,** 3567. This trend was supported by the recent observations reported in Traynelis, V. J.; Schield, J. A.; Lindley, W. A.; MacDowell, D. W. H. *J. Org. Chem.* **1978,** *43,* 3379.
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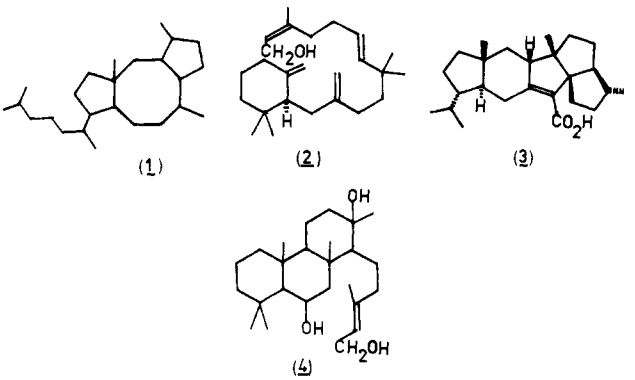
A Total Synthesis of Gascardic Acid

Sir:

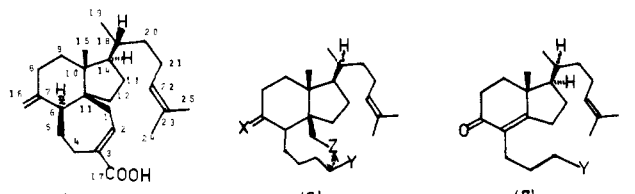
In 1960, Brochere and Polonsky reported the isolation and characterization of a new C_{25} terpene acid called gascardic acid from *Gascardia madagascariensis.*[1] Preliminary data suggested that this substance represented a new structural class of the rare C_{25} sesterterpenes. Among the known sesterterpenes, the ophiobolane class (**1**) has over the years proven to



(1) (2) (3) (4)

be the most numerous,[2,3] although other structural classes have been uncovered more recently, ranging from monocyclic and acylic polyenes such as diumycyminol (**2**)[4] to the unique polycyclic systems of retijeranic acid (**3**) and cheilanthatriol (**4**).[5,6]

A substantial effort to elucidate the structure, stereochemistry, and biosynthetic origin of gascardic acid was undertaken by Arigoni and Scartazzini.[7] These extensive chemical and spectroscopic studies resulted in the assignment of the carbocyclic skeleton of gascardic acid, as well as the partial elucidation of the relative stereochemistry. Intramolecular cyclization of gascardic acid under the influence of strong acid, as well as other evidence, tentatively suggested the stereostructure **5**.[7] This unique assemblage of three different



(5) (6) (7)

sized carbocyclic rings spiro-fused about a common carbon (C-11) remains the only example of this structural class yet uncovered in nature. The studies of Arigoni and Scartazzini seemingly failed to unambiguously establish only the relative configuration of C-14 and C-18. The relative stereochemistry of these centers was assigned on the basis of a plausible biogenetic scheme.[7] With the intention of verifying the proposed structure, we have undertaken the total synthesis of gascardic acid described herein.[8]

The spirocyclic system was expected to be derivable from a bicyclic precursor such as **6** by cyclization. Structure **6**, in turn, could be plausibly constructed from hydrindenone **7** by the stereospecific introduction of a suitable functionalized two-carbon appendage into the angular position. This operation, owing to the hindered nature of this site, was considered to be the pivotal transformation in the sequence. We, therefore, set out to devise a route for the efficient preparation of a system such as **7** controlling particularly the relative stereochemistry of the angular methyl and side chain. Since the configuration at C-18 was not firmly established when this work was begun, it was decided to prepare both possible epimers by leaving this center uncontrolled initially.

New methodology developed in our laboratories several

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