

Simple Routes to Sarkomycin

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Abstract: Two synthetic routes to sarkomycin (**6**) are demonstrated. The first involves a 3-carbon annelation to form the spirocyclopentenone (**2**) followed by regiospecific γ -alkylation and subsequent manipulation of the side chain in **15** to give the sarkomycin ester adduct **18**. The second route employs the itaconate-anthracene adduct **20** as the C-5 synthon in a tandem Michael addition-Dieckmann condensation between the anion derived from **20** and methyl acrylate. The reaction furnishes the diester **22**, which, upon selective decarboxylation, gives rise to the sarkomycin precursors **18** and **23** (1:3). Flash vacuum pyrolysis of either isomer **18** or **23** yields (\pm)-sarkomycin ester **7** which is then hydrolyzed to the acid **6**.

Subsequent to our previous report on the high-yield synthesis of α -methylene cyclopentenones via a 3-carbon annelation and retro-Diels-Alder reaction (Scheme I)¹ it was perceived that this route should conveniently lead to various cyclopentenoid antibiotics apart from methylenomycin B (**3**, R¹ = R² = Me), such as, for example, methylenomycin A (**4**),² deepoxy-4,5-didehydro-methylenomycin A (**5**),³ and sarkomycin (**6**).⁴

Sarkomycin (**6**), a simple looking molecule which has been called "deceptive", displays interesting biological activities in being both antitumor and antibiotic, and hence it has attracted much interest. Indeed, the recent years have seen several different methods reported for the synthesis of sarkomycin.⁵ Unfortunately, however, the methods are usually only suitable for small-scale preparations, employing exotic chemicals and/or highly sophisticated experimental procedures. As a result of the paucity of material, the reported NMR data of sarkomycin (**6**) and that of its methyl ester (**7**),⁵ which are frequently cited in the literature, appear to be oddly inconsistent.

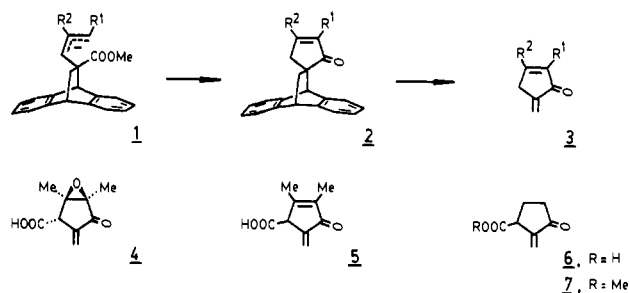
To solve these problems we decided to find a more suitable method for the synthesis of sarkomycin, which will conveniently accomplish large-scale preparations of the target molecule for further biological testings. Consequently two synthetic approaches were formulated.

The 3-Carbon Annelation Approach

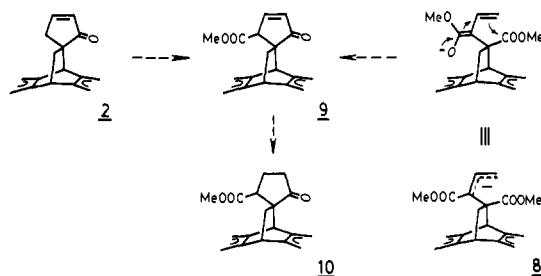
Unlike methylenomycin B (**3**, R¹ = R² = Me), sarkomycin (**6**) (and also other antibiotics in this series) contains a carboxylic group attached to the carbon adjacent to the methylene group. Hence the obvious precursor for such a compound would be the adduct **10**, the dihydro derivative of spirocyclopentenone **9**. In principle, **9** could be obtained either from the γ -carboxylation of the enone **2** (R¹ = R² = H) or from the cyclization of **8**, which is to say, either by introducing the carboxylic group into the molecule *before* or *after* the cyclization step (Scheme II).

This approach is attractive since large quantities of the starting material **2** are cheaply available.¹ Also, the volatility of sarkomycin methyl ester (**7**) is expected to be high enough so as not to cause any difficulty in the retro-Diels-Alders reaction of **10** under flash vacuum pyrolysis conditions. Furthermore, the acid-catalyzed conversion of **7** to sarkomycin (**6**) is a well-known process.⁶ The crucial steps that remain, therefore, are the regiospecific intro-

Scheme I



Scheme II



duction of the carbomethoxy group into the enone system **2** on the one hand and cyclization of the ester dienolate **8** on the other hand. This latter reaction is, however, anticipated to be sluggish due to the strain in the interacting p orbitals in the transition state. The reaction would be equivalent to a 5-(enolendo)-*exo*-trig cyclization which has been predicted by Baldwin to be a disfavored process.⁷ Indeed, it was found that under the standard cyclization conditions the ester dienolate **8** failed to give any detectable amount of the corresponding **9**.⁸ Therefore, we concentrated on finding a method for introducing the carboxylic group into the cyclopentenone **2** (R¹ = R² = H) at the γ position.

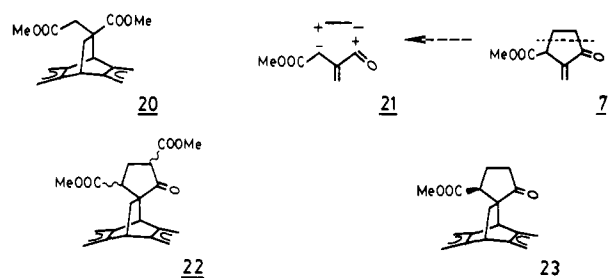
Various electrophiles reacted regiospecifically with the lithium dienolate derived from **2** (R¹ = R² = H) at the α position, as expected, to give cyclopentenones **11**. However, the reaction of the silyl enol ether **12**, isolated as a stable crystalline solid (mp 148-149 °C; ¹H NMR δ 4.98, 5.04, 6.06, (J = 1.5, 2.5, 6 Hz, three olefinic H)), with dithienium tetrafluoroborate (**13**)⁹ in CH₂Cl₂/CH₃NO₂ solution at -78 °C was both stereospecific and regiospecific, giving *only* the γ -alkylation product **14** (94%). The stereochemistry of **14** was at first tentatively assigned, by assuming the bulky electrophile approach from the less-hindered side, i.e., opposite to the methylene bridge in the anthracene adduct **12**. This

(1) Siwapinyoyos, T.; Thebtaranonth, Y. *J. Org. Chem.* **1982**, *47*, 598.(2) Haneishi, T.; Kitiyara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386.(3) Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977.(4) Umezawa, H.; Takeuchi, T.; Nitta, K.; Yamamoto, Y.; Yamaoka, S. *J. Antibiot.* **1953**, *6*, 101.(5) Syntheses of sarkomycin: (a) Govindan, S. V.; Hudlicky, T.; Koszyk, F. J. *J. Org. Chem.* **1983**, *48*, 3581. (b) Hewson, A. T.; MacPherson, D. T. *Tetrahedron Lett.* **1983**, *24*, 647. (c) Marx, J. N.; Minaskanian, G. *J. Org. Chem.* **1982**, *47*, 3306. (d) Wexler, B. A.; Toder, B. H.; Minaskanian, G.; Smith, A. B., III *Ibid.* **1982**, *47*, 3333. (e) Barreiro, E. J. *Tetrahedron Lett.* **1982**, *23*, 3605. (f) Kobayashi, Y.; Tsuji, J. *Ibid.* **1981**, *22*, 4295. (g) Boeckman, R. K., Jr.; Naegely, P. C.; Arther, S. D. *J. Org. Chem.* **1980**, *45*, 752. (h) Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, 4175.(6) Toki, K. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 333. See also ref 5.(7) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939.

(8) Full details of (enolendo)- and (enolexo)-vinylogous Dieckmann condensations will be reported elsewhere.

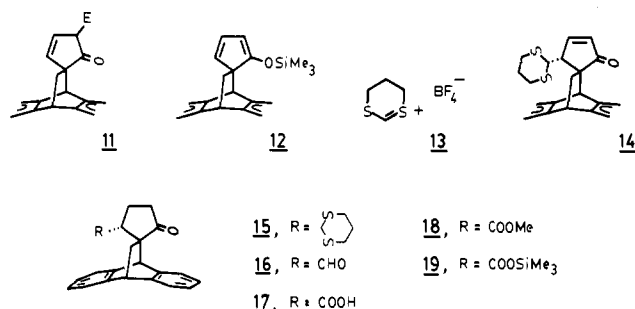
(9) (a) Dauben, H. J., Jr.; Honnen, L. R.; Harmon, K. M. *J. Org. Chem.* **1960**, *25*, 1442. (b) Corey, E. J.; Walinsky, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 8932. (c) Paterson, I.; Price, L. G. *Tetrahedron Lett.* **1981**, *22*, 2833.

Scheme III



has been confirmed by reactions described later.

The cyclopentenone **14** was catalytically hydrogenated (10% Pd/C in THF/EtOH) to give **15** (mp 187 °C) and then hydrolyzed (CuO/CuCl₂ in aqueous acetone) to **16** (mp 150 °C; δ 8.95 (d, $J = 2$ Hz, CHO)). Oxidation of the aldehyde **16** (KMnO₄, acetone, room temperature) afforded the acid **17** (mp 233 °C dec) which upon methylation and silylation yielded the sarkomycin ester-anthracene adduct **18** (mp 219–220 °C) and **19**, respectively.¹⁰ Ester **18** could be obtained from **14** in 74% overall yield without isolation of intermediates.



The Dimethyl Itaconate-Anthracene Adduct Approach

A shorter route to **18** was developed by using the dimethyl itaconate-anthracene adduct **20** as the C-5 synthon (**21**) in the synthesis as shown (Scheme III).

We believe that this route employing the adduct **20** is presently the most convenient method available for the preparation of sarkomycin. Here the construction of the cyclopentenone nucleus involves tandem Michael addition-Dieckmann condensation between the anion derived from **20** and methyl acrylate.

When the anion from **20** (LDA, THF, 0°, 1 hr) was allowed to react with excess methyl acrylate (3 molar equivalents) at -78 °C → 30 °C, Michael addition-Dieckmann cyclization took place.¹² The crude cyclization product,¹³ which presumably consisted of an isomeric mixture of **22**, was partially hydrolyzed and decarboxylated by boiling in methanol/concentrated HCl (4:1) to give, after separation, the adduct **23** (mp 191–192 °C) and **18** in a ratio of 3:1 (35% from **20**).¹⁴

The stereochemistry of the two isomeric esters **18** and **23** was easily assigned. The carbomethoxy group in **18** appears at δ 3.43 while that in **23** resonates at a higher field (δ 3.30), probably due to the small shielding effect of the aromatic nucleus.

Pyrolysis of **18**, **19**, and **23**

Having obtained sarkomycin precursors via the two synthetic routes described above, the synthesis of sarkomycin was at its final stage. Flash vacuum pyrolysis of both adducts **18** and **23** by the

(10) Attempted crystallization of **19** proved difficult, and a large amount of the acid **17** was formed. Since the crude product gave a satisfactory NMR spectrum, it was used in the next reaction without further purification.

(11) Golfier, M.; Prange, T. *Bull. Soc. Chim. Fr.* **1974**, 1158.

(12) Examples of Michael addition-Dieckmann condensations involving oxygen analogues have been reported: (a) Flavin, M. T.; Lu, M. C. *Tetrahedron Lett.* **1983**, *24*, 2335. (b) Gianturco, M. A.; Friedel, P.; Giammarino, A. S. *Tetrahedron* **1964**, *20*, 1763.

(13) The crude mixture of reaction products was partially purified by digestion in methanol and filtration of the unchanged starting material (43%) together with some polar, probably polymeric products.

(14) ~80% based on reacted **20**.

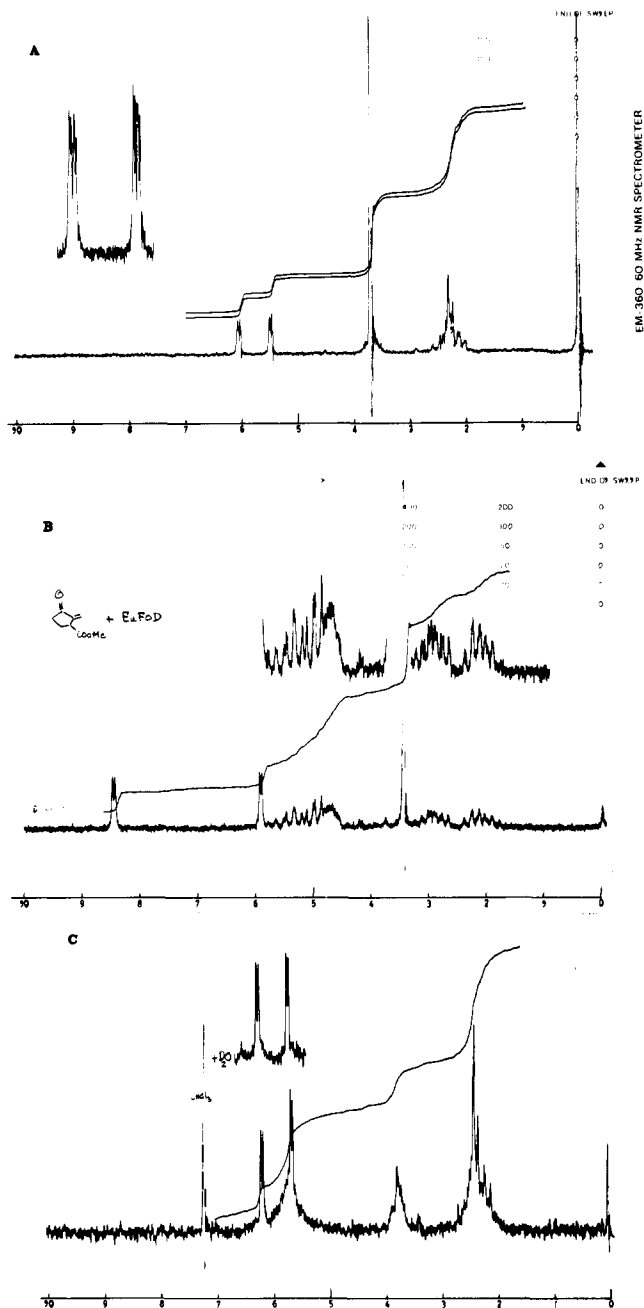
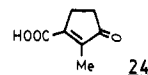


Figure 1. ¹H NMR spectra of sarkomycin methyl ester (**7**) in CCl₄ (A), A + EuFOD (B), and sarkomycin (**6**) in CDCl₃ (C).

method previously described¹ quantitatively yielded sarkomycin methyl ester **7**, which upon acid hydrolysis^{5f} afforded sarkomycin (**6**).

However, the crude pyrolysate from the pyrolysis of the silyl derivative **19** was found to be contaminated with several minor products, but, upon purification by PLC, it gave the rearranged acid **24** (61%, mp 168–169 °C) as the only isolable material.



Contrary to the reported spectra^{5a,c,g,h} which have been cited in the literature,^{5b,d} sarkomycin (**6**) exhibits an NMR spectrum identical with that obtained by Tsuji,^{5f,15} while its methyl ester **7** displays absorptions at δ 2.0–2.60 (m, 4 H), 3.75 (s, 3 H), 3.53–3.83 (overshadowed by OMe absorption, m, 1 H), 5.60 (d, $J = 3$ Hz, 1 H), 6.20 (d, $J = 3$ Hz, 1 H). The absorption at δ

(15) We thank Professor Tsuji for comparison of the NMR spectrum of sarkomycin (**6**).

3.53–3.83 has been clarified by the use of a chemical shift reagent (EuFOD), and the spectrum of **7** in CCl_4 also shows the splitting of both exocyclic methylene protons into a doublet of doublets ($J = 3$ and 1 Hz) (see Figure 1).

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR 20A spectrophotometer. ^1H NMR spectra were recorded in parts per million (δ) down field from tetramethylsilane (internal standard). Mass spectra were recorded on a Du Pont 21-490B GC/MS instrument. Elemental analyses were performed by The Department of Science Service, Ministry of Science, Technology, and Energy. THF was distilled from sodium/benzophenone ketyl. The molarity of *n*-butyllithium in hexane (purchased from Metallgesellschaft) was determined by titration according to the diphenylacetic acid method. Reactions were conducted under a nitrogen atmosphere, and reagents were introduced into the flasks via nitrogen-flushed syringes. Silica gel 60 PF₂₅₄ (Merck) was used for preparative layer chromatography.

9',10'-Dihydrospiro[2,4-cyclopentadiene-1,11'-[9,10]ethanoanthracen-2-yl]oxy)trimethylsilane (12). A solution of **2** ($R^1 = R^2 = \text{H}$)¹ (300 mg, 1.1 mmol) in THF (5 mL) was introduced into a solution of lithium diisopropylamide (LDA) (1.32 mmol) in THF (15 mL) at -78°C and the mixture left stirring at -78°C for 0.5 h. Trimethylsilyl chloride (0.5 mL, excess) was added and the reaction kept at 0°C for 0.5 h after which saturated ammonium chloride solution was added. The organic material was extracted into dichloromethane, and the dichloromethane solution was washed with water, dried (MgSO_4), and then evaporated to dryness. The crude product was crystallized from a mixture of dichloromethane–hexane to obtain **12** (358 mg, 94%) as colorless crystals: mp $148\text{--}149^\circ\text{C}$; IR (Nujol) $1600, 1300, 1255, 870, 760, 710\text{ cm}^{-1}$; ^1H NMR (CDCl_3) δ -0.06 (s, 9 H), 1.85 (d, $J = 3$ Hz, 2 H), 3.79 (s, 1 H), 4.35 (t, $J = 3$ Hz, 1 H), 4.98 (dd, $J = 1.5, 2.5$ Hz, 1 H), 5.04 (dd, $J = 1.5, 6$ Hz, 1 H), 6.06 (dd, $J = 2.5, 6$ Hz, 1 H), 6.92–7.25 (m, 8 H); mass spectrum, m/e (relative intensity) 344 (3), 178 (100). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{SiO}$: C, 80.23; H, 6.98. Found: C, 80.51; H, 7.12.

9',10'-Dihydro-5-[2-(1,3-dithianyl)]spiro[3-cyclopentene-1,11'-[9,10]ethanoanthracen]-2-one (14). A mixture of 1,3-dithienium tetrafluoroborate (**13**)⁹ (150 mg, 0.7 mmol), dichloromethane (15 mL), and nitromethane (5 mL) was stirred at -78°C for 10 min, and then a solution of **12** (200 mg, 0.58 mmol) in dichloromethane (5 mL) was added and the reaction mixture left stirring at -78°C for 30 min. After workup by the addition of saturated ammonium chloride solution, the crude product was taken up in dichloromethane, dried, filtered, and evaporated. Crystallization of the crude material from a mixture of dichloromethane–hexane yielded pure **14** (213 mg, 94%) as colorless crystals: mp $214\text{--}215^\circ\text{C}$; IR (Nujol) $1710, 1170, 765, 745\text{ cm}^{-1}$; ^1H NMR (CDCl_3) δ $1.55\text{--}2.28$ (m, 4 H), 2.45–2.75 (m, 4 H), 3.02 (m, 1 H), 3.45 (d, $J = 3$ Hz, 1 H), 3.78 (s, 1 H), 4.36 (t, $J = 3$ Hz, 1 H), 6.20 (dd, $J = 2, 6$ Hz, 1 H), 6.95–7.35 (m, 8 H), 7.57 (dd, $J = 3, 6$ Hz, 1 H); mass spectrum, m/e (relative intensity) 390 (0.5), 212 (64), 178 (100). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{S}_2\text{O}$: C, 73.85; H, 5.64. Found: C, 73.70; H, 5.88.

9',10'-Dihydro-5-[2-(1,3-dithianyl)]spiro[cyclopentane-1,11'-[9,10]ethanoanthracen]-2-one (15). A solution of **14** (250 mg, 0.64 mmol) in THF (20 mL) and ethanol (30 mL) was hydrogenated at atmospheric pressure with 10% Pd/C as catalyst. The mixture was then filtered and evaporated and the residue crystallized from dichloromethane–ethanol to give **15** (240 mg, 96%) as colorless crystals: mp 187°C ; IR (Nujol) $1735, 1275, 1250, 1170, 1150, 760\text{ cm}^{-1}$; ^1H NMR δ $1.55\text{--}2.79$ (m, 13 H), 3.69 (d, $J = 3$ Hz, 1 H), 4.05 (s, 1 H), 4.33 (t, $J = 3$ Hz, 1 H), 6.98–7.34 (m, 8 H); mass spectrum, m/e (relative intensity) 392 (1.5), 214 (58), 178 (100). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{S}_2\text{O}$: C, 73.47; H, 6.12. Found: C, 73.42; H, 6.30.

9',10'-Dihydro-5-carboxyspiro[cyclopentane-1,11'-[9,10]ethanoanthracen]-2-one (17). A mixture of **15** (300 mg, 0.77 mmol), copper(II) chloride dihydrate (260 mg, 1.53 mmol), and copper(II) oxide (240 mg, 3.02 mmol) in 95% aqueous acetone (8 mL) was heated under reflux with stirring for 30 min. The precipitate was filtered off, and the filtrate was concentrated in vacuo. The residue was triturated with ether and filtered. The filtrate was evaporated to dryness to give the crude product which was crystallized from a mixture of dichloromethane–hexane yielding the rather unstable **9',10'-dihydro-5-formylspiro[cyclopentane-1,11'-[9,10]ethanoanthracen]-2-one (16)** (206 mg, 89%) as colorless crystals: mp 150°C ; IR (Nujol) $1735, 1710, 760\text{ cm}^{-1}$; ^1H NMR (CDCl_3) δ 1.61 (dd, $J = 3, 12$ Hz, 1 H), 2.08 (dd, $J = 3, 12$ Hz, 1 H), 1.88–2.57 (m, 4 H), 2.68–2.88 (m, 1 H), 4.13 (s, 1 H), 4.34 (t, $J = 3$ Hz, 1 H), 7.01–7.36 (m, 8 H), 8.95 (d, $J = 2$ Hz, 1 H); mass spectrum, m/e (relative intensity) 302 (16), 178 (100), 124 (19).

A solution of potassium permanganate (120 mg, 0.75 mmol) in 95% aqueous acetone (10 mL) was added to the solution of aldehyde **16** (150

mg, 0.5 mmol) in 95% aqueous acetone (25 mL) with stirring at room temperature. The reaction mixture was left stirring for an additional 1 h and then acidified with 10% hydrochloric acid. The mixture was concentrated in vacuo and the residue extracted with dichloromethane. The dichloromethane solution was dried (MgSO_4), filtered, and evaporated, and the crude material was crystallized from ethanol to give **17** (145 mg, 92%) as colorless crystals: mp 233°C dec; IR (Nujol) $2700\text{--}2500$ (br), $1735, 1697, 1160, 755\text{ cm}^{-1}$; ^1H NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.48 (dd, $J = 3, 12$ Hz, 1 H), 2.20 (dd, $J = 3, 12$ Hz, 1 H), 2.03–2.70 (m, 5 H), 4.20 (s, 1 H), 4.33 (t, $J = 3$ Hz, 1 H), 7.03–7.39 (m, 8 H); mass spectrum, m/e (relative intensity) 318 (3), 178 (100), 140 (1.5). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3$: C, 79.25; H, 5.66. Found: C, 79.12; H, 5.81.

9',10'-Dihydro-5-carbomethoxyspiro[cyclopentane-1,11'-[9,10]ethanoanthracen]-2-one (18). A mixture of the acid **17** (500 mg, 1.57 mmol) in methanol (20 mL) and a few drops of thionyl chloride was heated to reflux for 6 h and evaporated to dryness under vacuo. The residue was taken up in ether (100 mL) and the ethereal solution washed successively with water, saturated sodium bicarbonate solution, and water and then dried (MgSO_4), filtered, and concentrated. The product was crystallized from dichloromethane–hexane to yield **18** (500 mg, 96%) as colorless crystals: mp $219\text{--}220^\circ\text{C}$; IR (Nujol) $1735, 1720, 1200, 1180, 1150, 760\text{ cm}^{-1}$; ^1H NMR (CDCl_3) δ 1.31 (dd, $J = 3, 12$ Hz, 1 H), 2.15 (dd, $J = 3, 12$ Hz, 1 H), 2.00–2.61 (m, 5 H), 3.43 (s, 3 H), 4.03 (s, 1 H), 4.23 (t, $J = 3$ Hz, 1 H), 6.96–7.26 (m, 8 H); mass spectrum, m/e (relative intensity) 332 (2), 178 (100), 154 (5). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_3$: C, 79.52; H, 6.02. Found: C, 79.49; H, 6.24.

18 and 23 from Dimethyl Itaconate–Anthracene Adduct (20). The adduct **20**, mp $154\text{--}155^\circ\text{C}$, was prepared in nearly quantitative yield by heating an equimolar mixture of dimethyl itaconate and anthracene in boiling xylene.¹¹

A solution of **20** (6.7 g, 20 mmol) in THF (160 mL) was introduced into a solution of LDA (24 mmol) in THF (200 mL) at -78°C and the mixture stirred at 0°C for 1 h and then cooled to -78°C and excess methyl acrylate (2.7 mL, 30 mmol) added. The reaction was then left to stir at room temperature for 15 h after which saturated ammonium chloride solution was added. The organic material was extracted into chloroform and the chloroform solution washed with water, dried (MgSO_4), and concentrated. The residue was stirred with methanol (30 mL), cooled, and then filtered to remove starting material **20** (2.9 g) and some high molecular weight material (1.01 g). The filtrate was evaporated to dryness to give an off-white semisolid. This substance was dissolved in a mixture of methanol/concentrated hydrochloric acid (4:1, 200 mL) and heated to reflux for 16 h. The reaction mixture was then evaporated to dryness and the residue chromatographed on a silica gel column with use of chloroform/hexane (1:1) as eluant to obtain esters **18** (580 mg, 9%) and **23** (1.74 g, 27%). **23**: colorless crystals; mp $191\text{--}192^\circ\text{C}$ from chloroform–hexane; IR (Nujol) $1730, 1720, 1190, 1170, 1150\text{ cm}^{-1}$; ^1H NMR (CDCl_3) δ $1.68\text{--}2.68$ (m, 7 H), 3.30 (s, 3 H), 4.33 (t, $J = 3$ Hz, 1 H), 4.38 (s, 1 H), 7.00–7.35 (m, 8 H); mass spectrum, m/e (relative intensity) 332 (7), 178 (100), 154 (9). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_3$: C, 79.52; H, 6.02. Found: C, 79.33; H, 6.18.

Sarkomycin Methyl Ester (7). The adduct **23** (500 mg) was placed in a 25-mL round-bottom flask connected to a gas-phase pyrolysis apparatus¹ and the system subjected to high vacuum (0.1 mm). The sample was then carefully vaporized with a free flame and the vapor passed through the heating column at 450°C . The crude products were trapped in a U-shape glass tube immersed in an ice bath. An NMR spectrum of this crude mixture indicated the presence of only anthracene and sarkomycin methyl ester (**7**), which suggests a quantitative conversion. Separation of **7** from anthracene by PLC (silica gel; chloroform/hexane (2:1) as developing solvent) yielded pure **7** (215 mg, 93%) as a viscous liquid: IR (film) 1720 (br), $1640, 1435, 1340, 1270, 1170, 1100, 990, 950\text{ cm}^{-1}$; ^1H NMR (CCl_4) δ $2.0\text{--}2.60$ (m, 4 H), 3.50–3.83 (m, 1 H, overshadowed by OMe absorption), 3.73 (s, 3 H), 5.50 (dd, $J = 1, 3$ Hz, 1 H), 6.06 (dd, $J = 1, 3$ Hz, 1 H); mass spectrum, m/e (relative intensity) 154 (3), 126 (87), 95 (100). Anal. Calcd for $\text{C}_8\text{H}_{10}\text{O}_3$: C, 62.34; H, 6.49. Found: C, 62.29; H, 6.63.

Identical results were obtained when **18** or a mixture of **18** and **23** was subjected to the same pyrolysis conditions.

Sarkomycin (6). Hydrolysis of the ester **7** was performed employing Tsuji's method^{5f} to obtain pure sarkomycin (**6**) (33%) as well as recovered starting material (46%) after PLC separation (silica gel, 8% chloroform in methanol as the developing solvent): IR (CHCl_3) $2900\text{--}2700$ (br), 1720 (br), 1200 cm^{-1} ; ^1H NMR (CDCl_3) δ $2.00\text{--}2.68$ (m, 4 H), 3.55–3.92 (m, 1 H), 5.64 (d, $J = 3$ Hz, 1 H), 5.70 (br, 1 H, removed with D_2O), 6.18 (d, $J = 3$ Hz, 1 H); mass spectrum, m/e (relative intensity) 140 (44), 112 (82), 95 (100).

2-Methyl-2-cyclopenten-1-one-3-carboxylic Acid (24). To a solution of LDA (0.8 mmol) in THF (10 mL) at -78°C was slowly added a

solution of the acid **17** (250 mg, 0.79 mmol) in THF (15 mL) followed by trimethylsilyl chloride (0.5 mL) and the reaction was left stirring at 0 °C for 1 h. The reaction mixture was then concentrated in vacuo, the residue dissolved in dry dichloromethane and filtered, and the filtrate evaporated to dryness. The crude product was pyrolyzed and the pyrolyzate purified by PLC (silica gel, ethyl acetate as eluant) to obtain the acid **24** (67 mg, 61%) as colorless crystals: mp 168–169 °C (dichloromethane–hexane); IR (Nujol) 2800–2600 (br), 1715, 1665, 1215, 910, 720 cm⁻¹; ¹H NMR (CDCl₃) δ 2.10 (t, *J* = 2 Hz, 3 H), 2.45–2.60 (m, 2 H), 2.73–2.91 (m, 2 H), 9.29 (br s, 1 H, removed with D₂O); mass spectrum, *m/e* (relative intensity) 140 (100), 112 (40). Anal. Calcd for C₇H₈O₃: C, 60.00; H, 5.71. Found: C, 59.88; H, 5.95.

Conclusion

It should be emphasized that the tandem Michael addition–Dieckmann condensation method shown above is extremely attractive for the construction of such a cyclopentenoid nucleus, and it makes large quantities of sarkomycin easily obtainable. Con-

sequently, we were able to obtain good-quality NMR spectra for both sarkomycin and its ester. In addition, the method is not limited and should extend readily to other antibiotics in this series.

Acknowledgment. We thank The National Research Council (Thailand) for support of this work.

Registry No. (±)-**2** (R¹ = R² = H), 90913-14-7; (±)-**6**, 72581-31-8; (±)-**7**, 72525-99-6; (±)-**12**, 90913-15-8; **13**, 39915-66-7; (±)-**14**, 90913-16-9; (±)-**15**, 90913-17-0; (±)-**16**, 90913-18-1; (±)-**17**, 90913-19-2; (±)-**18**, 90913-20-5; (±)-**20**, 90913-21-6; (±)-**23**, 90941-10-9; **24**, 1909-79-1; dimethyl itaconate, 617-52-7; anthracene, 120-12-7; methyl acrylate, 96-33-3.

Supplementary Material Available: ¹H NMR spectra of **12**, **14–18**, **20**, **10**, **7**, **7** + EuFOD, **6**, **24**, and **24** methyl ester (13 pages). Ordering information is given on any current masthead page.

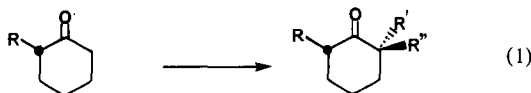
Substituent Effects on the Stereochemistry of Substituted Cyclohexanone Dimethylhydrazone Alkylations. An X-ray Crystal Structure of Lithiated Cyclohexanone Dimethylhydrazone

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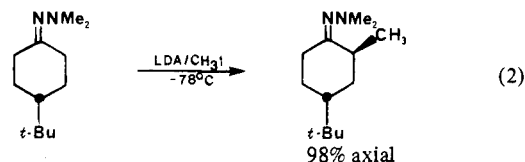
Abstract: Substituent effects on the alkylations of the dimethylhydrazones of 2,4- and 2,6-disubstituted cyclohexanones are reported. High axial selectivities are observed in the alkylations of cyano-substituted metalated hydrazones, but not with alkoxycarbonyl-substituted cases. Hydrazones of 2-substituted cyclohexanones appear to alkylate axially out of a conformer with the 2-substituent pseudoaxially disposed. The possible origins of the stereoselectivities are addressed in light of an X-ray crystal structure of lithiated cyclohexanone dimethylhydrazone.

During the course of a total synthesis effort in our laboratory, we required a geminal difunctionalization of a 2-substituted ketone as depicted in eq 1. The major portion of any relative stereo-



selectivity would have to arise via a stereoelectronically controlled axial entry of an electrophile to the corresponding ketone enolate or its equivalent. Although ketone enolates exhibit mediocre selectivities toward axial alkylation,^{1,2} the corresponding di-

methylhydrazones and related Schiff's base derivatives show remarkable preferences for axial alkylation (eq 2).^{3,4}



We report herein substituent effects on the stereochemistry of the alkylations of metalated cyclohexanone dimethylhydrazones. Dramatic substituent-dependent stereoselectivities are observed in the alkylations of highly stabilized 4-*tert*-butylcyclohexanone-derived hydrazone anions, as well as unanticipated stereochemical reversals in the alkylations of 2-substituted and 2,6-disubstituted cyclohexanone hydrazones. The stereoselectivities are discussed in relation to an X-ray crystal structure of lithiated cyclohexanone dimethylhydrazone.

Results

Product Characterization. Hydrazones **3a–6a** could not be rigorously characterized by simple spectroscopic methods. Ac-

(1) (a) Huff, B. J. L.; Tuller, F. N.; Caine, D. *J. Org. Chem.* **1969**, *34*, 3070. (b) House, H. O.; Umen, M. *J. J. Org. Chem.* **1973**, *38*, 1000. (c) Howe, R.; McQuillin, F. *J. Chem. Soc.* **1958**, 1194. (d) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257. (e) Djerassi, C.; Osiecki, J.; Eisenbraun, E. *J. Am. Chem. Soc.* **1961**, *83*, 4433. (f) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935. (g) Kuehne, M. E. *J. Org. Chem.* **1970**, *35*, 171. (h) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025.

(2) Trans decalones can alkylate axially with high stereoselectivity when axial entry is sterically accessible: Agami, C.; Levisalles, J.; Lo Cicero, B. *Tetrahedron* **1979**, *35*, 961. Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5464. However, these selectivities can be attributed to allylic strain unique to fused-ring systems: Lansbury, P. T.; Dubois, G. E. *Tetrahedron Lett.* **1972**, 3305. Although high axial selectivities are observed in the condensation of tetrabutylammonium enolates with aldehydes, the corresponding alkylations are poorly selective.^{1h}

(3) (a) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337. (b) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687.

(4) Review: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.