Total Synthesis of (−)-Palasonin and (+)-Palasonin and Related Chemistry†

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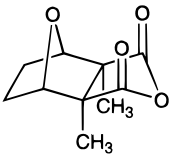
Received February 1, 1996

Introduction

In the past few years, the interaction by cantharidin and its analogues as inhibitors of phosphorylation/dephosphorylation events mediated by protein phosphatase 2A (PP2A) and protein phosphatase 1 (PP1) has been actively investigated.[1] Both PP2A and PP1 are enzymes involved in dephosphorylation of serine and threonine residues of cellular phosphoproteins. Reversible phosphorylation of proteins is a major regulatory mechanism in signal transduction pathways that control cell proliferation, differentiation, and development. PP2A and PP1 have several kinds of roles in these signal transduction pathways. Generally, they act as cell proliferation inhibitors and/or tumor suppressors by opposing the actions of protein kinases that stimulate cell proliferation.[2]

Improved inhibitor specificity is needed with respect to both the organ and the type of protein phosphatase. The 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid derivatives, i.e., cantharidin (**1**), (−)-palasonin (**2**), and demethylated cantharidin (**3**), are structurally simple and potent probes to study the structures of PP2A and PP1 molecules and to understand the mechanism of action related to the inhibition of protein phosphatases activity and the intracellular transductions in eukaryotic cells.[3] In recent biological testing and clinical trials with **1** and **3**, these materials were found to affect cancer cells in several ways.[4]



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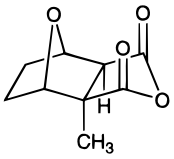

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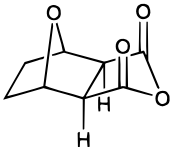

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Palasonin was first isolated by Raj and Kurup[5] from the seeds of *Butea frondosa* and in the following year was shown to be a cantharidin analogue lacking one angular methyl group by Bochis and Fisher.[6] Later, **2** was further characterized by Barua[7] and Schmid[8] and shown to be levoratatory, i.e., (−)-palasonin ($[\alpha]^{25}_{D}$ −2.1°, $CHCl_3$). However, **2** has received little attention in biological testing due to its scarcity.

In 1990, **2** was synthesized in this laboratory and its biological effects were studied by Casida.[9] The chemical and the biological results were reported in preliminary form. This cantharidin analogue lacking one methyl group shows a toxicity toward PP2A and PP1 with intermediate potency among these cantharidin analogues.[1b,9] The presence or the absence of the methyl substituent has a major influence on the biological activity, and so the enantiomers should also vary in activity, thereby helping to define the stereospecificity of the binding site. Due to the asymmetry of palasonin, the structure offers the potential of new types of analogues in optically pure form. We report a detailed study of the synthesis and the chemistry of **2**.

Results and Discussion

Total Synthesis of (±)-Palasonin (2). Recently, Rydberg and Meinwald reported a total synthesis of (±)-**2** starting with α-carbomethoxymaleic anhydride and furan to give crude **2** in poor yield (9 steps), and the crude material was purified by preparative gas chromatography.[10] Although dimethylmaleic anhydride does not add to furan even at pressures up to 40[11] or 60[12] kbar, earlier our laboratory showed that **2** could be synthesized in two steps and in moderate yield (57%) by using the high-pressure (15 kbar for 8 h) Diels−Alder procedure as the key step in the reaction between citraconic anhydride (**6**) and furan, followed by hydrogenation of the (±)-dehydropalasonin (**7**) in non-protic solvent over 10% palladium on carbon.[9] In view of the recent interest in the biological activity of cantharidin analogues, an active study of the high-pressure Diels−Alder reaction between **6** and furan was undertaken in order to develop an efficient way of synthesizing (±)-**2**.

In general, three factors, namely, (a) the molar equiv of furan, (b) the pressure applied, and (c) the reaction time, will determine the yield of dehydropalasonin.[13] In order to optimize the yield of **7** in the reaction between **6** and furan at 8 kbar pressure, excess furan was used. However, when **6** was allowed to react with more than 1.1 molar equiv of furan, substantial amounts of secondary Diels−Alder products **4** and **5** were formed in the reaction, i.e., a mixture of **4** (57%), **5** (27%), and **7** (16%) was formed under 10 molar equiv of furan after 64 h.[14] To minimize the formation of secondary products, a correlation of molar excess of furan and the extent of formation of **4** and **5** was studied. It was found that minimal amounts of **4** and **5** were formed when 1.05 molar equiv of furan was used in the reaction. Further-

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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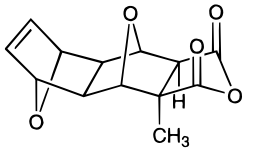

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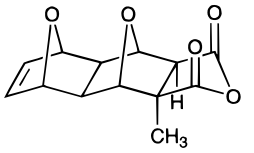

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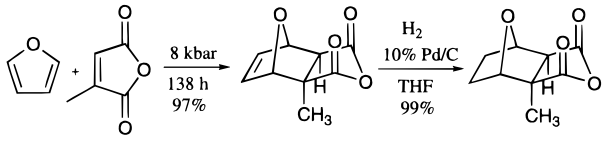
more, a detailed systematic study of the yield of **7** and time relationship was undertaken (see supporting information). It was found that **7** could be obtained in up to 97% yield after 138 h. In all cases, no endo isomer could be detected in the final reaction mixture. Hydrogenation of the **7** in THF over 10% Pd/C gave (±)-**2** in 99% yield. The results are summarized in Scheme 1.

Scheme 1



6 7 (±)-**2**

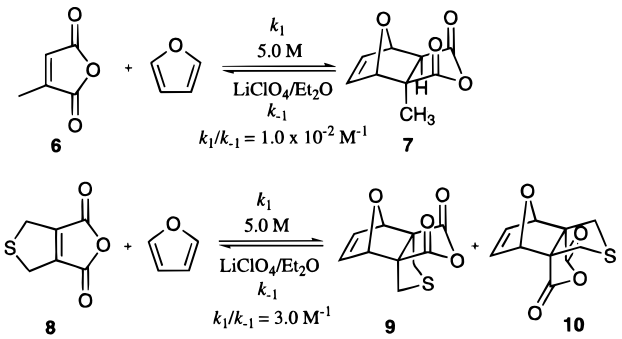
Resolution of (±)-Palasonin. (±)-Palasonin was resolved by allowing it to react, sequentially, with 2 equiv of (*S*)-(−)-α-methylbenzylamines to yield a pair of diastereomeric (*S*)-(−)-α-methylbenzyl-2-methylendothall-diamides. The diastereomeric amides were readily separated and saponified to the diacids. The individual diacids upon reaction with thionyl chloride yielded the corresponding (−)-palasonin and (+)-palasonin.

Diels−Alder Reaction of Citraconic Anhydride and Furan under Normal Pressure. During the synthesis of (±)-**2** using α-carbomethoxymaleic anhydride and furan,[10] **6** (α-methylmaleic anhydride) was used as a dienophile in the Diels−Alder reaction with an excess of furan under hydrogenation conditions. However, no **2** was detected and the only product obtained was methylsuccinic anhydride. There are many reasons why Diels−Alder reaction of **6** and furan failed (steric, electronic), and with the present availability of **7**, the primary cycloaddition product, the effect of temperature upon the Diels−Alder reaction could be studied.

Citraconic anhydride (**6**) (0.7 M) was allowed to react with furan (10.7 mL) under pseudo-first-order conditions (furan used as solvent) to give only 1.5% of **7** (with respect to **6**) at the equilibrium state at 20 °C. Attempts to shift the equilibrium to the product side at elevated temperature failed as the reaction gave a poorer yield of 1.1% of **7** (with respect to **6**) at 40 °C. The equilibrium constants ($K = k_1/k_{-1}$) were determined. Their values are $K = 1.1 \times 10^{-3}$ M^{-1} at 20 °C and $K = 8 \times 10^{-4}$ M^{-1} at 40 °C. The higher temperature, in this case, favors the retro Diels−Alder reaction, the decomposition of **7** to **6** and furan, and shifts the equilibrium slightly to the starting materials.

The kinetic studies showed that **7** (0.5 M) reverted to **6** and furan, exponentially, in a stirred solution of THF (0.5 mL) and furan (1.6 mL) with rates of $k_{-1} = 3.7 \times 10^{-6}$ s^{-1} ($t_{1/2} = 52$ h) at 20 °C and $k_{-1} = 5.9 \times 10^{-5}$ s^{-1} ($t_{1/2} = 3.3$ h) at 40 °C. Thus from the k_{-1} and the equilibrium constant values, the forward rates in the reaction between **6** and furan to give **7** are $k_1 = 4.0 \times 10^{-9}$ M^{-1} s^{-1} at 20 °C and $k_1 = 4.7 \times 10^{-8}$ M^{-1} s^{-1} at 40 °C. A 20 °C increase in temperature accelerates both forward and backward reaction rates by a factor of 10, with a greater accelerating effect on the backward reaction rate. This is in agreement with the general phenomena that **7** is susceptible to thermal cycloreversion due to the aromaticity of furan.[15] Thus high reaction temperature cannot be used to synthesize **7** under these conditions.

Scheme 2



6 7 8 9 10

Herndon[16] found that maleic anhydride reacted with furan to give, initially, the kinetic endo adduct and, eventually, to give the more stable thermodynamic exo adduct. Interestingly, when **6** was allowed to react with furan at high pressure, no endo isomer could be detected. The only product observed in the reaction was the thermodynamically stable exo adduct **7**.

Reversible Diels−Alder Reactions in 5.0 M Lithium Perchlorate−Diethyl Ether. Since a high-pressure apparatus is not common in many laboratories, efforts have been made to develop another methodology for the synthesis of **2**. Attempts to synthesize **7** from **6** and furan in the presence of Lewis acid, i.e., $BF_3 \cdot Et_2O$ and $ZnCl_2$, were unsucessful. The only isolated product was unreacted **6**.

In 1990, Grieco showed that 5.0 M lithium perchlorate in diethyl ether as a medium for affecting the Diels−Alder reaction between furan and dienophile 2,5-dihydrothiophene-3,4-dicarboxylatic anhydride (**8**) proceeded at ambient temperature and pressure to give cycloadducts **9** and **10** in an 85:15 ratio and in 70% yield (Scheme 2).[17] This ionic medium, 5.0 M $LiClO_4/Et_2O$ was studied as an alternative synthetic procedure, in place of the high-pressure method, for the preparation of **2**.

However, our attempts to synthesize **7** from **6** and furan in 5.0 M $LiClO_4/Et_2O$ under Grieco's conditions always gave less than 10% of **7**. For a better understanding of the nature of this medium for this particular reaction, a solution of **6** (0.45 M) and furan (4.41 M) in 5.0 M $LiClO_4/Et_2O$ (2 mL) was stirred at room temperature and the extent of formation of product **7** was monitored with time. A plot of the product ratio of [**7**]/[**6**] versus time finally levels off at the value of 0.044 as shown in Figure 1. This result indicated that the reaction had reached a state of equilibrium with $LiClO_4/Et_2O$ promoting both the forward [4 + 2] Diels−Alder and the retro Diels−Alder reactions with $K = 1.0 \times 10^{-2}$ M^{-1} ($K = k_1/k_{-1}$). Interestingly, again there is no detectable endo isomer in the reaction.

With the availability of **7**, prepared under high-pressure conditions, a study of the retro Diels−Alder reaction was undertaken. A solution of **7** and furan in 5.0 M $LiClO_4/Et_2O$ under the same conditions at room

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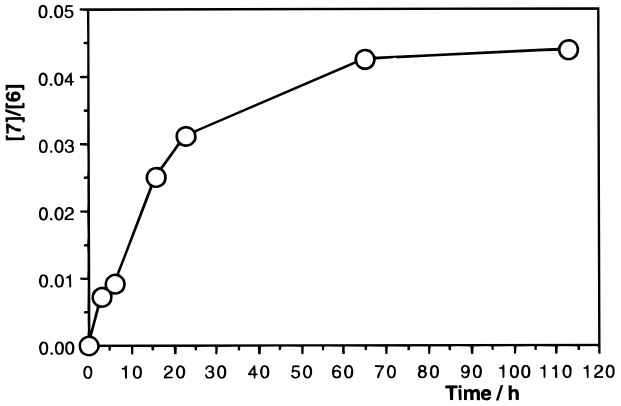

Figure 1. Time-product-ratio profile for the [4 + 2] Diels–Alder reaction between [**6**] = 4.5×10^{-1} M and [furan] = 4.41 M in Et_2O with [$LiClO_4$] = 5.0 M at 20 °C. At equilibrium [**7**]/[**6**] = 0.044 and $k_1/k_{-1} = 1 \times 10^{-2}$ M^{-1}.

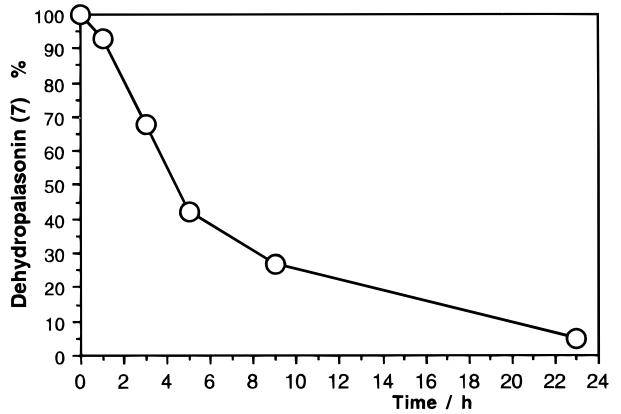

Figure 2. Plot of **7** versus time in the retro Diels–Alder reaction of [**7**] = 2.8×10^{-1} M in Et_2O with [$LiClO_4$] = 5.0 M at 20 °C to give **6** and furan. The first-order rate constant is $k_{-1} = 4.4 \times 10^{-5}$ s^{-1} ($t_{1/2}$ = 4.4 h).

temperature and pressure when stirred for 48 h gave 97% of **6** and 3% of **7**. The rate of solvolysis of **7** in Et_2O with [$LiClO_4$] = 5.0 M at 20 °C was measured, and it was demonstrated that **7** reverted to **6** and furan, exponentially, with a first-order rate constant, $k_{-1} = 4.4 \times 10^{-5}$ s^{-1} ($t_{1/2}$ = 4.4 h), as shown in Figure 2.

From the product ratio of [**7**]/[**6**] = 0.044 at equilibrium, the ratio of forward rate k_1 to the backward rate k_{-1} was found to be $k_1/k_{-1} = 1.0 \times 10^{-2}$ M^{-1} and therefore $k_1 = 4.4 \times 10^{-7}$ M^{-1} s^{-1}. Grieco reagent accelerated both k_1 and k_{-1} in the reaction to the extent that the forward rate k_1 is increased by 110-fold in magnitude while the backward rate k_{-1} is only 12-fold faster. The net result is in shifting the equilibrium constant 9-fold toward the product side ($K = 1.1 \times 10^{-3}$ M^{-1} to $K = 1.0 \times 10^{-2}$ M^{-1}) or, in other words, the forward reaction is 9-fold faster than without the Grieco reagent. Even though the Grieco reagent promotes the cycloadduct formation, with $K = 1.0 \times 10^{-2}$ M^{-1}, it is still not a practical way of synthesizing **7** in the reaction between **6** and furan.

In order to substantiate the generality of $LiClO_4/Et_2O$ of promoting the retro [4 + 2] cycloaddition reaction, a solution of **9** and furan in 5.0 M $LiClO_4/Et_2O$ was stirred at room temperature for 15 h. It was found that **9** underwent retro Diels–Alder reaction to give a mixture of **9** and **8** in the ratio of 47:3. The results pointed to the fact that the reaction of **8** and furan in 5.0 M $LiClO_4/Et_2O$ was also reversible. However, in this case, the forward rate is three times faster than the backward rate, $k_1/k_{-1} = 3.0$ M^{-1}. Therefore, by using excess furan, the equilibrium of the reaction between **8** and furan was shifted to give **9** and **10** in high yield. The results are shown in Scheme 2.

Grieco reagent, 5 M $LiClO_4/Et_2O$, is an excellent medium to promote intermolecular [4 + 2] Diels–Alder reaction. The versatility of this process depends on the relative stabilities of the substrates and the products. The Diels–Alder reaction products **9** and **10** are thermodynamically more stable than **8**, and therefore the reaction proceeds smoothly with the excess of furan. Dehydropalasonin (**7**), however, is thermodynamically unstable with respect to **6** and furan and quickly reverts to the starting material.

Conclusions

Neither high reaction temperature nor Grieco reagent conditions can provide an effective means for the Diels–Alder reaction between citraconic anhydride (**6**) and furan. (±)-Palasonin (**2**) can be synthesized, efficiently, from **6** and furan at 8 kbar of pressure for 138 h, followed by hydrogenation in non-protic solvent over 10% palladium on carbon in 96% yield in two steps. (±)-Palasonin (**2**) has readily been resolved by standard methods into (−)-palasonin and (+)-palasonin.

Experimental Section

General. ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) were measured in $CDCl_3$ solutions calibrated with $MeSi_4$. IR spectra was recorded using KBr pellets for solid samples. Melting points were determined in capillary tubes and were uncorrected. Et_2O and THF were distilled over CaH_2. 2,5-Dihydrothiophene-3,4-dicarboxylic acid anhydride (**8**) was prepared as described.[13] Unless otherwise stated, other solvents and reagents were reagent grade commercial materials used as supplied. Flash chromatography was done on 230–400 mesh silica gel applying medium pressure.[18] Solvent evaporation after extraction was carried out under reduced pressure using a rotary evaporator. The high-pressure apparatus has been described,[13b,19] except that a commercially available electric hydraulic pump and a hydraulic cylinder were used.

General Procedures for High-Pressure Reactions. A solution of the reactants was contained in a Teflon tubing (wall thickness 0.020 in.) which was sealed at both ends by two pairs of brass clamps. The sample tube was placed in the reaction cylinder bore, followed by oil-driven hydraulic pressurization to the required pressure at room temperature. After the reaction was pressurized for a specified period of time, the reactor was depressurized slowly and the reaction mixture processed as described in the text.

(±)-Dehydropalasonin (7). A solution of citraconic anhydride (**6**) (3.0 g, 26.8 mmol) and furan (2.0 g, 29.4 mmol) was pressurized to 8 kbar for 4 days. The crude product was stirred with anhydrous ether, and the mixture was filtered to give a pale yellow solid of dehydropalasonin (4.10 g, 22.8 mmol) in 85% yield. The solid was recrystallized from EtOAc/hexane to give colorless crystals of **7** (3.95 g, 21.9 mmol) in 82% yield: mp 92–93 °C; IR ν_{max} 1383, 1458, 1570, 1774, 1849, 2882, 2941, 3005 cm^{-1}; ^1H NMR δ 1.34 (s, 3H), 2.64 (s, 1H), 5.14 (s, 1H), 5.37 (s, 1H), 6.61 (dd, J = 1.63, 5.79 Hz, 1H), 6.64 (dd, J = 1.68, 5.81 Hz, 1H); ^{13}C NMR δ 17.7, 53.5, 55.5, 83.4, 84.7, 135.8, 137.0, 170.0, 174.3. Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.07, H, 4.66.

(±)-Palasonin (2). To a solution of dehydropalasonin (**7**) (3.95 g, 21.9 mmol) and THF (30 mL) was added 10% Pd/C (0.8 g), the mixture was stirred under hydrogen (3 L inflated balloon) for 20 h, and the reaction mixture was filtered. The filtrate was

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evaporated to give colorless oil which solidified upon standing to give palasonin (3,96 g, 21.8 mmol) in 99% yield. The solid obtained was recrystallized from CH_2Cl_2/*n*-pentane to give colorless crystals of palasonin (3.59 g, 19.7 mmol) in 90% yield: mp 85−86 °C; IR ν_{max} 1791, 1850, 2885, 2941, 2979, 3000, 3021 cm^{-1}; ^1H NMR[5,6,9] δ 1.44 (s, 3H), 1.55−1.63 (m, 1H), 1.73−1.83 (m, 1H), 1.87−1.98 (m, 2H), 2.66 (s, 3H), 4.79 (d, J = 5.1 Hz, 1H), 4.92 (d, J = 5.3 Hz, 1H); ^{13}C NMR δ 16.2, 23.7, 28.2, 54.9, 56.4, 81.4, 83.3, 171.0, 175.6; exact mass calcd for $C_9H_{10}O_4$ 182.0591, found 182.0576. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.22; H, 5.74.

(−)-Palasonin and (+)-Palasonin. 1,3-Dicyclohexylcarbodiimide (DCC) (3.62 g, 17.6 mmol) in THF (10 mL) was added, dropwise, to a stirred solution of (±)-palasonin (3.2 g, 17.6 mmol), (*S*)-(−)-α-methylbenzylamine (2.2 g, 18.0 mmol), Et_3N (1.8 g, 18.0 mmol), and THF (200 mL), and the solution was stirred for 18 h. A second equiv of (*S*)-(−)-α-methylbenzylamine (2.2 g, 18 mmol) was added to the solution. The reaction mixture was filtered, and the filtrate was concentrated to a small volume (20 mL) and stirred at rt for 48 h. Hexane/EtOAc (7/3) was added to the reaction mixture, and the mixture was filtered. The crystals collected were (*S*)-(−)-α-methylbenzyl-2-methylendothalldiamide (2.86 g, 40%): mp 195 °C; $[\alpha]^{20}_D$ −83.9° (*c* 0.6, $CHCl_3$). The filtrate was concentrated and was chromatographed with EtOAc to give the other isomer (*S*)-(−)-α-methylbenzyl-2-methylendothalldiamide (3.10 g, 43%): $[\alpha]^{20}_D$ −78.5° (*c* 0.7, $CHCl_3$). Each diamide (2.5 g, 6.2 mmol) was saponified in refluxing aqueous NaOH/EtOH (50 mL, 2.5 M) for 18 h and the solution was neutralized by adding hydrochloric acid. The solution was evaporated, and the residue was chromatographed through a cation exchange resin column with MeOH/H_2O (1:1). The elutant was evaporated, MeOH was added to the residue, and the mixture was filtered. The filtrate was evaporated to give the diacid which was refluxed in $SOCl_2$ for 1.5 h. Unreacted $SOCl_2$ was removed under reduced pressure. Hexane/EtOAc (3/2) was added to the brown residue, and the solution was filtered. The filtrate was concentrated to give the corresponding palasonin (0.73 g, 65%) and ^1H NMR showed greater than 95% purity. A sample was chromatographed with hexane/EtOAc (3/2) and crystallized out in cold ether/hexane. (−)-Palasonin [mp 104−105 °C; $[\alpha]^{20}_D$ −2.3° (*c* 0.2, $CHCl_3$)] and (+)-palasonin [mp 105−106 °C; $[\alpha]^{20}_D$ +2.2° (*c* 0.3, $CHCl_3$)]. Their spectral data were identical to those of (±)-palasonin.

Stoichiometric Studies of Cycloaddition of Citraconic Anhydride (6) with Furan. (a) A solution of **6** (0.22 g, 1.9 mmol), and furan (1.31g, 19 mmol) was pressurized to 8 kbar for 64 h. The reaction mixture was evaporated under reduced pressure to give a white solid, and the ^1H NMR spectrum indicated the presence of **7**:**4**:**5** in a ratio of 16:57:27. The mixture was chromatographed (EtOAc/hexane: 3/2) to give (i) **4** [mp 205−206 °C (EtOAc/hexane); IR ν_{max} 1799, 1858, 2979, 3016 cm^{-1}; ^1H NMR δ 1.49 (s, 3H), 2.58 (dd, 1H), 2.61 (s, 3H), 2.83 (dd, 1H), 4.38 (s, 1H), 4.47 (s, 1H), 4.96 (s, 1H), 4.98 (s, 1H), 6.29 (dd, 1H); ^{13}C NMR δ 15.1, 42.9, 47.6, 57.2, 79.1, 79.3, 79.5, 80.5, 133.4, 134.1, 170.2, 174.8; exact mass calcd for $C_{13}H_{12}O_5$ 248.0685, found 248.0680] and (ii) **5** [^1H NMR δ 1.46 (s, 3H), 2.01 (d, 1H), 2.20 (d, 1H), 2.66 (s, 1H), 4.76 (s, 1H), 4.88 (s, 1H), 4.98 (s, 1H), 6.41 (dd, 1H), 6.44 (dd, 1H); ^{13}C NMR δ 15.6, 42.4, 47.9, 56.5, 56.6, 80.5, 80.6, 83.1, 84.3, 137.0, 137.6, 170.4, 174.8; exact mass calcd for $C_{13}H_{12}O_5$ 248.0685, found 248.0680]. (b) A solution of **6** (1.17g, 10.5 mmol) and furan (0.75 g, 11.0 mmol) was pressurized to 8 kbar for 138 h. The reaction mixture was evaporated under reduced pressure to give a white solid, and the ^1H NMR spectrum showed a 99% conversion of the substrates to **7**:**4**:**5** in a ratio of 98:1:1.

Cycloaddition of 2,5-Dihydrothiophene-3,4-dicarboxylic Acid Anhydride (8) with Furan. A solution of **8** (0.12 g, 0.79 mmol), furan (0.17 g, 2.5 mmol), and CH_2Cl_2 (0.5 mL) was pressurized to 7.5 kbar for 24 h. The reaction mixture was extracted with $CHCl_3$ and evaporated *in vacuo* to give a pale brown solid: ^1H NMR showed **8**:**9**:**10** in a ratio of 2:6:1. The mixture was chromatographed (EtOAc/hexane: 2/3) to give (i) the exo isomer **9** (0.09 g, 0.4 mmol) in 50% yield [R_f 0.43; ^1H NMR δ 2.69, 3.14 (AB quartet, J = 12.6 Hz, 4H), 5.18, (s, 2H), 6.74 (s, 2H); ^{13}C NMR δ 35.6, 76.6, 83.7, 138.0, 173.0] and (ii) the endo isomer **10** (0.0127g, 0.06 mmol) in 7% yield [R_f 0.57; ^1H NMR δ 3.11, 3.48 (AB quartet, J = 12.7 Hz, 4H), 5.03 (s, 2H), 6.66 (s, 2H); ^{13}C NMR δ 38.3, 74.9, 83.6, 137.0, 170.3]. ^1H NMR values of **9** and **10** are in agreement with those reported.[13b]

Solvolysis of 7 in 5.0 M $LiClO_4$/Et_2O and 4.4 M Furan. A solution of **7** (0.1076 g, 0.6 mmol, 0.3 M), furan (0.6 g, 8.8 mmol), $LiClO_4$ (1.1 g, 5.0 M), and Et_2O (2 mL) was stirred at 20 °C for 48 h. The reaction was quenched with water. and the mixture was extracted with chloroform. The organic extract was dried ($MgSO_4$) and evaporated to give a brown oil (0.04 g, 60% yield): ^1H NMR (**6**, δ 2.19; **7**, δ 1.33) showed **6**:**7** in a ratio of 97:3.

Solvolysis of 9 in 5.0 M $LiClO_4$/Et_2O and 2.2 M Furan. A solution of **9** (0.0521 g, 0.33 mmol, 0.17 M), furan (0.3 g, 4.4 mmol), $LiClO_4$ (1.1 g, 5.0 M), and Et_2O (2 mL) was stirred at 20 °C for 15 h. The reaction was quenched with water, and the mixture was extracted with chloroform. The organic extract was dried ($MgSO_4$) and evaporated to give a pale yellow solid: ^1H NMR (**8**, δ 4.00; **9**, δ 5.20) showed **8**:**9** in a ratio of 47:3.

General Procedures for Kinetics. At Normal Pressure. A solution of reactants was stirred at the specified temperature with the reaction followed by taking an aliquot at time T for ^1H NMR analysis. The relative quantities of [**7**] and [**6**] were determined by ^1H NMR intergrals: **7**, δ 1.32; **6**, δ 2.18. **With Grieco Reagent.** A solution of reactants was stirred in 2 mL of 5.0 M $LiClO_4$ in Et_2O at 20 °C. The reaction was quenched at time T with water, and the solution was extracted with $CHCl_3$. The organic extract was dried ($MgSO_4$) and evaporated. The reaction was followed until the equilibrium state was attained. The relative quantities of [**7**] and [**6**] were determined by ^1H NMR intergrals: **7**, δ 1.32; **6**, δ 2.18.

The amount of **7** left unreacted was calculated by the equation [**7**]/{[**7**] + [**6**]} × 100%. A plot of ln [**7**] versus time (up to 75% conversion of **7**) gave a straight line. The slope obtained gave the first-order rate constant k_{-1}. The half-life was calculated from the equation, $t_{1/2} = \ln 2/k_{-1}$.

Kinetics. Retro Diels−Alder Reactions under Normal Condition. The initial concentration of **7** was 5.1×10^{-1} M at both 20 and 40 °C in THF (0.5 mL) and furan (1.6 mL). **Diels−Alder Reactions under Normal Condition.** The initial concentration of **6** was 6.9×10^{-1} M in furan (10.7 mL) at 20 °C and **6** was 1.4 M in furan (5.3 mL) at 40 °C. The equilibrium constant K (k_1/k_{-1}) was calculated from the equation k_1[**6**][furan] = k_{-1}[**7**] where [furan] = 13.75 M. At 20 °C, [**7**]/[**6**] = 0.015 and $K = 1.1 \times 10^{-3}$ M^{-1}; at 40 °C, [**7**]/[**6**] = 0.011 and $K = 8 \times 10^{-4}$ M^{-1}. **Retro Diels−Alder Reactions in Grieco Reagent.** The initial concentration of **7** was 2.8×10^{-1} M. **Diels−Alder Reactions in Grieco Reagent.** (a) The initial concentration of **6** was 4.5×10^{-1} M and furan was 4.41 M. The equilibrium constant K (k_1/k_{-1}) was calculated from the equation k_1[**6**][furan] = k_{-1}[**7**]: at equilibrium, [**7**]/[**6**] = 0.044 and [furan] > [**6**] > [**7**], i.e., $k_1/k_{-1} = 1.0 \times 10^{-2}$ M^{-1} and $k_1 = 4.4 \times 10^{-7}$ M^{-1} s^{-1} (see Figure 1). (b) The initial concentration of 2,5-dihydrothiophene-3,4-dicarboxylic acid anhydride (**8**) was 2.0×10^{-1} M and furan was 2.2 M in 2 mL of 5.0 M $LiClO_4$ at 20 °C. At equilibrium, {[**9**] + [**10**]}/[**8**] = 7.1, i.e., $k_1/k_{-1} = 3.0$ M^{-1}.

Acknowledgment. This research was supported by National Science Foundation Grant 8618303. We thank Professor J. E. Casida and Dr. N. Kawamura for their advice and encouragement.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of two diastereomeric (*S*)-(−)-α-methylbenzyl-2-methylendothalldiamides and a table of the correlation of molar equiv of furan and the yield of compounds **7**, **4**, and **5** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960210N