Dyotropic Rearrangement of Cycloalkyl β-Lactones. Formation of Spiro vs Fused Butyrolactones as a Function of Ring Size

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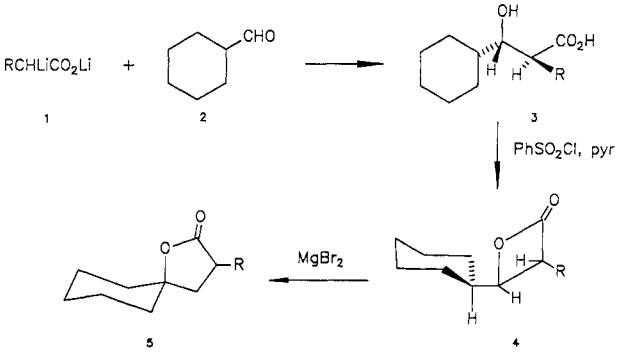
Trans 3-substituted-4-cycloalkyl β-lactones **4** and **8** have been prepared via the condensation of appropriately substituted acetic acid dianions **1** with cyclohexane- or cyclopentanecarboxaldehyde to afford the corresponding diastereomerically pure β-hydroxy acids **3** and **7**, which were then lactonized via treatment with benzenesulfonyl chloride in pyridine. Exposure of these molecules to magnesium bromide in ether prompted a dyotropic rearrangement to either α-substituted spiro butyrolactones **5** (from the cyclohexyl β-lactones) or trans-fused butyrolactones **9** (from the cyclopentyl β-lactones). The latter sequence is particularly useful since the three contiguous asymmetric centers are stereospecifically fixed in the trans,trans relative configuration common to several sesquiterpene lactones.

Introduction

Spiro butyrolactones are found in a variety of naturally occurring molecules[1] and form a pharmacologically important subunit in several drugs.[2] Additionally, they comprise a useful class of synthetic intermediates, being easily convertable into spiro ethers, cyclopentenones, and other functionalities.[3] Not surprisingly, a significant number of synthetic approaches to this structural type have been recorded, often involving the cyclization of the corresponding 3-hydroxy acid (or a derivative thereof) as the final step.[4] Preparative access to the penultimate products encompasses a wide diversity of methods involving nucleophilic attack on a cycloalkanone precursor, including the Reformatsky reaction of bromomethyl acrylate esters,[5] β-lithio propionic acid derivatives,[6] and a variety of homoenolate anion equivalents.[7] Other approaches employ the condensation of bis-Grignard reagents with cyclic anhydrides[8] and the Baeyer–Villiger oxidation of spiro cyclobutanones.[9]

Although generally well-suited for the preparation of unsubstituted spiro butyrolactones, the above methods are generally incapable of placing substituents on the lactone ring in a regiochemically defined manner. If such groupings are desired, which is quite common regardless of the ultimate utilization of the lactone moiety, additional synthetic manipulations become necessary. If the required substituent is not capable of attachment via alkylation of the lactone enolate, major adjustments to the synthetic protocol are mandated, involving the preparation of suitably functionalized precursor molecules. As part of a program aimed at the exploration of dyotropic rearrangements as a tool for stereospecific organic synthesis,[10] we have developed a general, regio- and stereospecific route to either spiro[11] or fused[12] substituted butyrolactones, depending only upon the choice of cycloalkanecarboxaldehyde starting material, which is characterized by expediency, ease of availability of starting materials, and high overall yield. We herein report the details of this methodology.

Scheme I



Results and Discussion

Organic dyotropic rearrangements[13] are characterized by the simultaneous positional interchange of two adjacent atoms on a carbon backbone, shown below in its most general form. The concerted nature of the process requires an anticoplanar alignment of the migrating bonds; as a consequence, a high degree of stereospecificity should be achievable given appropriate substrate molecules. Our research to date has focused on the ring expansion of β-lactones, accompanied by the migration of an atom from

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Table I.[a] Yield Data for the Synthesis of Spiro Butyrolactones 5

entry	suffix	R	yield, % 3[b]	4[c]	5d
1	a	phenyl	83	94	76
2	b	phenoxy	62	95	86
3	c	phenylthio	85	94	72
4	d	ethyl	100[e]	77	50
5	e	1-naphthyl	87	79	92
6	f	methyl	93[e]	90	75
7	g	4-methoxyphenyl	61	96	98
8	h	4-chlorophenyl	81	93	94
9	i	2-thienyl	94	81	77
10	j	3,4-dimethoxyphenyl	89	89	90

[a] All yields pertain to material purified as specified. [b] Recrystallized from ethyl acetate or hexane. [c] Filtered through silica gel. [d] Recrystallized from hexane (if crystalline) or distilled (if oil). [e] Attempted purification resulted in decomposition.

the pendant alkyl substituent into the butyrolactone ring of the product molecule. The general reaction is outlined below. Although dyotropic rearrangements typically be-

have as dynamic equilibria, the ring strain inherent in β-lactones serves to drive the reaction essentially to completion. In theory, any of the three atoms affixed to the attached carbon atom are capable of migration; however, the migratory aptitude of hydrogen over carbon for these reactions predisposes the molecule toward hydride migration if the requisite anticoplanar alignment can be achieved. For the β-lactone precursor molecules examined in this study, such a conformation is easily attained provided the two lactone substituents bear a trans relationship to one another. However, as shall be seen, the migratory aptitude is also markedly dependent on energetic factors such as the release of strain in a pendant cycloalkyl ring.

Synthesis of Spiro Butyrolactones. The sequence leading to α-substituted spiro butyrolactones, which is outlined in Scheme I, begins with the condensation of substituted acetic acid dianion 1 (derived from the acid via treatment with 2 equiv of LDA) with cyclohexanecarboxaldehyde (2) to afford the corresponding β-hydroxy acid 3. Reactions of this nature are known to favor the formation of the threo diastereomer,[14] especially when long reaction times are employed. The small amounts of erythro product that formed were routinely removed via recrystallization.

The β-hydroxy acids thus obtained were converted to the β-lactones 4 via treatment with 2 equiv of benzenesulfonyl chloride in pyridine at 0 °C.[15] The predominant spectral characteristic of these molecules is an intense carbonyl stretch at 1820–1850 cm^{-1}. β-Lactones are somewhat thermally labile, however, and are best converted to the final products without delay.

The dyotropic rearrangement leading to the spiro butyrolactone products 5 was initiated by treatment with a molar equivalent of anhydrous magnesium bromide etherate in diethyl ether. Although an early report indicated very short (ca. 5 min) reaction times,[16] we found a 6-h

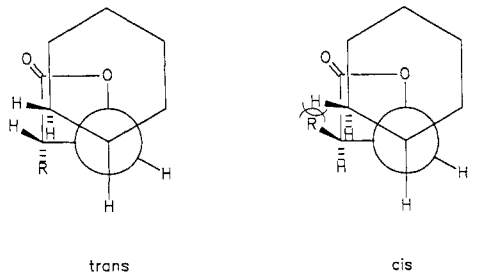

Figure 1.

reaction period necessary to achieve complete conversions. Product purity is highly reflective of the purity of the precursor molecules, so that additional purification was usually unnecessary if the β-lactone was very pure.

The spiro butyrolactones prepared, along with the yields for each step, are collected in Table I. Overall, the yields are extremely good, although it is worth noting that β-lactones 4d and 4f were more thermally labile than the other cases and that prompt isomerization to the corresponding butyrolactones was necessary to achieve the stated yields. In general, β-lactones are stabilized by the presence of large substituents adjacent to the carbonyl group; however, judicious handling of compounds bearing small attached groups, along with the shortest feasible storage times, allowed overall conversions in line with the other molecules. Nevertheless, the unsubstituted parent spiro butyrolactone (5, R = H) cannot be prepared via this sequence due to the extreme instability of the β-lactone, although it is available via reductive desulfurization[17] of 5c or by various published routes.[18]

The success of this approach hinges upon the purity of the β-hydroxy acids 3. Fortunately, a single recrystallization usually suffices to achieve spectral and chromatographic homogeneity. If the small quantities of erythro diastereomers are not removed, they will form β-lactones in the next step wherein the pendant cyclohexane ring and the other ring substituent will bear a cis relationship. As seen in Figure 1, this situation results in steric interference, impeding the free rotation about the cyclohexyl–lactone bond (as exists in the trans cases) necessary to allow preferential hydrogen migration. The primary consequence is contamination of the products with isomeric impurities and a significant reduction in yield. It should be noted that the cis/trans isomer pairs of β-lactones do not resolve on thin layer chromatographic analysis and, considering the limited shelf life of these compounds, purification at this stage is not practical.

Synthesis of Fused Butyrolactones. At this point, we wished to ascertain whether conditions might be discovered that would allow carbon migration during the rearrangement step without resorting to an attempt at synthesis of cis β-lactones. Since expansion from a six- to a seven-membered ring is endothermic, and since acyclic cases all exhibit hydrogen migration,[10] it was not surprising that the cyclohexyl β-lactones proceeded via the same reaction pathway. It occurred to us that the exothermic nature of a cyclopentane to cyclohexane ring expansion (ca. 6 kcal/mol[19]) might thwart this observed propensity and allow for carbon migration, resulting in expansion of the cyclopentyl ring, in addition to the attached β-lactone, to produce a cyclohexano-fused butyrolactone. Thus, a small

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(18) For instance, see: Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395.
(19) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.

Scheme II

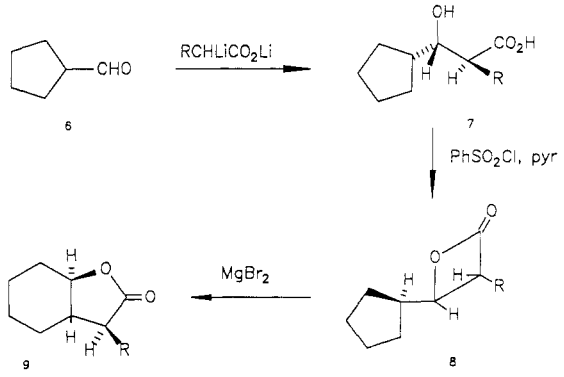
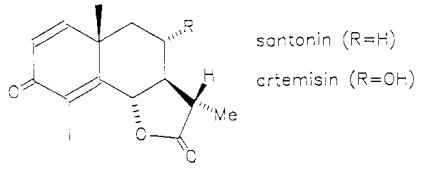


Table II.[a] Yield Data for the Synthesis of Fused Butyrolactones 9

entry	suffix	R	yield, % 7[b]	8[c]	9[d]
1	a	phenyl	79	89	98
2	b	phenoxy	90	93	82
3	c	phenylthio	99[e]	65	90

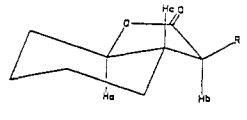
[a] All yields pertain to material purified as specified. [b] Recrystallized from hexane. [c] Filtered through silica gel. [d] Recrystallized from hexane (if crystalline) or chromatographed (if oil). [e] Attempted purification resulted in decomposition.

ancillary study was carried out that was strictly analogous to the earlier work, except that cyclopentanecarboxaldehyde (6) was employed in place of the six-membered homologue. We were most gratified to discover that this facile change in the sequence in fact caused a complete change in the rearrangement step to produce trans-fused butyrolactones in high yield. The overall sequence is outlined in Scheme II, and the yield data are arranged in Table II. The most potentially useful aspect of this development is that all three contiguous asymmetric centers in the products are stereospecifically fixed in the same relative configuration as that which occurs in many natural products. α-Santonin and α-artemisin, for example,



possess the same trans,trans configuration as in **9**, but to date have been synthesized only via stereoselective techniques that produce significant amounts of undesired stereoisomers.[20]

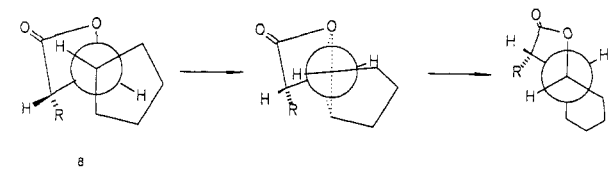
The trans,trans stereochemistry of fused butyrolactones **9** was established via 360-MHz ^{1}H NMR spectroscopy. Ha



appeared as a triplet of doublets centered at 3.90 ppm for **9a**; not only is this splitting pattern expected for a proton in this environment but a chemical shift in this range has been demonstrated to be indicative of a trans ring fusion regardless of substituent patterns on the lactone ring.[21]

(20) Heathcock, C. H. *The Total Synthesis of Natural Products, Vol. II*; ApSimon J., Ed.; J. Wiley and Sons: New York, 1973; pp 315–326 and references cited therein.

Scheme III



Hb appeared as the expected doublet, with coupling constants of sufficient magnitude (**9a**, J = 11.60; **9b**, J = 12.91) to confirm the trans relationship of Hb and Hc.[22] The NMR spectra were exceptionally clean and uncontaminated with isomeric reaction products.

Probably the greatest attribute of the reaction is its stereospecificity, which lends substantial support to the proposition that dyotropic rearrangements are concerted. In Scheme III, the trans β-lactone 8 is represented in the lowest energy conformation in which a carbon–carbon bond in the cyclopentane ring is aligned with the lactone carbon–oxygen bond; this arrangement situates the methine protons anti to one another. This relationship is maintained during the simultaneous σ bond migrations, as is the relative configuration of the R substituent and the adjacent center established during the initial condensation reaction.

Although our accumulated evidence thus far supports a concerted reaction, it is theoretically possible that this process involves an initial ionization of the β-lactone and subsequent carbon migration to the resulting carbocation. If this scenario is indeed operative, however, the migration must be extremely rapid to account for the isomeric purity of the products. We are pursuing this question and will report our results in the future.

In summary, we have developed a short, inexpensive, and high-yield process for the synthesis of either spiro or fused butyrolactones from cyclic aldehydes and substituted acetic acid derivatives, wherein a stereospecific dyotropic rearrangement serves as the cornerstone transformation. We are actively extending this investigation to more complex substrates with an eye toward utilization in natural product synthesis.

Experimental Section

All reactions were carried out under nitrogen, unless otherwise specified. Glassware was routinely oven-dried at 120 °C for a minimum of 4 h and then was assembled under a nitrogen stream. Anhydrous solvents were obtained by distillation, immediately prior to use, from sodium benzophenone ketyl (diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran), barium oxide (diisopropylamine, dimethylformamide), or sodium (toluene). ^{1}H NMR spectra were recorded at 60, 360, or 500 MHz. The peak multiplicity e means "envelope". Thin-layer chromatographic analyses were carried out on Analtech silica gel G (250 μm) plates using the specified solvent as eluent; visualization was effected by either ultraviolet light or by charring with phosphomolybdic acid. Preparative column chromatography employed Merck silica gel 60 (230–400 mesh ASTM).

General Procedure for the Preparation of β-Hydroxy Acids.[23] An oven-dried, three-necked flask, equipped with a low

(21) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.

(22) Das Gupta, T. K.; Felix, D.; Kempe, U. M.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2198.

(23) We examined several potential enhancements to this step, including using freshly distilled ether, newly opened magnesium dibromide etherate, and even magnesium bromide prepared[24] immediately prior to use. In all cases, the positive effects on the reaction outcome were minimal or nonexistent. Thus, even (anhydrous) ether from an opened container and magnesium bromide etherate from an opened (but atmosphere-protected) bottle serve admirably and add considerably to the overall convenience of the reaction sequence.

temperature thermometer, nitrogen inlet, rubber septum, and magnetic stirring bar, was charged with 30 mL of tetrahydrofuran (THF) followed by 4.05 g (5.61 mL, 40 mmol) of diisopropylamine. The solution was stirred and cooled to −78 °C with a dry ice–acetone bath, and 25.0 mL of a 1.6 M solution (40 mmol) of *n*-butyllithium in hexanes was added over 10 min. The resulting clear yellow solution of lithium diisopropylamide was stirred at ca. −40 °C for 15 min, whereupon 20 mL of a 1.0 M solution (20 mmol) of the acetic acid derivative in THF was added dropwise via syringe over 10 min. The cooling bath was removed and the resulting mixture was stirred for 1 h, returning to room temperature. An 8-mL portion of a 2.5 M solution (20 mmol) of cyclohexanecarboxaldehyde (1) or cyclopentanecarboxaldehyde (6) was then added via syringe, causing an exotherm to ca. 35 °C and a lessening of the yellow color. Stirring at ambient temperature was continued for 16 h, at which point the mixture was poured onto ca. 50 g of ice, the layers were separated, and the aqueous phase was extracted twice with 20 mL of ether. The ether was discarded, the aqueous phase was acidified with 6 N hydrochloric acid, and the resulting mixture was extracted with three 20-mL portions of ether. The consolidated extracts were washed with brine and dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford the crude product. A single recrystallization from ethyl acetate or chloroform rendered the material sufficiently pure to proceed to the next step. Purification to analytical standards was attempted for all β-hydroxy acids through additional recrystallizations, but in several cases this was not possible due to instability, presumably via facile dehydration, as evidenced by irreproducible carbon and hydrogen analyses. The above procedure was employed for the acquisition of the following intermediates.

3-Cyclohexyl-3-hydroxy-2-phenylpropanoic acid (3a), a crystalline white solid, was obtained in 83% yield; an analytical sample was secured via recrystallization from hexane: mp 137–138 °C; IR (KBr) 2826, 2653, 1702, 1448, 1270, 650 cm^{-1}; NMR ($CDCl_3$) δ 7.40–7.10 (m, 5 H, Ar *H*), 6.51 (s, 1 H, COO*H*), 4.82–4.60 (m, 1 H, PhC*H*), 4.01–3.79 (m, 1 H, HOC*H*), 1.80–1.01 (e, 11 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.33. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.78; H, 8.16.

3-Cyclohexyl-3-hydroxy-2-phenoxypropanoic acid (3b), a crystalline white solid, was obtained in 62% yield; an analytical sample was secured via recrystallization from hexane: mp 94–95 °C; IR (KBr) 3081, 2955, 1715, 1481, 1220, 1121 cm^{-1}; NMR ($CDCl_3$) δ 10.51 (s, 1 H, COO*H*), 7.39–6.72 (m, 5 H, Ar H), 4.73 (d, 1 H, PhOC*H*), 3.90 (t, 1 H, HOC*H*), 2.15–0.95 (e, 11 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.44. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.32, 7.77.

3-Cyclohexyl-3-hydroxy-2-(phenylthio)propanoic acid (3c), a crystalline clear solid (needles), was obtained in 55% yield; purification to analytical standards was not possible: mp 109–110 °C; IR (KBr) 3019, 3135, 2920, 2878, 1718, 1128 cm^{-1}; NMR ($CDCl_3$) δ 9.21 (s, 1 H, COO*H*), 7.60–7.00 (m, 5 H, Ar *H*), 3.81 (m, 1 H, PhSC*H*), 3.62 (m, 1 H, HOC*H*), 2.09–0.91 (e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.57.

3-Cyclohexyl-3-hydroxy-2-ethylpropanoic acid (3d), a clear, colorless oil, was obtained in quantitative yield. Attempted purification via distillation resulted in decomposition; thus, the material was used directly in the next step: IR (film) 3600, 2955, 2854, 1707, 1450, 1199 cm^{-1}; NMR ($CDCl_3$) δ 12.2 (s, 1 H, COO*H*), 4.31–3.92 (m, 1 H, HOC*H*), 3.61–3.06 (m, 1 H, EtC*H*), 2.10–0.90 (br e, 13 H, cycloalkyl C*H* + CH_3CH_2), 1.05 (t, 3 H, CH_3); TLC (EtOAc) R_f 0.40.

3-Cyclohexyl-3-hydroxy-2-(1-naphthyl)propanoic acid (3e), a white, crystalline solid, was obtained in 87% yield; purification to analytical standards was not possible: mp 180–182 °C; IR (KBr) 2931, 2844, 1693, 1418, 793, 771 cm^{-1}; NMR ($CDCl_3$) δ 8.22–7.10 (br m, 7 H, Ar *H*), 6.15 (s, 1 H, COO*H*), 4.62 (d, *J* = 6 Hz, 1 H, naphthyl-C*H*), 4.28–4.00 (m, 1 H, HOC*H*), 1.96–0.80 (e, 11 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.28.

3-Cyclohexyl-3-hydroxy-2-methylpropanoic acid (3f), a clear, colorless oil, was obtained in 93% yield. Attempted purification via distillation resulted in decomposition; thus, the material was used directly in the next step: IR (film) 3590, 2995, 2882, 1710, 1392, 1201 cm^{-1}; NMR ($CDCl_3$) δ 12.2 (s, 1 H, COO*H*), 4.33–3.90 (m, 1 H, HOC*H*), 3.59–3.05 (m, 1 H, CH_3CH), 2.11–0.91 (br e, 11 H, cycloalkyl C*H*), 1.38 (d, *J* = 2 Hz, 3 H, CH_3); TLC (EtOAc) R_f 0.45.

3-Cyclohexyl-3-hydroxy-2-(4-methoxyphenyl)propanoic acid (3g), a white crystalline solid, was obtained in 61% yield; an analytical sample was secured via recrystallization from ethyl acetate: mp 156–158 °C; IR (KBr) 3485, 2926, 1716, 1514, 1248, 1172 cm^{-1}; NMR ($CDCl_3$) δ 7.42–6.82 (m, 4 H, Ar *H*), 4.40–3.63 (m, 2 H, HOC*H* + ArC*H*), 2.20 (s, 3 H, OCH_3), 1.90–0.90 (e, 11 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.48. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.02; H, 7.75.

3-Cyclohexyl-3-hydroxy-2-(4-chlorophenyl)propanoic acid (3h), a white crystalline solid, was obtained in 81% yield; an analytical sample was secured via recrystallization from hexane: mp 120–121 °C; IR (KBr) 3406, 2828, 1729, 1492, 1206, 1091 cm^{-1}; NMR ($CDCl_3$) δ 7.48–7.31 (m, 4 H, Ar *H*), 6.22 (s, 1 H, COO*H*), 4.10–3.88 (m, 2 H, HOC*H* + ArC*H*), 1.99–1.02 (e, 11 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.82. Anal. Calcd for $C_{15}H_{19}ClO_3$: C, 63.72; H, 6.77. Found: C, 63.98; H, 6.54.

3-Cyclohexyl-3-hydroxy-2-(2-thienyl)propanoic acid (3i), a white crystalline solid, was obtained in 84% yield; an analytical sample was secured via recrystallization from hexane: mp 129–130 °C; IR (KBr) 3400, 2940, 2850, 1705, 1257, 714 cm^{-1}; NMR ($CDCl_3$) δ 7.42–6.95 (m, 3 H, Ar *H*), 5.29 (s, 1 H, COO*H*), 4.40–4.06 (m, 2 H, HOC*H* + Ar*H*), 2.02–1.11 (e, 11 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.52. Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13. Found: C, 61.75; H, 6.98.

3-Cyclohexyl-3-hydroxy-2-(3,4-dimethoxyphenyl)propanoic acid (3j), a white, powdery solid, was obtained in 89% yield; an analytical sample was secured via recrystallization from ethyl acetate/cyclohexane (1:1): mp 212–215 °C; IR (KBr) 2928, 2850, 1682, 1520, 1197, 1034 cm^{-1}; NMR ($CDCl_3$) δ 7.26 (s, 1 H, COO*H*), 6.97–6.81 (m, 3 H, Ar *H*), 3.97 (d, *J* = 10.3 Hz, 1 H, ArC*H*), 2.18 (s, 1 H, O*H*), 1.74–1.06 (e, 11 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.23. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.39; H, 7.57.

3-Cyclopentyl-3-hydroxy-2-phenylpropanoic acid (7a), a white, crystalline solid, was obtained in 79% yield; an analytical sample was secured via recrystallization from hexane: mp 140–143 °C; IR (KBr) 3320, 2960, 2857, 1698, 1279, 699 cm^{-1}; NMR ($CDCl_3$) δ 7.51–7.32 (m, 5 H, Ar *H*), 6.11 (s, 1 H, COO*H*), 4.29–4.11 (m, 1 H, ArC*H*), 3.91–3.72 (m, 1 H, HOC*H*), 1.82–1.43 (m, 9 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.26. Anal. Calcd for $C_{14}H_{18}O_3$: C, 72.55; H, 8.12. Found: C, 72.74; H, 8.01.

3-Cyclopentyl-3-hydroxy-2-phenoxypropanoic acid (7b), a white, crystalline solid, was obtained in 90% yield; an analytical sample was secured via recrystallization from hexane: mp 106–107.5 °C; IR (KBr) 3480, 3371, 2954, 1701, 1588, 1266 cm^{-1}; NMR ($CDCl_3$) δ 7.30–6.75 (m, 5 H, Ar *H*), 3.10–2.91 (m, 1 H, PhOC*H*), 2.15 (dd, *J* = 2 Hz, 1 Hz, 1 H, HOC*H*), 1.70–1.31 (e, 9 H, cycloalkyl C*H*); TLC ($CHCl_3$) R_f 0.94. Anal. Calcd for $C_{14}H_{18}O_4$: C, 68.16; H, 7.63. Found: C, 67.95; H, 7.77.

3-Cyclopentyl-3-hydroxy-2-(phenylthio)propanoic acid (7c), a very thick yellow oil, was prepared in 98.6% yield. Purification via distillation resulted in decomposition; thus, the material was used directly in the next step: IR (film) 3034, 3019, 2955, 2916, 2870, 1709 cm^{-1}; NMR ($CDCl_3$) δ 8.31 (s, 1 H, COO*H*), 7.72–7.09 (m, 5 H, SC_6H_5), 3.91–3.82 (m, 1 H, PhSC*H*), 3.79–3.55 (m, 1 H, HOC*H*), 2.09–1.85 (m, 9 H, cycloalkyl C*H*); TLC (EtOAc) R_f 0.44 (major), 0.18 (trace).

General Procedure for the Preparation of β-Lactones. An oven-dried 25-mL Erlenmeyer flask was fitted with a rubber septum and magnetic stirring bar and was charged with 10 mL of pyridine. A 500-mg portion of β-hydroxy acid **3** or **7** was added, and the stirred solution was cooled in an ice bath to 0 °C. Benzenesulfonyl chloride (2 equiv) was added dropwise via syringe with stirring, and the resulting solution was stored at 35 °C for 16 h. The resulting orange/red solution was poured onto ca. 50 g of ice and the mixture was extracted with three 15-mL portions of ether. The consolidated extracts were sequentially washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, water, and finally brine. After being dried ($MgSO_4$) and filtered, the solvents were removed under reduced pressure to afford the crude product. Filtration through silica gel, employing dichloromethane as the eluent, afforded material of sufficient purity

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to proceed to the next step. This protocol afforded the following molecules, for which reproducible combustion analyses were not possible due to thermal instability.

4-Cyclohexyl-3-phenyloxetan-2-one (4a), a clear, colorless oil, was obtained in 94% yield: IR (film) 2933, 2927, 1828, 1140, 975, 867 cm^{-1}; NMR ($CDCl_3$) δ 7.22 (s, 5 H, Ar *H*), 4.42 (d, J = 4 Hz, 1 H, PhC*H*), 4.18 (m, 1 H, OC*H*), 2.09–0.80 (br e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.78.

4-Cyclohexyl-3-phenoxyoxetan-2-one (4b), a clear, colorless oil, was obtained in 95% yield: IR (film) 2933, 2927, 1828, 1140, 975, 867 cm^{-1}; NMR ($CDCl_3$) δ 7.22 (s, 5 H, Ar *H*), 4.42 (d, J = 4 Hz, 1 H, PhC*H*), 4.18 (m, 1 H, OC*H*), 2.09–0.80 (br e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.72.

4-Cyclohexyl-3-(phenylthio)oxetan-2-one (4c), a clear, colorless oil, was obtained in 94% yield: IR (film) 2928, 1828, 1440, 1132, 1113, 742 cm^{-1}; NMR ($CDCl_3$) δ 7.62–7.08 (m, 5 H, Ar *H*), 4.38 (d, J = 4 Hz, 1 H, PhSC*H*), 4.09 (m, 1 H, OC*H*), 2.09–0.75 (br e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.72.

4-Cyclohexyl-3-ethyloxetan-2-one (4d), a clear, colorless oil, was obtained in 77% yield: IR (film) 2931, 2855, 1822, 1451, 1131, 898 cm^{-1}; NMR ($CDCl_3$) δ 4.29–3.70 (m, 1 H, CH_3CH), 3.65–3.11 (m, 1 H, OC*H*), 2.09–0.80 (br e, 11 H, cycloalkyl C*H*), 1.39 (m, 2 H, CH_3CH_2), 0.91 (t, 3 H, CH_3); TLC (CH_2Cl_2) R_f 0.68.

4-Cyclohexyl-3-(1-naphthyl)oxetan-2-one (4e), a white, crystalline solid, was obtained in 79% yield; a small sample was recrystallized twice from hexane but gave irreproducible combustion analyses (the best is provided below): mp 99–100 °C; IR (KBr) 2927, 2852, 1819, 1118, 855, 799 cm^{-1}; NMR ($CDCl_3$) δ 8.18–7.37 (br m, 7 H, Ar *H*), 5.19 (d, J = 2 Hz, 1 H, C*H*=O), 4.60 (dd, J = 2 Hz, 3 Hz, 1 H, naphthyl C*H*), 2.40–1.02 (br e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.63. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 80.71; H, 7.65.

4-Cyclohexyl-3-methyloxetan-2-one (4f), a clear, colorless oil, was obtained in 90% yield: IR (film) 2931, 2855, 1827, 1451, 1130, 983 cm^{-1}; NMR ($CDCl_3$) δ 4.31–3.72 (m, 1 H, CH_3CH), 3.67–3.09 (m, 1 H, OC*H*), 2.12–0.80 (br e, 11 H, cycloalkyl C*H*), 1.43 (d, J = 2 Hz, 3 H, CH_3); TLC (CH_2Cl_2) R_f 0.63.

4-Cyclohexyl-3-(4-methoxyphenyl)oxetan-2-one (4g), a clear, colorless oil, was obtained in 96% yield: IR (film) 2931, 2855, 1822, 1516, 1250, 1181 cm^{-1}; NMR ($CDCl_3$) δ 6.91 (dd, 4 H, C_6H_4), 4.22 (d, J = 4 Hz, 1 H, C*H*=O), 4.08 (m, 1 H, OC*H*), 3.60 (s, 3 H, OCH_3), 1.89–0.85 (br e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.51.

4-Cyclohexyl-3-(4-chlorophenyl)oxetan-2-one (4h), a clear, colorless oil, was obtained in 93% yield: IR (film) 2950, 2871, 1825, 1501, 1122, 1095 cm^{-1}; NMR ($CDCl_3$) δ 7.48–7.11 (m, 4 H, C_6H_4), 4.44 (d, J = 4 Hz, 1 H, C*H*=O), 4.28–4.09 (m, 1 H, OC*H*), 2.15–1.29 (e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.85.

4-Cyclohexyl-3-(2-thienyl)oxetan-2-one (4i), a clear, colorless oil, was obtained in 81% yield: IR (film) 2940, 2852, 1827, 1455, 1109, 842 cm^{-1}; NMR ($CDCl_3$) δ 7.36–6.95 (m, 3 H, thienyl C*H*), 4.66 (d, J = 4 Hz, 1 H, C*H*C=O), 4.24 (m, 1 H, OC*H*), 2.15–0.89 (e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.78.

4-Cyclohexyl-3-(3,4-dimethoxyphenyl)oxetan-2-one (4j), a clear, colorless oil, was obtained in 89% yield: IR (film) 2954, 1821, 1729, 1518, 1465, 1264 cm^{-1}; NMR ($CDCl_3$) δ 7.51–6.71 (m, 3 H, C_6H_3), 4.98 (d, J = 6 Hz, 1 H, C*H*C=O), 4.58 (m, 1 H, OC*H*), 3.89 (s, 6 H, OCH_3), 1.98–1.00 (e, 11 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.29.

4-Cyclopentyl-3-phenyloxetan-2-one (8a), a clear, yellow oil, was obtained in 89% yield: IR (film) 2956, 1827, 1451, 1117, 868, 699 cm^{-1}; NMR ($CDCl_3$) δ 7.61–7.10 (br s, 5 H, Ar *H*), 4.36 (d, J = 1.5 Hz, 1 H, C*H*C=O), 3.40 (dd, J = 2 Hz, 1 H, OC*H*), 2.11–1.00 (e, 9 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.73.

4-Cyclopentyl-3-phenoxyoxetan-2-one (8b), a clear, colorless oil, was obtained in 93% yield: IR (film) 2961, 1841, 1599, 1496, 1231, 1267 cm^{-1}; NMR ($CDCl_3$) δ 7.48–6.89 (m, 5 H, Ar *H*), 5.15 (d, J = 3 Hz, 1 H, C*H*C=O), 4.30 (m, 1 H, OC*H*), 2.11–1.12 (e, 9 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.68.

4-Cyclopentyl-3-(phenylthio)oxetan-2-one (8c), a clear, colorless oil, was obtained in 65% yield: IR (film) 2975, 1826, 1440, 1137, 742, 691 cm^{-1}; NMR ($CDCl_3$) δ 7.61–7.08 (m, 5 H, Ar *H*), 4.31 (d, J = 3 Hz, 1 H, C*H*C=O), 4.19 (m, 1 H, OC*H*), 1.93–1.60 (e, 9 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.63.

General Procedure for the Preparation of Butyrolactones. An oven-dried 25 mL three-necked flask was equipped with a nitrogen inlet and stirring bar and was charged with 10 mL of a 1.0 M solution (10 mmol) of β-lactone **4** or **8** in anhydrous ether. Stirring was begun, and 2.58 g (10 mmol) of magnesium bromide etherate was added in one portion. The light yellow mixture was stirred under nitrogen for 6 h, whereupon the reaction was terminated by the cautious addition of 10 mL of water. The layers were separated, the ether layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to afford the product. Recrystallization from hexane (or, in the case of **5c**, distillation under reduced pressure) afforded material of near analytical purity. Using this protocol, these butyrolactones were prepared and characterized, displaying the following analytical data.

9-Phenyl-7-oxaspiro[5.4]decan-8-one (5a), a white, highly crystalline solid, was obtained in 76% yield; an analytical sample was obtained via recrystallization from hexane: mp 62.5–63 °C; IR (KBr) 2932, 1750, 1450, 1212, 1125, 937 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (s, 5 H, Ar *H*), 3.95 (dd, J = 9,11 Hz, PhC*H*), 2.74–2.01 (m, 2 H, lactone CH_2), 1.90–12.0 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.62. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.84; H, 7.69.

9-Phenoxy-7-oxaspiro[5.4]decan-8-one (5b), a white, crystalline solid, was obtained in 86% yield; an analytical sample was obtained via recrystallization from hexane: mp 126–127 °C/0.08 mm; IR (KBr) 2943, 1753, 1443, 1220, 1035, 940 cm^{-1}; NMR ($CDCl_3$) δ 7.34–6.61 (m, 5 H, Ar *H*), 4.97 (t, 1 H, PhOC*H*), 2.72–2.09 (m, 2 H, lactone CH_2), 1.95–0.95 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.64. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.12; H, 7.48.

9-(Phenylthio)-7-oxaspiro[5.4]decan-8-one (5c), a white, crystalline solid, was obtained in 72% yield; an analytical sample was obtained via column chromatography (CH_2Cl_2): mp 109–110 °C; IR (KBr) 3011, 2936, 1768, 1610, 1206, 897 cm^{-1}; NMR ($CDCl_3$) δ 7.69–7.19 (m, 5 H, Ar *H*), 4.03 (t, 1 H, PhSC*H*), 2.70–1.92(m, 2 H, lactone CH_2), 1.98–1.28 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.83. Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.57; H, 6.92. Found: C, 68.61; H, 6.80.

9-Ethyl-7-oxaspiro[5.4]decan-8-one (5d), a clear, colorless oil, was obtained in 50% yield; an analytical sample was obtained via evaporative distillation: bp 166–175 °C/0.08 mm; IR (KBr) 2954, 2937, 1788, 1450, 1201, 1157 cm^{-1}; NMR ($CDCl_3$) δ 2.95–2.17 (m, 5 H, lactone C*H* + CH_3CH_2), 1.98–1.35 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.54. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.11; H, 10.10.

9-(1-Naphthyl)-7-oxaspiro[5.4]decan-8-one (5e), a white crystalline solid, was prepared in 92% yield; an analytical sample was secured via recrystallization from hexane: mp 102.5–103.5 °C; IR (KBr) 2932, 2856, 1764, 1158, 1126, 775 cm^{-1}; NMR ($CDCl_3$) δ 7.91–7.26 (m, 8 H, Ar *H*), 4.67 (t, J = 10.2 Hz, 1 H, C*H*C=O), 2.78–2.71 (m, 2 H, lactone C*H*), 2.02–1.26 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.40. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.47; H, 7.14.

9-Methyl-7-oxaspiro[5.4]decan-8-one (5f), a white, highly crystalline solid, was obtained in 75% yield; an analytical sample was obtained via recrystallization from hexane: mp 70.5–71 °C; IR (KBr) 2929, 2838, 1765, 1449, 1216, 1131 cm^{-1}; NMR ($CDCl_3$) δ 3.09–2.21 (m, 3 H, lactone CH_2), 1.89–1.42 (e, 10 H, cycloalkyl C*H*), 1.28 (d, J = 6 Hz, 3 H, CH_3); TLC (CH_2Cl_2) R_f 0.60. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.18; H, 9.67.

9-(4-Methoxyphenyl)-7-oxaspiro[5.4]decan-8-one (5g), a white, highly crystalline solid, was obtained in 98% yield; an analytical sample was obtained via recrystallization from hexane: mp 77–78.5 °C; IR (KBr) 2937, 1761, 1517, 1262, 1252, 1202 cm^{-1}; NMR ($CDCl_3$) δ 7.19 (d, J = 8 Hz, 2 H Ar *H*), 6.89 (d, J = 8 Hz, 2 H, Ar *H*), 3.93 (m, 1 H, C*H*C=O), 3.79 (s, 3 H, OCH_3), 2.59 (m, 2 H, lactone CH_2), 1.89–1.42 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.26. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.46; H, 7.59.

9-(4-Chlorophenyl)-7-oxaspiro[5.4]decan-8-one (5h), a white, highly crystalline solid, was obtained in 94% yield; an analytical sample was obtained via recrystallization from hexane: mp 88–88.5 °C; IR (KBr) 2937, 1760, 1401, 1207, 1152, 836 cm^{-1}; NMR ($CDCl_3$) δ 7.29 (s, 4 H, Ar *H*), 4.05 (dd, J = 9,11 Hz, 1 H, C*H*C=O), 2.92–2.11 (m, 2 H, lactone CH_2), 1.96–1.35 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.66. Anal. Calcd for $C_{15}H_{17}ClO_2$: C, 68.05; H, 6.47. Found: C, 67.75; H, 6.38.

9-(2-Thienyl)-7-oxaspiro[5.4]decan-8-one (5i), a white, highly crystalline solid, was obtained in 77% yield; an analytical sample was obtained via recrystallization from hexane: mp 54–54.5 °C; IR (KBr) 2930, 1773, 1207, 1197, 1124, 730 cm^{-1}; NMR ($CDCl_3$) δ 7.33–6.92 (m, 3 H, thienyl C*H*), 4.30 (dd, *J* = 9,11 Hz, 1 H, C*H*C=O), 2.92–2.11 (m, 2 H, lactone CH_2), 2.05–1.31 (e, 10 H, cycloalkyl C*H*); TLC (CH_2Cl_2) R_f 0.67. Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 66.02; H, 6.68.

9-(3,4-Dimethoxyphenyl)-7-oxaspiro[5.4]decan-8-one (5j), a white, powdery solid, was obtained in 90% yield; an analytical sample was obtained via column chromatography ($CHCl_3$): mp 88–88.5 °C; IR (KBr) 2937, 1760, 1522, 1269, 1121, 937 cm^{-1}; NMR ($CDCl_3$) δ 6.81 (s, 3 H, Ar *H*), 3.92 (s, 6 H, OCH_3), 3.93–3.65 (m, 1 H, C*H*C=O), 2.62–2.11 (m, 2 H, lactone CH_2), 1.81–1.29 (e, 10 H, cycloalkyl C*H*); TLC ($CHCl_3$) R_f 0.11. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.66; H, 7.77.

***trans,trans*-3-Phenyl-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzofuranone (9a)**, a white, crystalline solid, was obtained in 98% yield; an analytical sample was secured via recrystallization from hexane: mp 67–70 °C; IR (KBr) 2948, 2863, 1777, 1168, 1139 cm^{-1}; NMR ($CDCl_3$) δ 7.39–7.21 (m, 5H, Ar *H*), 3.92 (m, 1 H, C*H*OC=O), 3.44 (d, *J* = 12.91 Hz, 1 H, PhC*H*), 2.17–1.29 (e, 9 H, aliphatic C*H*); TLC (CH_2Cl_2) R_f 0.43. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.50, H, 7.56.

***trans,trans*-3-Phenoxy-3a,4,5,6,7,7a-hexahydro-2(3*H*)-benzofuranone (9b)**, a white, crystalline solid, was obtained in 82% yield; an analytical sample was secured via recrystallization from hexane: mp 110–112 °C; IR (KBr) 2980, 2834, 1785, 1596, 1589 cm^{-1}; NMR ($CDCl_3$) δ 7.29–7.05 (m, 5 H, Ar *H*), 4.73 (d, *J* = 11.60 Hz, 1 H, PhOC*H*), 3.90 (m, 1 H, C*H*OC=O), 2.30–1.32 (e, 9H, aliphatic C*H*); TLC (CH_2Cl_2) R_f 0.46. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.32; H, 7.17.

***trans,trans*-3-(Phenylthio)-3a,4,5,6,7,7a-hexahydro-2-(3*H*)-benzofuranone (9c)**, a beige oil, was obtained in 90% yield; an analytical sample was secured via chromatography using dichloromethane as eluent: IR (film) 2941, 1780, 1480, 1440, 1203, 1166 cm^{-1}; NMR ($CDCl_3$) δ 7.62–6.89 (m, 5 H, Ar *H*), 4.26–3.55 (m 2 H, PhSC*H* + OC*H*), 2.41–1.02 (e, 9 H, aliphatic C*H*); TLC (CH_2Cl_2) R_f 0.39. Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 68.02; H, 6.55.

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Formation of N–N and N–C Bond-Cleavage Products in Displacements with N,N-Disubstituted Hydrazines on 1-Halo- or 1,4-Dihaloanthracene-9,10-diones

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The displacements of 1-halo- and 1,4-dihaloanthracene-9,10-diones by N,N-disubstituted hydrazines have been studied. These reactions proceed via N–N bond cleavages of the hydrazine to yield products with the regiospecific incorporation of an N,N-disubstituted amino group. In addition, pyrazoles which arise from intermediates which undergo N–C bond cleavage are also formed. The ratio of the N–N to N–C cleavage products is dependent on the reaction solvent, temperature, structure of the hydrazine, and the nature of the leaving group being displaced from the anthracene-9,10-dione. For example, treatment of **1a** with *N,N*-dimethylhydrazine in pyridine or dimethyl sulfoxide (DMSO) leads to **3a**:**2c** ratios of 6 and 3, respectively. Compound **1e** under comparable reaction conditions gives **3a**:**2c** product ratios of 49 and 4, respectively. The dichloro dione **1c** with *N,N*-dimethylhydrazine in pyridine or DMSO leads predominantly to **3b** in 76% and 72% yields, respectively, with relatively little pyrazole **2d**. The more reactive difluoro dione **1h** on reaction with *N,N*-dimethylhydrazine in pyridine leads to N–N bond-cleavage products **3c** (48%) and **3d** (40%). Treatment of **1e** with 1-piperidinamine in pyridine yields **3f**. The results will be discussed.

As part of a program dealing with the synthesis of hydrazino-substituted anthracene-9,10-diones for antitumor evalation, we have studied the displacement reactions of N,N-disubstituted hydrazines and halo-substituted anthracene-9,10-diones.[1,2] It has been reported that **1a** with hydrazine leads to the hydrazino dione **1b**.[3] On the other hand, when **1c** is heated with hydrazine the initially formed hydrazine **1d** undergoes a facile cyclization to yield pyrazole **2b**.[4]

The pyrazoles **2c** or **2d** are obtained when **1a** or **1c** is treated with methylhydrazine in pyridine, respectively.[4] The nitrogen atom bearing the methyl group initially displaces the chloride anion and the resultant hydrazines undergo cyclizations to the pyrazoles. In other reported

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(2) Krapcho, A. P.; Avery, K. L., Jr.; Shaw, K. J., presented in part at the Northeast Regional Meeting of the American Chemical Society, SUNY Binghamton, June 1986, Abstract 188.

(3) (a) Mohlau, R. *Chem. Ber.* **1912**, *45*, 2244. (b) Our examination of the reaction products shows the presence of some **2a**.

(4) Bradley, W.; Geddes, K. W. *J. Chem. Soc.* **1952**, 1630.

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