Metalation and Methyl Iodide Reaction of Dispiroindanyl Ether 7. To 0.090 g (0.448 mmol) of **7** in 6 mL of dry Et_2O cooled to 0 °C was added 1.44 mmol of *s*-BuLi (1.2 mL, 1.2 M). The reaction mixture was allowed to warm to room temperature, stirred for 24 h, and then quenched by addition of excess (0.4 mL) CH_3I. Standard workup provided a pale yellow oil, which was shown by GC to contain 90% of one new product and 10% starting material. After being passed through a short silica flash column, the product was isolated by HPLC (2% EtOAc/hexane) to provide 0.075 g (0.350 mmol, 78%) of *anti*-2-methyldispiro[cyclopropane-1,1'-indan-3',1''-cyclopropan]-2'-yl methyl ether (**12**) as a clear oil: ^1H NMR ($CDCl_3$) δ 0.86–0.96 (m, 3 H), 1.16–1.26 (m, 2 H), 1.39 (d, J = 6.22 Hz, CH_3), overlapping with multiplet at 1.36–1.42 (total, 4 H), 1.70–1.79 (m, 1 H), 3.17 (s, 3 H, OCH_3), 3.77 (s, 1 H, OC*H*), 6.63–6.67 (m, 2 H), 7.07–7.10 (m, 2 H); ^{13}C NMR δ 9.4, 16.2, 18.8, 20.1, 27.9, 29.6, 32.2, 52.2, 91.4, 117.1, 126.1, 126.2, 146.7; IR (neat, cm^{-1}) 3067, 2930, 2824, 1607, 1485, 1462, 1196, 1086. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.15; H, 8.42.

Representative Metalation and Methyl Iodide Reaction of 6. To 0.103 g (0.426 mmol) of **9** in 6 mL of Et_2O cooled to 0 °C was added 3.64 mmol of *s*-BuLi (2.6 mL, 1.4 M). The ice bath was removed, and the reaction mixture was stirred at room temperature for 20 h; then excess (0.5 mL) methyl iodide was added and the reaction mixture was stirred for 15 h. Standard workup yielded a yellow oil, which was purified by passage through a short silica column, followed by HPLC (5% EtOAc/hexane) to yield 0.0242 g of 2'-butyl-*anti*-2-methyldispiro[cyclopropane-1,1'-indan-3',1''-cyclopropan]-*syn*-2'-ol (**8**) (0.0945 mmol, 22%) as a clear oil and 0.0541 g (0.200 mmol, 47%) of 2'-butyl-*anti*-2,2''-dimethyldispiro[cyclopropane-1,1'-indan-3',1''-cyclopropan]-*syn*-2'-ol (**9**) as a clear oil. **8**: ^1H NMR ($CDCl_3$) δ 0.70–0.79 (m, 1 H), 0.846 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.47 (d, J = 6.3 Hz, 3 H, $CHCH_3$) overlapping with multiplet at 1.0–1.6 (total = 16 H), 6.56–6.63 (m, 2 H, aromatic H), 7.07–7.10 (m, 2 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.0, 15.9, 22.3, 23.4, 25.2, 26.9, 36.1, 37.4, 39.4, 82.2, 117.3, 117.6, 126.1, 126.4, 145.5, 147.3. Anal. Calcd for $C_{18}H_{24}O$: C, 84.33; H, 9.44. Found: C, 84.17; H, 9.49. **9**: ^1H NMR ($CDCl_3$) δ 0.841 (t, J = 6.7 Hz, 3 H, CH_2CH_3), 1.08–1.30 (m, 11 H), 1.44 (d, J = 6.3 Hz, 6 H, $CHCH_3$), 1.55–1.60 (m, 2 H), 6.40–6.52 (m, 2 H), 7.02–7.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.3, 23.4, 23.8, 25.5, 27.4, 37.8, 40.7, 85.8, 117.3, 126.1, 146.7. Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.36; H, 9.65.

Lithiation of 1 and Addition of 19-Li Followed by Reaction with Methyl Iodide. To 0.0467 g (0.251 mmol) of **1** in 2 mL of dry Et_2O cooled to 0 °C was added 1.56 mmol of *s*-BuLi (1.2 mL, 1.3 M, 6 equiv.). The ice bath was removed, and the reaction mixture was stirred at room temperature for 24 h, and then cooled to −78 °C.

To 0.0308 g (0.153 mmol) of **19** in 2 mL of dry Et_2O cooled to 0 °C was added 0.156 mmol of *s*-BuLi (0.12 mL, 1.3 M, 1.0 equiv). The ice bath was removed, and the solution was stirred for 30 min and then cooled to −78 °C. This solution was transferred by cannula to the lithiation reaction above. After ~1 min, 0.5 mL of CH_3I was added, and the reaction mixture was slowly allowed to warm to room temperature and stirred for 15 h. Standard workup provided a yellow solid, which contained **1**:**2**:**3** in a ratio of 2.5:6.9:1 as shown by capillary GC. FIMS analysis relative to an undeuterated standard showed that the dimethyl product **3** had a deuterium incorporation of 9%.

Lithiation of 6 and Addition of 1-Li Followed by Reaction with Methyl Iodide. To 0.0681 g (0.281 mmol) of **6** in 4 mL of dry Et_2O cooled to 0 °C was added 1.70 mmol of *s*-BuLi (1.3 mL, 1.3 M, 6 equiv). The ice bath was removed, and the reaction mixture was stirred at room temperature for 24 h and then cooled to −78 °C.

To 0.0308 g (0.153 mmol) of **1** in 2 mL of dry Et_2O cooled to 0 °C was added 0.182 mmol of *s*-BuLi (0.14 mL, 1.3 M, 1.1 equiv). The ice bath was removed, and the solution was stirred for 30 min and then cooled to −78 °C. This solution was transferred by cannula to the lithiation reaction above. After ~30–45 s, 1 mL of a mixture of acetic acid-*d* and methanol-*d* (50% v/v) was added, and the reaction mixture was slowly allowed to warm to room temperature and stirred for 5 h. Standard workup provided a yellow solid. FIMS analysis relative to undeuterated standards showed that there was no deuterium (<3%) incorporation in **1**, while the *n*-butyl compound **6** was shown to be 48% d_2 and 28% d_1.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for support of this work, to Dr. S. Wilson for assistance with the X-ray structure determination, and to Professor G. Boche and Professor G. W. Klumpp for helpful discussions. We also thank Lithium Corporation of America for a generous gift of *s*-BuLi.

Supplementary Material Available: ORTEP plots of **3** with selected distances, angles, and thermal parameters and experimental procedures for the synthesis of **19** and the lithiation and methanol-*d* trapping of **7** (12 pages). Ordering information is given on any current masthead page.

Assignment of the Configuration of Disubstituted 1,3-Dienes by Nuclear Overhauser Effect Measurements

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As a rule, the geometry of simple substituted olefins can be safely predicted from the coupling constants and chemical shifts of their ^1H and ^{13}C NMR spectra.[1,2] However, when several substituents are present, prediction becomes uncertain since the chemical shift differences are usually smaller and the number of informative couplings is reduced.[3] Conjugated dienes are subject to the same limitations, although chemical evidence, such as Diels–Alder additions and experiments involving 1,5-hydride shifts, should permit their structures to be deduced.[4,5] However, these methods, where feasible,[2b] need to be carried out on both the *E* and *Z* isomers in order to minimize ambiguity. We now describe how nuclear Overhauser effect (NOE) difference spectroscopy[6] can be used in a

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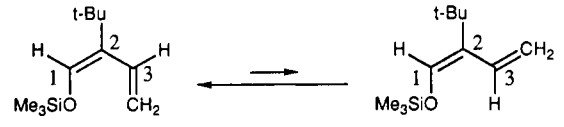
Table I. Correlations of NOE Enhancements with the Geometry and Conformation of Some Dienes

diene[a]	protons irradiated	signals enhanced (%)[b]	geometry	conformation
1	$OSiMe_3$	C1-H (10)	*E*	s-cis
	t-Bu	C1-H (15)		
2	$OSiMe_3$	C1-H (10)	*Z*	s-cis
	t-Bu	C3-H (15)		
3	$OSiMe_3$	C2-H (16)	*E*	s-trans
	t-Bu	C3-H (18)		
4	$OSiMe_3$	C3-H (21)	*Z*	s-trans
	t-Bu	C2-H (23)		
5	OMe	C2-H(23)	*E*	*c*
	t-Bu	*d*		
6	OMe	*d*	*Z*	*c*
	t-Bu	C2-H (16)		
7	Me	C3-H (19)	*E*	s-trans
8	Me	C2-H (9)	*Z*	s-trans
9	Me	C3-H (14)	*E*	s-trans
10	Me	C2-H (8)	*Z*	s-trans
11	Me	C3-H (17)	*E*	s-trans
12	Me	C2-H (16)	*Z*	s-trans
13	Me	C3-H (12)	*E*	s-trans
14	Me	C3-H (11)	*Z*	s-trans

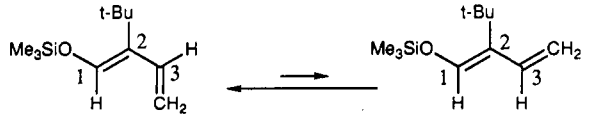
[a] Benzene-d_6 used as solvent throughout, except for 11 and 12, which were dissolved in D_2O containing 15% NaOD. [b] Pairs of noncontiguous protons gave enhancements of not more than ~3%. [c] Indeterminate. [d] No enhancement.

simple, straightforward fashion to elucidate the configurations and preferred conformations of some disubstituted 1,3-butadienes. By way of illustration, seven pairs of dienes having the *E* and *Z* configurations respectively (1–14) were examined (Table I).

Irradiation of the protons of either the trimethylsiloxy or *tert*-butyl group in 1 enhanced the C1-H signal, thereby demonstrating the *E* configuration for the C1–C2 double bond. The additional enhancement of the C3-H signal observed on irradiation of the *tert*-butyl group indicates that the s-trans conformation is avoided owing to the spatial demands of the *tert*-butyl group. In complementary fashion, the C1-H signal intensity in 2 was increased by irradiation of the trimethylsiloxy group, but remained unaffected by irradiation of the *tert*-butyl group, which nevertheless magnified the C3-H signal. This result establishes the *Z* geometry of the C1-C2 bond and reveals that 2 like 1 prefers to avoid the congestion encountered in the s-trans conformation. In both 1 and 2, the preferred ground-state structure could be a fully planar or an out-of-plane s-cis conformation.



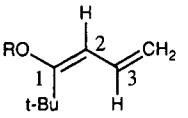
1 (E, s-cis) 1 (E, s-trans)

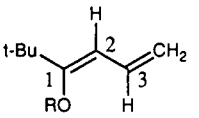


2 (Z, s-cis) 2 (Z, s-trans)

When the *tert*-butyl group is placed on the diene terminus, its bulk clearly dictates the rotational freedom about the C2–C3 bond. Separate irradiations of the geminal substituents at C1 in 3 and 4 markedly influenced the respective contiguous protons to each substituent, permitting the unambiguous assignment of the *E* and *Z* configurations, respectively. These enhancements also reflect the dominance of planar or near-planar s-trans conformations.

When the trimethylsiloxy group in 3 and 4 is replaced by the methoxy group to give 5 and 6, a subtle conformational difference is revealed by NOE. Irradiation of the methoxy group of 5 and the *tert*-butyl group of 6 augmented the signal of the cis proton at the C2 position in each case, thereby securing their respective *E* and *Z* geometries. On the other hand, irradiation of the *tert*-butyl and methoxy groups in 5 and 6, respectively, had no influence whatsoever on the C3-H signal, thereby showing that the planar s-trans conformation is not populated. This conformational finding may be a reflection of the different steric requirements of the methoxy and trimethylsiloxy groups. Evidently, less coplanarity obtains in 5 and 6 than in 3 and 4, favoring nonetheless a transoid arrangement overall.

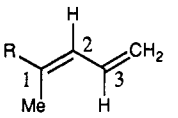


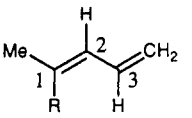


3 (E, s-trans) R = $SiMe_3$ 4 (Z, s-trans)

5 (E, s-trans) R = Me 6 (Z, s-trans)

Lastly, the less sterically crowded dienes 7–14 were examined and found to display a regular spectral pattern. Irradiation of the methyl resonances intensified alternately the C3-H and C2-H signals, identifying unequivocally the corresponding *E* and *Z* configurations and confirming at the same time that all olefins prefer s-trans conformations.





7 (E, s-trans) R = CN 8 (Z, s-trans)

9 (E, s-trans) R = COOH 10 (Z, s-trans)

11 (E, s-trans) R = COONa 12 (Z, s-trans)

13 (E, s-trans) R = COOMe 14 (Z, s-trans)

For most of the aforementioned dienes, the NOE experiment is not only the most convenient method but the only sure way of determining configuration. This is particularly true for dienes 1–8. 1,5-Hydrogen shifts are excluded for dienes 1–6, while 7 and 8 failed to rearrange even when heated to 310 °C.[7] Moreover, the assignment of configuration of *E* and *Z* silyl enol ethers on the basis of their ^{13}C NMR spectra, a recommended procedure,[8] is not always unambiguous.[2c,9] A pertinent exception is provided by dienes 3 and 4. An incorrect structural assignment would have been deduced from a consideration of the ^{13}C NMR spectra, because the ^{13}C chemical shift of the quaternary atom of the *tert*-butyl group (37.83 ppm) in the *E* isomer (3) should be *upfield* from that of the *Z* isomer (4, 36.51 ppm) according to Heathcock's rule.[2a]

In conclusion, the present results amply confirm that NOE offers a convenient and unambiguous means for

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assigning configuration and conformation in molecules characterized by the 1,3-diene entity.[10,11]

Experimental Section

Materials. Dienes 1–6 were prepared by the thermolysis of cyclobutenes.[12]

Dienes 7 and 8 are known compounds,[7] but they were prepared as follows: thermolysis of 3-methyl-3-cyanocyclobutene afforded 8. The dehydration of 4-cyano-3-hydroxypent-1-ene, which was obtained from the condensation of acrolein with ethyl cyanide, gave mainly 7, contaminated with 8. The treatment of diene 8 with iodine in benzene at room temperature gave an equilibrium mixture of 7 and 8. Both dienes had 60-MHz NMR spectra identical with those reported.[7] 7: NMR (360 MHz, C_6D_6) δ 6.12 (dd, J = 1, 11 Hz, 1 H), 5.87 (m, small couplings and J = 11, 16.5 Hz, 1 H), 4.93 (d, J = 11 Hz, 1 H), 4.84 (d, J = 16.5 Hz, 1 H), 1.21 (s, 3 H). 8: NMR (360 MHz, C_6D_6) δ 6.63 (m, small couplings and J = 11, 17 Hz, 1 H), 5.73 (d, J = 11 Hz, 1 H), 4.90 (d, J = 17 Hz, 1 H), 4.89 (d, J = 11 Hz, 1 H), 1.25 (s, 3 H).

Diene 9 is already known.[13] However, it was conveniently prepared as a single isomer by hydrolysis of the ethyl ester[14] obtained by condensation of acrolein with ethyl propionate followed by dehydration of the resulting hydroxy ester. The Z isomer, diene 10, was produced by the thermal electrocyclic reaction of 1-methylcyclobut-2-enecarboxylic acid. It is unstable and isomerizes quantitatively to the more stable isomer 9 under acidic conditions. 9: NMR (360 MHz, C_6D_6) δ 7.34 (dd, J = 1, 11.5 Hz, 1 H), 6.26 (m, small couplings and J = 10, 11.5, 17 Hz, 1 H), 5.09 (m, 2 H), 1.73 (s, 3 H). 10: NMR (360 MHz, C_6D_6) δ 7.56 (m, small couplings and J = 11, 17 Hz, 1 H), 6.13 (dd, J = 1, 11 Hz, 1 H), 5.09 (m, 2 H), 1.76 (s, 3 H).

The sodium dienecarboxylate 11 was obtained by dissolving 9 in NaOD solution. Sodium carboxylate 12 was prepared by the thermolysis of sodium 1-methylcyclobut-2-enecarboxylate in D_2O. When the isomerization of 10 to 9 was interrupted with base, a mixture of 11 and 12 was formed. No isomerization of these two salts was observed. 11: NMR (360 MHz, 15% NaOD/D_2O, HDO, δ 4.67, as standard) δ 6.24 (d, J = 11 Hz, 1 H), 6.13 (m small couplings and J = 10, 11, 16 Hz, 1 H), 4.94 (d, J = 16 Hz, 1 H), 4.82 (d, J = 10 Hz, 1 H), 1.30 (s, 3 H). 12: NMR (360 MHz, 15% NaOD/D_2O, HDO, δ 4.67, as standard) δ 6.01 (m, small couplings and J = 11, 17 Hz, 1 H), 5.38 (d, J = 11 Hz, 1 H), 4.53 (d, J = 11 Hz, 1 H), 1.32 (s, 3 H), one proton signal was hidden by the solvent peak.

Diene 13 is known[15] but was readily obtained by acid-catalyzed isomerization of its Z isomer 14. Similarly, the latter is known,[13a] and was prepared, in the present instance, by heating methyl 1-methylcyclobut-2-enecarboxylate in benzene. 13: NMR (360 MHz, C_6D_6) δ 7.30 (d, J = 11 Hz, 1 H), 6.35 (m, small couplings and J = 10, 11, 17 Hz, 1 H), 5.17 (d, J = 17 Hz, 1 H), 5.05 (d, J = 10 Hz, 1 H), 3.40 (s, 3 H), 1.82 (s, 3 H). 14: NMR (360 MHz, C_6D_6) δ 7.71 (m, 1 H), 6.13 (d, J = 11 Hz, 1 H), 5.13 (d, J = 15 Hz, 1 H), 5.12 (d, J = 11.5 Hz, 1 H), 3.33 (s, 3 H), 1.80 (s, 3 H).

Procedure for NOE Difference Spectroscopy. Samples where prepared by dissolving the diene in deuterated benzene or in deuterium oxide containing NaOD in an NMR tube. Degassing to remove oxygen was effected by passing a stream of dry, pure N_2 through the solution for 5 min. Tubes were sealed and examined. The irradiation of protons on substituents invariably caused an NOE enhancement of the signal of the contiguous proton by some 8–23% (Table I).

All the spectra were recorded at 360 MHz on a Bruker AM 360 or WM 360 spectrometer. Depending on the sample, the decoupler power (DP) was selected in the range 22–33 L. The relaxation time was 4–5 times greater than the longest T_1 of the diene. The % NOEs was calculated by using the irradiated inverted peaks as the reference. Error limits were ±2%.

Acknowledgment. We are grateful to Dr. M. Geckle and Mr. A. Pinto for assistance with the NMR measurements and the U.S. and Swiss National Science Foundations for financial support of this research.

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Synthesis of 3*H*-Pyrrolo[1,2-*c*]imidazole-3,5(2*H*)-diones

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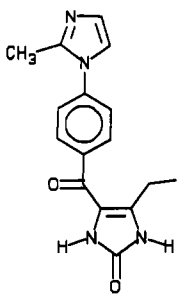
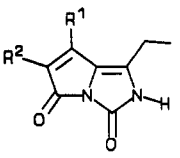
During the course of a program aimed toward the development of nitrogen acylated prodrugs[1] of cardiotonic agent 1,[2] it was noted that acylation by certain anhydrides produced unexpected fluorescent byproducts. These fluorescent compounds were determined to be 3*H*-pyrrolo[1,2-*c*]imidazole-3,5(2*H*)-diones, 2. This heterocyclic system has not been previously reported.[3] Several of the pyrrolo[1,2-*c*]imidazoledione derivatives derived from compounds such as 1 displayed cardiotonic properties similar to the parent [4-(1*H*-imidazol-1-yl)benzoyl]-imidazolones.[4] The synthesis and activities of these analogues will be reported elsewhere. This paper describes a synthetic study of the novel system 2 by the reaction of imidazolones 3 with anhydrides 4 (Scheme I). A ring-opening reaction in which pyrrolo[1,2-*c*]imidazoledione 2d is treated with aqueous NaOH is also reported.



1



2

Imidazolone 3a was prepared in an 87% yield by Friedel–Crafts reaction of 5-ethyl-2-oxoimidazole-4-carboxylic acid with CH_3CO_2H in a manner similar to the reported synthesis of compound 3b.[5] Reactions of 3 with 4 using excess NaH at 0–65 °C in DMF afforded varying mixtures of 2 and 5 (Scheme I). The intermediate N-acylated derivatives 5 could be isolated, or the crude reaction mixtures completely deacylated with $NaOCH_3$ in MeOH to afford

(1) Detailed results will be published elsewhere. For a preliminary review of the chemistry and biology, see: Erhardt, P. W.; Hagedorn, A. A., III. U.S. Patent 4,743,612, 1988.

(2) Hagedorn, A. A., III; Erhardt, P. W.; Lumma, W. C., Jr.; Wohl, R. A.; Cantor, E.; Chou, Y.-L.; Ingebretsen, W. R.; Lampe, J. W.; Pang, D.; Pease, C. A.; Wiggins, J. *J. Med. Chem.* **1987**, *30*, 1342.

(3) The saturated 1*H*-pyrrolo[1,2-*c*]imidazole-3,5-dione ring system has been reported: Butler, D. E.; Leonard, J. D. U.S. Patent 4,582,838, 1986. For a general review of pyrrolo[1,2-*c*]imidazole derivatives, see: Preston, P. N. Condensed Imidazoles, 5-5 Ring Systems. In *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1986; p 42.

(4) Shaw, K. J. U.S. Patent 4,937,258, 1990.

(5) Erhardt, P. W.; Hagedorn, A. A., III; Davey, D.; Pease, C. A.; Venepalli, B. R.; Griffin, C. W.; Gomez, R. P.; Wiggins, J. R.; Ingebretsen, W. R.; Pang, D. Cantor, E. *J. Med. Chem.* **1989**, *32*, 1173.

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