the solvent evaporated. The residue was applied to half of an analytical TLC plate (20 × 20 cm) and eluted twice with 2:1:1 hexane–CH_2Cl_2–ether. The minor, fast-moving band (R_f 0.47, 1 mg) corresponded to independently synthesized keto lactone **D7**. The major band (4.9 mg, 44%) was isolated as the diastereomeric dithioketal: NMR (270 MHz, $CDCl_3$) δ 5.05 (d of quartets, J = 6.2, 2.3 Hz, 1 H), 4.90 (ddd, J = 10.1, 4.5, 2.3 Hz, 1 H), 3.27 (m, 4 H), 2.50 (ddd, J = 14.4, 6.4, 4.1 Hz, 1 H), 2.24 (ddd, J = 4.0, 11.3, 14.4 Hz, 1 H), 2.13 (s, 3 H), 1.89–1.76 (m, 12 H), 1.22 (d, J = 6 Hz, 2 H); IR (CCl_4) 2970, 1745 cm^{-1}; m/e, calcd for $C_{16}H_{26}O_4S_2$ 346.12723, found 346.1271. The sample was recrystallized from hexane at −25 °C, mp 136–139 °C.

Epoxidation; Elimination of 6. The epoxidation, DBU sequence as described for **5E** starting with 17 mg of **6** gave a mixture of two products, separable by TLC (50% ethyl acetate–hexane). The more polar band (R_f 0.1) was **21** (3.4 mg, 18%): IR (neat) 3580 (w), 2930, 1730, 1690, 1640 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 6.56 (d, J = 15.8 Hz, 1 H), 6.42 (d, J = 15.8 Hz, 1 H), 4.90 (dd, J = 9.5, 4.0 Hz, 1 H), 2.66 (ddd, J = 12.5, 7.0, 6.3 Hz, 1 H), 2.50 (ddd, J = 3.0, 11.5, 14.5 Hz, 1 H), 2.33 (m, 2 H), 2.00–1.40 (m, 11 H), 1.34 (s, 3 H), 0.92 (t, J = 7.3 Hz, 3 H); m/e, calcd for $C_{14}H_{22}O_4$ 254.2247, found 254.2247. The sample crystallized on standing and was recrystallized (hexane/CH_2Cl_2) giving white needles, mp 141–143 °C. The faster moving band (R_f 0.15) proved to be the diastereomeric lactone **20**[13] (5.5 mg, 29%), identical with an authentic sample provided by Prof. M. Yamaguchi.

Osmylation of 6. The same procedure used for **5E** converted **6** (24 mg) into a crude hydroxy enone mixture. The less polar product (6.4 mg, 23%) again corresponded to the Yamaguchi lactone **20** while the more polar isomer was **21** (9.7 mg, 36%).

Appendix

MACROMODEL Parameters. The structures found in Figures 1–4 were minimized with use of the Multiconformer routine in MACROMODEL using the default values of 60° dihedral angle resolution and 10° bond angle resolution. The closure bond for each molecule was chosen according to the guidelines set forth in the MACROMODEL documentation. In each case, the closure bond was chosen to be the bond between the third and fourth atoms away from the lactone carbonyl carbon. In the case of 2,3-dimethylcyclododecene, the bond between the fourth and fifth atoms away from the unsubstituted alkene carbon was chosen. The closure distance was varied between 1.0 and 2.0 Å to generate between 500 and 800 conformations as suggested by the MACROMODEL documentation. These values were highly dependent on the structure of the molecule. For example, for structure **5Z** 822 starting conformations were generated with a minimum closure distance of 1.0 Å and a maximum closure distance of 1.85 Å. The torsional angle defined by the lactone subunit was constrained to be 180° in all cases. In the case of the cycloalkenes, the angle defined by the double bond was contrained to be 0° or 180°, depending upon its cis or trans nature. For the epoxides studied, the torsional angle defined by the epoxide was allowed to assume four angles. For the epoxides derived from the cis alkenes, the angles were −40, −20, 0, and 20°; for the trans epoxides the angles were 140, 160, 180, and 200°. All other torsional angles were permitted to freely rotate within the 60° resolution constraints. Default values were used for all other parameters in the Multiconformer routine.

Acknowledgment. This work was supported by the National Science Foundation (CHE-8306121) and, in part, by an NIH postdoctoral fellowship to W.D. (GM.11546). The NIH instrument grant (RRO 2388-01) used to obtain the AM-500 MHz NMR spectrometer is also acknowledged. Special thanks are due to Prof. W. C. Still for providing the MACROMODEL program used in the computations.

An Asymmetric Synthesis of (−)-Steganone. Further Application of Chiral Biaryl Syntheses

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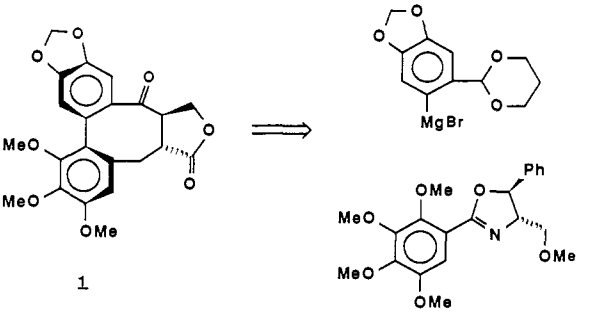
Abstract: An asymmetric synthesis of the title compound has been achieved by initially forming an axially chiral biphenyl precursor **11a** mediated by a chiral aromatic oxazoline (+)-**10**. The eight-membered ring was constructed around the biphenyl with particular attention addressing the rotational barrier for biphenyls to avoid racemization. The efficiency of this total synthesis was quite good until the last step, which incorporates the lactone moiety. Furthermore, approximately 10% racemization occurred in one of the latter steps (**17–18**) which was not evident until the final target was reached.

We have shown in previous reports that an aromatic system containing a chiral oxazoline is capable of being coupled with aromatic Grignard or lithium reagents furnishing chiral biphenyls,[1] binaphthyls,[2] and related systems.[3] We now describe the total synthesis of (−)-steganone (**1**) which originates from a diastereoselective coupling of two aryl moieties furnishing the axially chiral biphenyl required to construct the target compound (Scheme I).

(−)-Steganone (**1**), an antileukemic bisbenzocyclooctadiene lignan lactone, one of four isolated from *Steganotaenia araliacea* by Kupchan in 1973,[4] has attracted considerable synthetic interest. These lignans have demonstrated significant in vivo activity against P-388 leukemia in mice and have displayed significant in vitro activity against cells derived from human carcinoma of the nasopharynx (KB). The natural product contains three stereochemical elements, two of which are on the lactone ring and the

Scheme I



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(1) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682.
(2) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879.
(3) Meyers, A. I.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1135.
(4) Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 1335.

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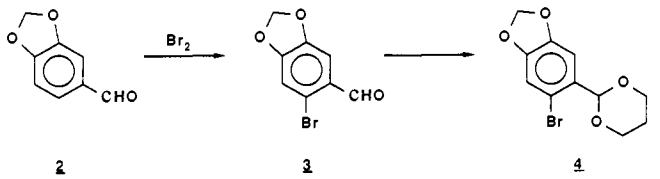
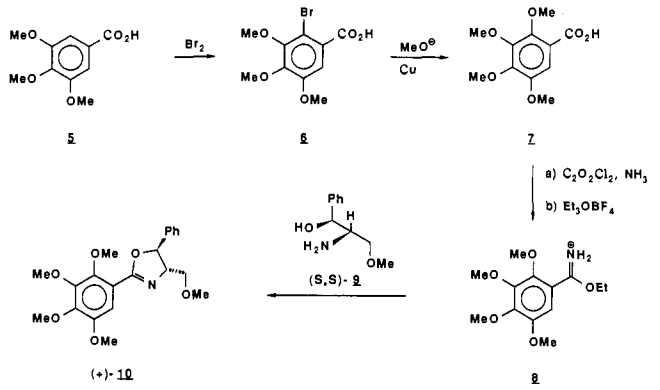
Scheme II



Scheme III



third is the asymmetric biaryl bond between the two phenyl rings.

To date there have been a total of nine successful syntheses of steganone. Six of these are syntheses of (±)-steganone[5] and three have been enantioselective syntheses of (−)-steganone.[6] Of the latter three syntheses, Raphael's[6b] employs a resolution step while the remaining two arrive at the natural product from a lactone fragment of known absolute stereochemistry derived from L-glutamic acid.[6a,c] The strategy of the past enantioselective syntheses was to initially synthesize the two stereocenters of the lactone ring and subsequently form the asymmetric biaryl bond. Thus, the axial asymmetry of the biaryl bond was induced by the two asymmetric centers on the lactone.

The novel feature of the present approach, based on earlier studies from this laboratory,[1-3] was to initially form the axially chiral biaryl system, containing the requisite functional groups, in addition to the proper substituents to avoid aryl–aryl bond rotation. The failure to hinder bond rotation would result in racemization and therefore preclude any acquisition of chiral, nonracemic product. The retrosynthetic plan, as shown Scheme I, was therefore inaugurated, which required preparation of the upper and lower fragments. The coupling of the Grignard reagent by displacing the *o*-methoxyl to the chiral oxazoline was anticipated to proceed with some degree of axial diastereoselectivity.

The upper portion of **4** was readily prepared from piperonal **2** by bromination to *o*-bromopiperonal **3**,[7] followed by acetalization with 1,3-propanediol.

The lower portion of (+)-**10** was also prepared by using a series of well-precedented steps. Thus, bromination[8] of commercially available 3,4,5-trimethoxybenzoic acid gave the 2-bromo derivative **6** and treatment with NaOMe–Cu[9] displaced the bromine furnishing the tetramethoxybenzoic acid **7**. The latter was transformed into the amide (oxalyl chloride, NH_3) and after treatment

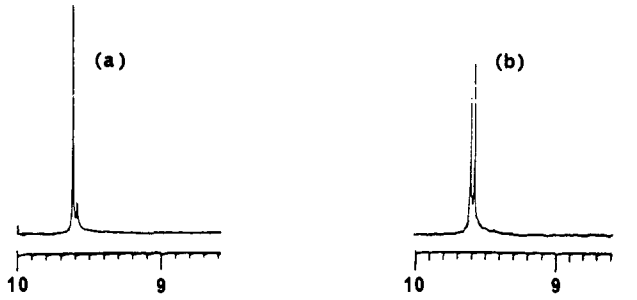
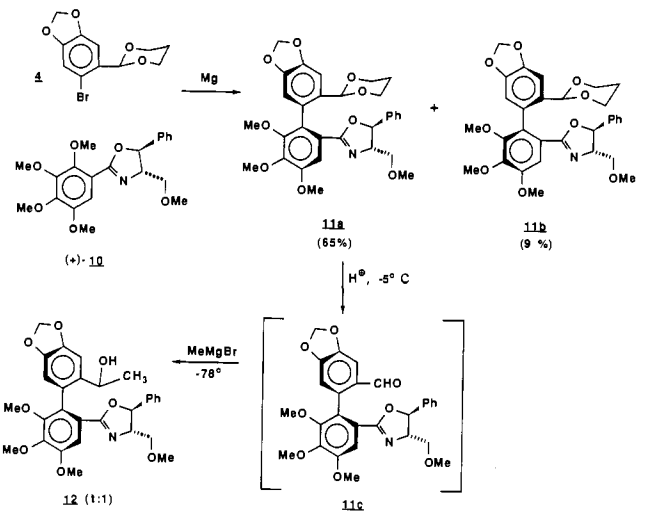


Figure 1. Aldehyde signal of **11c**: (a) immediately after isolation; (b) after 4 days at 25 °C.

Scheme IV



with triethyloxonium fluoroborate it gave the imidate **8**. As previously described,[10] the imidate was stirred with (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol (**9**) producing the completed lower portion of **10**. The overall yield of (+)-**10** was 67% based on the benzoic acid **7**.

With the two precursors for the biaryl coupling in hand, the next stage of our effort was to generate the Grignard reagent of **4**, and this was performed by using the entrainment method.[11] Addition of **4** to 3 equiv of magnesium in THF followed by 2 equiv of 1,2-dibromoethane gave the corresponding Grignard reagent in quantitiative yield. Addition of 0.7 equiv of the (tetramethoxyphenyl)oxazoline **10** and refluxing (THF) overnight furnished the biaryl coupling products **11a** and **11b** in 85% yield as a 7:1 mixture of diastereomers (NMR).[12] Flash chromatography cleanly separated **11a** (65% yield) and **11b** (9% yield). At this juncture, assignment of the major diastereomer to **11a** and the minor to **11b** was purely arbitrary. This assumption, however, proved to be correct as the synthesis reached its final target. With a pure diastereomer **11a** in hand, it was now necessary to unmask the functionality to elaborate the biaryl to the 8-membered ring

(5) (a) Magnus, P.; Schultz, J.; Gallagher, T. *J. Am. Chem. Soc.* **1985**, *107*, 4984. (b) Dhal, R.; Robin, J. P.; Brown, E. *Tetrahedron* **1983**, *39*, 2787. (c) Mervic, M.; Ben-David, Y.; Ghera, E. *Tetrahedron Lett.* **1981**, *22*, 5091. (d) Ziegler, F. E.; Chliwner, I. C.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790. (e) Brown, E.; Dhal, R.; Robin, J. P. *Tetrahedron Lett.* **1979**, 733. (f) Larson, E. R.; Raphael, R. A. *Tetrahedron Lett.* **1979**, 5041. (g) Becker, D.; Hughes, L. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674. (h) Hughes, L. R.; Raphael, R. A. *Tetrahedron Lett.* **1976**, 1543. (i) Kende, A. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 267.

(6) (a) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303. (b) Larson, E. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 521. (c) Robin, J. P.; Gringgore, O.; Brown, E. *Tetrahedron Lett.* **1980**, 2704.

(7) Becker, D.; Hughes, L. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674.

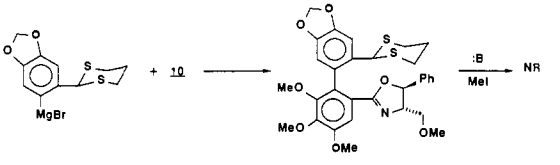
(8) Mayer, W.; Fikentschen, R. *Chem. Ber.* **1956**, *89*, 511.

(9) Mayer, W.; Fikentschen, R. *Chem. Ber.* **1958**, *91*, 1536.

(10) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

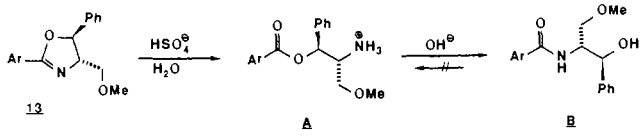
(11) Lai, Y. H. *Synthesis* **1981**, 585.

(12) The original plan of the synthesis involved the dithiane derivative A and coupling to the (tetramethoxyphenyl)oxazoline, **10**. This process proceeded to give B in 60% yield, isolated as a single diasteromer. However, all



attempts to metalate the dithiane and introduce the methyl group met with failure. No deprotonation was observed on B with a wide range of bases and reaction conditions.

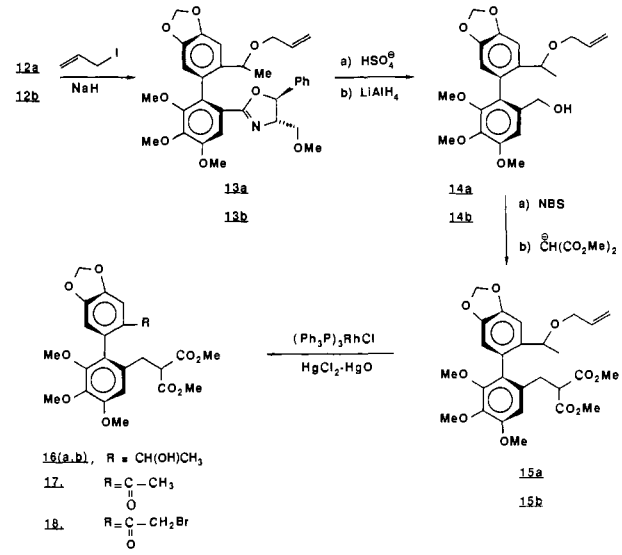
Scheme V



present in steganone. This series of manipulations required that conditions be found to avoid rotation of the aryl–aryl bond, and therefore avoid epimerization. The first transformation to be addressed involved removal of the acetal in **11a** affording the aldehyde **11c**. It had previously been observed[1] that an sp^2 substituent (HCO) ortho to the biaryl linkage reuslts in aryl–aryl bond rotation. However, the presence of the bulky oxazoline at the other ortho position should raise the barrier to bond rotation and allow **11c** to have some reasonable half-life. With this under consideration, the acetal was smoothly cleaved with 3 N HCl–THF at room temperature. Examination of the NMR spectrum of the resulting aldehyde (270 MHz) revealed that the pure diasteromer of acetal **11a** had given rise to *two* aldehydes in the ratio 7:1, indicating that under these hydrolytic conditions, some epimerization (aryl–aryl bond rotation) had occurred. Repeating the hydrolysis (3 N HCl–THF) at 0 °C gave the aldehyde **11c** in a 15:1 ratio, thus much improved over the earlier hydrolysis (Figure 1). A stability study was performed by monitoring the 15:1 mixture of **11** by NMR and observing the changes in the formyl proton over time. After 4 days at 25 °C, the mixture had reached equilibrium (Figure 1b). Thus, bond rotation in the biaryl system was indeed a problem to be reckoned with, although proceeding rather slowly. Finally, the cleavage of **11a** to **11c** was performed at −5 °C with the HCl–THF mixture and workup carried out at 0 °C, including solvent evaporation. Under these conditions, no trace of the epimer of **11c** could be detected when its NMR spectrum was taken immediately after isolation. Since the next step in the synthesis involved addition of methylmagnesium bromide to the aldehyde and the resulting secondary alcohol should, with its sp^3 nature, be stable to bond rotation, a protocol was invoked which required that the immediately isolated aldehyde **11c** be rapidly treated with the Grignard reagent. In this fashion **12** was formed in 92% yield as 1:1 diastereomeric mixture of secondary alcohols. This mixture was cleanly separated by flash chromatography, and each diasteromer of **12** was completely characterized. Thus, if any aryl–aryl bond rotation had occurred during the acetal hydrolysis or the methylmagnesium bromide addition, it would have been easily detected by examining their respective NMR spectra. Furthermore, each diasteromeric secondary alcohol of **12** could be used in the synthetic route since at a later stage in the synthesis this alcohol function was to be oxidized to a methyl ketone (vide infra). These epimers of **12** were also found to be completely stable to aryl–aryl bond rotation even when heated to reflux as a toluene solution. Each diasteromer of **12** was carried forward separately until they converged to the same compound (**17**), and both gave **19** which was characterized as being identical from both series (**12a** → **19**; **12b** → **19**).

Protection of the respective secondary alcohols (**12a**, **12b**) was accomplished by transforming them into their allyl ethers (**13a**, **13b**) with sodium hydride and allyl iodide. At this point in the synthetic scheme, the chiral oxazoline was removed and once again concern arose that the conditions for removal had to be compatible with the rotational barrier of the aryl–aryl bond. The method of choice of oxazoline removal involved treatment of **13(a** or **b)** with a slurry of sodium bisulfate–water in THF for 3–4 h, which protonated the oxazoline nitrogen. After 40–48 h the ring slowly opened to the amino ester sulfate salt (A). Isolation was performed with acidic media followed by reduction of A with lithium aluminum hydride to afford the alcohol **14(a** or **b)**. If the ester A was exposed to neutral or alkaline conditions during the workup, rearrangement to the amide B became a serious side reaction (see Experimental Section). In fact, if water was present during the hydride reduction, the Li_2O produced caused the rearrangement (A → B) to occur very rapidly and the amide was the only product obtained. The resulting benzyl alcohols **14a,b** were not sufficiently

Scheme VI

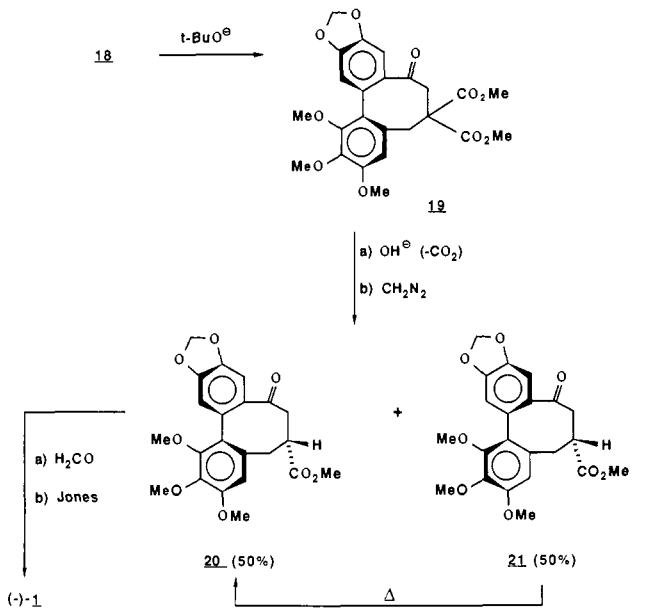


stable to allow complete characterization, and thus they were transformed quickly to the bromide with *N*-bromosuccinimide–triphenylphosphine, which were directly converted to the malonate esters **15a,b** under the usual malonate ion substitution conditions. In this fashion, **15(a** or **b)** was obtained pure and characterized. The yield of **15** was 56–61%, based on the oxazoline **13(a** or **b)**. With the successful removal of the chiral oxazoline performed under unusually mild conditions and each diasteromer **15a** and **15b** apparently devoid of any aryl–aryl bond rotation (via NMR), it was now necessary to remove the allyl protecting group. This was readily done by rhodium-catalyzed isomerization[13] to the vinyl ether followed by hydrolytic cleavage catalyzed by mercuric chloride–mercuric oxide.[14] In this manner, each diasteromer **16a,b** was obtained in 83% yield. The latter were stable products and showed no signs of aryl–aryl bond rotation. This is to be expected since both ortho positions contained sp^3-bonded substituents which inhibited bond rotation. The alcohols **16** were individually oxidized to the methyl ketone **17** with pyridinium chlorochromate, and in view of the sp^2 substituent now present, it was immediately brominated with pyridinium bromide perbromide in trifluoroacetic acid, according to Ziegler.[5d] The resulting α-bromo ketone **18** was also presumed to be a racemizable intermediate, capable of allowing aryl–aryl bond rotation, and thus it, too, was treated without delay with potassium *tert*-butoxide to afford the cyclic ketone **19**, in an overall yield of 54% from the alcohol **16**. At this point it is noteworthy to mention again that each diastereomer, individually, from **12** gave **19**, which confirmed that the only difference in their stereochemistry arose from the secondary alcohol on the "top" half of the biaryl system.

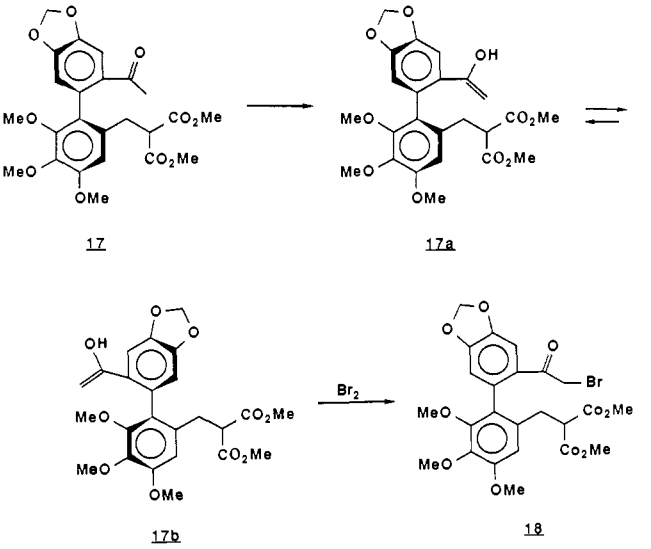
The remainder of the synthetic scheme now relied completely on the Ziegler[5d] synthesis of racemic steganone. Thus, the cyclic ketone **19**, combined from both individual diastereomeric sequences, was treated with potassium hydroxide to produce the dicarboxylic acid, which was thermally decarboxylated to the monocarboxylic acid and esterified to the methyl esters **20** and **21**. However, this sequence led to a conformational mixture (1:1) of the biphenyl system. Each (**20** and **21**) could be easily separated by flash chromatography to give pure **20** and **21** which were individually characterized. However, the undesired conformer, which is stable at ambient temperature, is known to intercovnert upon heating.[5d,f,15] Thus, **21** was heated in xylene and gave **20** and **21** again as a 1:1 mixture of rotamers. This mixture was again separated, and the thermal interconversion was repeated several times. In this manner, >90% of the appropriate isomer **20** was readily obtained.

(13) Gent, P. A.; Gigg, R. *Chem. Commun.* **1974**, 277.
(14) Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1968**, 1903.
(15) Kende, A. S.; Liebeskind, L. S.; Kubiak, C.; Eisenberg, R. *J. Am. Chem. Soc.* **1976**, *98*, 6389.

Scheme VII



Scheme VIII



The final step in this synthetic effort was performed by introducing the hydroxymethyl group α to the ketone in **20** followed by Jones' oxidation to give (−)-steganone in a disappointing yield of 11%. This poor conversion of the ketone **20** into (−)-steganone has already been observed by previous workers.[5d,i,f] Several attempts to improve this step met with failure.

Comparison of (−)-**1** to the literature values reported by Koga ($[\alpha]_D$ −191°),[6a] Kupchan ($[\alpha]_D$ −202°),[4] and Raphael ($[\alpha]_D$ −197°)[6b] showed a meaningful discrepancy. The synthetic material (−)-**1** obtained in this study exhibited $[\alpha]_D$ −161° in the same solvent and at the same concentration, while all the other physical data were in excellent agreement (mp, NMR). However, the specific rotation (−161°) possessed by the product indicated an optical purity of 80–84% when compared with Koga's and Kupchan's values. Furthermore, an authentic sample was obtained[16] which in direct comparison with the sample from the present study verified that (−)-**1** had an $[\alpha]_D$ about 30° too low. Convinced that our rotation was indeed indicative of approximately 10% of (+)-steganone in the product, the only meaningful conclusion that could be drawn is that some racemization (aryl–aryl bond rotation) had taken place in the last stages of the synthesis involving **17** or **18**. Since no complete physical characterization was performed for these two labile intermediates, the PCC oxidation of the carbinol **16** which gave ketone **17** can be assumed to proceed without aryl bond rotation; however, the bromination step to **18** undoubtedly proceeds via the enol **17a**, and it is felt that rotation to **17b** was the stage at which racemization occurred. It is unlikely that the 10–12% racemization occurred at the stage where the eight-membered ring was already in place (e.g., **19**), thus precluding any racemization in the decarboxylation step (**19** → **20**). On the other hand, it is possible that the racemization had occurred during the ring closure involving the α-bromo ketone and the malonate ion (**18** → **19**). There was no way for this rotation to be detected until the final product was reached and the specific rotations compared to optically pure steganone. Therefore, if the bromination or cyclization were to be repeated under milder conditions, this racemization, amounting to 10%, could possibly be avoided.

Experimental Section

6-Bromopiperonal (3). To a stirred solution of 55.0 g (0.36 mmol) of piperonal (**2**) in 120 mL of acetic acid was added 21 mL (0.41 mmol) of bromine. The resultant dark red solution was stirred for 18 h after which a red precipitate was present. The solution was filtered and the crude product recrystallized with 95% ethanol. A second crop of crystals was isolated from the mother liqueur by addition of 50 mL of water. The solution was filtered and the crude product recrystallized from 95% ethanol. Combination of the two crops of crystals afforded 44.5 g (54%) of **3** as white needles: mp 131–132 °C (lit.[8] mp 131 °C); IR ($CHCl_3$) 3030, 3010, 2980, 2900, 1672, 1610, 1600, 1465, 1390, 1240, 1202, 1102, 1028 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 10.17 (1 H, s), 7.35 (1 H, s), 7.05 (1 H, s), 6.09 (2 H, s); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 190.16, 153.48, 148.40, 128.52, 121.50, 113.46, 108.38, 102.89.

1-[1-(2-Bromo-4,5-methylenedioxyphenyl)]-1,3-dioxane (4). A solution of 12.0 g (52.4 mmol) of 6-bromopiperonal (**3**), 4.2 mL (58.1 mmol) of 1,3-propanediol, and 200 mg (1.05 mmol) of *p*-toluenesulfonic acid in 100 mL of benzene was heated under reflux with azeotropic removal of water (Dean-Stark trap) for 4 h. The solution was cooled to ambient temperature, washed with water (50 mL), and dried ($MgSO_4$) and the solvent evaporated to give light orange crystals. Recrystallization from ethyl acetate produced 13.1 g (87%) of **4** as white crystals: mp 94–95 °C; IR (CCl_4) 3005, 2965, 2945, 2915, 2880, 2840, 1498, 1476, 1460, 1415, 1369, 1238, 1140, 1112, 1091, 1032, 995, 930 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.17 (1 H, s), 6.96 (1 H, s), 5.96 (2 H, s), 5.68 (1 H, s), 4.24 (2 H, ddd, J = 10.7, 5.0, 1.2 Hz), 4.00 (2 H, td, J = 12.2, 2.5 Hz), 2.21 (1 H, complex m), 1.43 (1 H, d of heptets, J = 13.4, 1.3 Hz); ^{13}C NMR (67.9 MHz, $CDlC_3$) δ 148.87, 147.71, 131.69, 113.30, 112.56, 108.43, 101.94, 101.09, 67.63 (2 C), 25.93. Anal. Calcd for $C_{11}H_{11}Br$: C, 46.02; H, 3.86; Br, 27.83. Found: C, 46.19; H, 3.81; Br, 27.88.

2-Bromo-3,4,5-trimethoxybenzoic Acid (6). To a stirred refluxing solution of 24.2 g (114 mmol) of 3,4,5-trimethoxybenzoic acid (**5**), 2.5 mL of water, and 240 mL of chloroform was added a solution of 5.9 mL (115 mmol) of bromine in 50 mL of chloroform. Following addition the resultant red solution was refluxed for 18 h and then cooled to ambient temperature. The solution was washed with water (2 × 100 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to afford 32.0 g (96%) of **6** as a light orange solid which was used without further purification: mp 147–148 °C (lit.[9] mp 149–150 °C); IR ($CHCl_3$) 3500–2600, 3030, 3010, 2970, 2940, 1725, 1700, 1585, 1560, 1487, 1465, 1450, 1385, 1200, 1160, 1105, 1000 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 11.60 (1 H, br s), 7.42 (1 H, s), 3.98 (1 H, s), 3.92 (1 H, s), 3.91 (1 H, s); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 170.87, 152.36, 151.83, 147.22, 125.67, 111.61, 110.93, 61.19, 61.03, 56.42. Anal. Calcd for $C_{10}H_{11}O_5Br$: C, 41.26; H, 3.81; Br, 27.45. Found: C, 41.37; H, 3.77; Br, 27.39.

2,3,4,5-Tetramethoxybenzoic Acid (7). To a stirred solution of 7.3 g (317 mmol) of Na metal dissolved in 380 mL of anhydrous methanol was added 31.0 g (106 mmol) of 2-bromo-3,4,5-trimethoxybenzoic acid (**6**). Once the acid had dissolved, 3.0 g (47 mmol) of Cu powder was added and the mixture refluxed for 18 h. The mixture was cooled, filtered through a bed of Celite, and concentrated in vacuo to give a crude white solid. This was dissolved in 400 mL of water and acidified to pH 3 with concentrated HCl. The solution was extracted with methylene chloride (2 × 300 mL), dried ($MgSO_4$), filtered, and concentrated to produce a light orange oil. Recrystallization [hexane:ethyl acetate (5:1)] yielded 23.3 g (90%) of **7** as white prisms: mp 87–88 °C (lit.[9] mp 87–88 °C); IR (CCl_4) 3400–3100, 3060, 2995, 2935, 2830, 1743, 1685, 1485, 1462, 1409, 1370, 1332, 1110, 1060, 845 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 11.16 (1 H, br s), 7.41 (1 H, s), 4.09 (3 H, s), 3.99 (3 H, s), 3.94 (3 H, s), 3.90 (3 H, s); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 165.63, 149.97,

(16) We thank Professor K. Koga for this sample of (−)-steganone ($[\alpha]_D$ −191°).

148.14, 147.76, 146.39, 116.26, 109.54, 62.46, 61.29, 61.08, 56.34. Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.82. Found: C, 54.39; H, 5.77.

(+)-2-(2,3,4,5-Tetramethoxyphenyl)-4(*S*)-(methoxymethyl)-5(*S*)-phenyl-2-oxazoline (10). To a stirred solution of 18.4 g (76.0 mmol) of 2,3,4,5-tetramethoxybenzoic acid (7) dissolved in 350 mL of dry methylene chloride was added 13.4 mL (154 mmol) oxalyl chloride. The yellow solution was stirred overnight at room temperature, the solvent evaporated, and the yellow solid dissolved in 60 mL of diethyl ether. To this stirred solution was added an excess of 30% NH_4OH which caused a white precipitate to form. This was dissolved in methylene chloride (300 mL), washed with water (100 mL), dried ($MgSO_4$), filtered, and concentrated to afford a white solid. Recrystallization from ethyl acetate produced 17.3 g (94%) of the benzamide as white crystals: mp 121–122 °C; IR (CCl_4) 3390, 3180, 2990, 2970, 2940, 2830, 1645, 1490, 1465, 1400, 1315, 1215, 1115, 949, 845, 658 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.96 (1 H, br s), 7.46 (1 H, s), 6.75 (1 H, br s), 3.94 (3 H, s), 3.93 (6 H, s), 3.90 (3 H, s); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 166.64, 149.46, 146.91, 146.60, 146.49, 120.01, 108.72, 61.45, 60.97, 60.77, 56.10. Anal. Calcd for $C_{11}H_{15}O_5N$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.60; H, 6.28; N, 5.69. A solution of 10.0 g (41.5 mmol) of 2,3,4,5-tetramethoxybenzamide and 8.2 g (43.1 mmol) of triethyloxonium tetrafluoroborate in 100 mL dry 1,2-dichloroethane under an argon atmosphere was stirred at room temperature for 24 h. To the light yellow solution was added 7.8 g (43.1 mmol) of (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol [(+)-**9**][10] and the resultant dark yellow solution refluxed for 48 h. The solution was cooled to ambient temperature, washed with aqueous Na_2CO_3 (50 mL) and water (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a dark yellow oil which was purified by Kugelrohr distillation to afford 13.2 g (82%) of **10** as a pale yellow oil: bp 240–250 °C (0.05 Torr); $[\alpha]_{589}$ +73.7° (c 2.9, THF); IR (film) 3060, 3030, 2980, 2930, 2890, 2825, 1645, 1595, 1575, 1492, 1463, 1410, 1115, 1063, 795, 745, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.42–7.33 (5 H, m), 7.15 (1 H, s), 5.50 (1 H, d, J = 6.6 Hz), 4.32 (1 H, ddd, J = 9.7, 6.5, 4.5 Hz), 3.95 (3 H, s), 3.94 (3 H, s), 3.87 (3 H, s), 3.86 (3 H, s), 3.77 (1 H, dd, J = 9.7, 4.3 Hz), 3.62 (1 H, dd, J = 9.6, 6.7 Hz), 3.45 (3 H, s); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 162.57, 149.14, 148.08, 147.61, 146.07, 141.16, 128.48, 127.89, 127.73, 125.30, 116.58, 108.75, 83.39, 74.82, 74.50, 61.45, 60.92, 60.76, 58.91, 56.22. Anal. Calcd for $C_{21}H_{25}O_6N$: C, 65.10; H, 6.50; N, 3.62. Found: C, 64.82; H, 6.69; N, 3.61.

Biphenyl Oxazolines 11a and 11b. To a stirred mixture of 720 mg (29.6 mmol) of Mg metal in 10 mL of dry THF under an argon atmosphere was added a solution of 2.58 g (8.99 mmol) of 1-[1-[(2-bromo-4,5-methylenedioxyphenyl)]-1,3-dioxane (**4**) in 25 mL of anhydrous THF. The mixture was heated to reflux and then a solution of 1.77 mL (20.6 mmol) of 1,2-dibromoethane in 5 mL of dry THF was slowly added (ca. 2.5 h). The dark yellow solution was refluxed for 1 h and cooled to ambient temperature, and then 2.37 g (6.11 mmol) of oxazoline **10** in 5 mL of dry THF was added to the yellow mixture and the solution heated to reflux. The dark yellow-brown solution was refluxed overnight, cooled, and then poured into 25 mL of saturated NH_4Cl. The layers were separated and the organic layer washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and evaporated to afford a dark yellow-brown oil. Flash chromatography (ethyl acetate) afforded the major diastereomer **11a** (R_f 0.30, ethyl acetate) which was recrystallized from ethyl acetate to yield 2.24 g (65%) of light yellow prisms and 373 mg (9%) of the minor diasteromer **11b** (R_f 0.19, ethyl acetate) as a light yellow glass.

Major diastereomer 11a: mp 164–165 °C; $[\alpha]_{589}$ +33.5 (c 2.7, THF); IR (CCl_4) 3060, 3030, 2990, 2950, 2925, 2885, 2870, 2840, 2340, 2318, 1640, 1588, 1555, 1497, 1480, 1460, 1420, 1410, 1368, 1332, 1232, 1125, 1104, 1035, 860, 686 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32–7.20 (4 H, m), 7.17 (1 H, s), 7.11–7.07 (2 H, m), 6.66 (1 H, s), 5.93 (1 H, d, J = 1.4 Hz), 5.91 (1 H, d, J = 1.4 Hz), 5.07 (1 H, s), 5.02 (1 H, d, J = 7.6 Hz), 4.17–3.87 (5 H, complex m) on which is superimposed 3.97 (3 H, s) and 3.94 (3 H, s), 3.73–3.54 (1 H, complex m) on which is superimposed 3.61 (3 H, s), 3.46–3.34 (1 H, m) on which is superimposed 3.38 (3 H, s), 2.19–2.01 (1 H, complex m), 1.26 (1 H, br d, J = 13.3 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 164.47, 152.42, 151.89, 146.71, 144.49, 140.38, 131.16, 128.89, 128.10, 127.41, 125.19, 123.61, 110.13, 108.70, 105.91, 100.67, 99.81, 84.07, 74.56, 73.76, 66.80, 60.44, 60.34, 58.70, 55.90, 25.41. Anal. Calcd for $C_{31}H_{33}O_9N$: C, 66.06; H, 5.90; N, 2.48. Found: C, 66.06; H, 5.91; N, 2.35.

Minor diastereomer 11b: $[\alpha]_{589}$ +100.9° (c 2.7, THF); IR (CCl_4) 3060, 3030, 2990, 2960, 2930, 2890, 2870, 2850, 2340, 1645, 1587, 1557, 1495, 1480, 1460, 1420, 1409, 1368, 1233, 1120, 1102, 1035, 858, 685 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.28–7.17 (4 H, m), 6.99–6.95 (3 H, m), 6.66 (1 H, s), 5.93 (1 H, d, J = 1.4 Hz), 5.83 (1 H, d, J = 1.4 Hz), 5.13 (1 H, d, J = 7.6 Hz), 5.04 (1 H, s), 4.13–3.85 (5 H, complex m) on which is superimposed 3.97 (3 H, s) and 3.94 (3 H, s), 3.72–3.47 (2 H, complex m) on which is superimposed 3.61 (3 H, s), 3.37 (3 H, s) 2.17–1.99 (1 H, complex m), 1.24 (1 H, br d, J = 13.2 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 164.41, 152.52, 151.99, 146.92, 146.81, 144.37, 140.27, 131.16, 128.68, 128.05, 127.46, 127.09, 125.57, 124.19, 110.45, 108.55, 106.17, 100.67, 99.82, 84.18, 74.27, 66.94, 66.75, 60.55, 60.45, 58.81, 55.96, 25.45.

Biphenyl Carbinol Oxazolines 12a and 12b. To a stirred solution of 3.37 g (5.98 mmol) of the biaryl oxazoline **11a** in 50 mL of THF at −5 °C (cooling bath temperature) was sowly added (ca. 0.5 h) 20 mL of 3 N HCl. The resultant yellow solution was stirred for 2.5 h and then poured into a cold (ca. 0 °C) solution of saturated $NaHCO_3$ (50 mL) and this mixture extracted with cold (ca. 0 °C) ether (2 × 50 mL). The combined organic layers were washed with cold (ca. 0 °C) brine (50 mL), dried over $MgSO_4$ at 0 °C, filtered, and concentrated on a rotary evaporator at 0 °C. The yellow residue was cooled to −78 °C (dry ice–acetone) and 50 mL of anhydrous THF added. To the stirred solution was slowly added (ca. 5 min) an excess of methylmagnesium bromide (5 mL of 2.9 M in ether) and the resultant yellow mixture stirred for 1 h at −78 °C and then allowed to slowly warm to ambient temperature (ca. 5 h). The reaction was quenched with 10 mL of saturated NH_4Cl, poured into water (50 mL), and extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to afford a crude yellow oil which was a mixture of diasteromers (1:1, NMR). Flash chromatography (ethyl acetate) afforded 1.45 g (47%) of **12a** (R_f 0.31, ethyl acetate) and 1.39 g (45%) of **12b** (R_f 0.20, ethyl acetate).

Diastereomer 12a: mp 145–146 °C; $[\alpha]_{589}$ +88.2° (c 1.7, THF); IR ($CHCl_3$) 3600–3100, 3070, 3030, 3010, 2980, 2940, 2900, 2840, 1655, 1595, 1505, 1485, 1460, 1402, 1351, 1240, 1130, 1108, 1038, 980, 938 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.40–7.20 (5 H, m), 7.07 (1 H, s), 7.05 (1 H, s), 6.49 (1 H, s), 5.96 (1 H, d, J = 1.4 Hz), 5.95 (1 H, d, J = 1.4 Hz), 5.23 (1 H, d, J = 6.3 Hz), 5.17 (1 H, br s, exchanges with D_2O), 4.62 (1 H, q, J = 6.4 Hz), 4.14–4.08 (1 H, complex m), 3.94 (3 H, s), 3.92 (3 H, s), 3.68 (3 H, s), 3.28–3.22 (1 H, apparent dd, J = ca. 13.8, 9.7 Hz) on which is superimposed 3.25 (3 H, s), 3.05 (1 H, dd, J = 9.7, 6.4 Hz), 1.40 (3 H, d, J = 6.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 164.52, 153.05, 152.12, 147.77, 146.23, 144.86, 140.52, 139.15, 128.89, 128.43, 125.67, 123.62, 109.34, 108.61, 105.58, 101.04, 83.60, 74.08, 73.82, 66.26, 60.98, 59.07, 56.45, 21.89. Anal. Calcd for $C_{29}H_{31}O_8N$: C, 66.91; H, 5.81; N, 2.69. Found: C, 66.74; H, 6.02; N, 2.64.

Diastereomer 12b: mp 153–154 °C; $[\alpha]_{589}$ +49.0° (c 2.2, THF); IR ($CHCl_3$) 3600–3300, 3060, 3010, 2970, 2940, 2890, 2820, 1650, 1590, 1560, 1503, 1480, 1460, 1401, 1348, 1230, 1200, 1120, 1102, 1035, 975, 931 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.30–7.21 (4 H, m), 7.04 (1 H, s), 6.80–6.76 (2 H, m), 6.57 (1 H, s), 5.96 (1 H, d, J = 1.4 Hz), 5.91 (1 H, d, J = 1.4 Hz), 5.23 (1 H, d, J = 7.4 Hz), 4.60 (1 H, q, J = 6.4 Hz), 4.22–4.11 (1 H, complex m), 3.96 (3 H, s), 3.95 (3 H, s), 3.64 (1 H, dd, J = 9.7, 4.4 Hz), 3.55 (3 H, s), 3.49 (1 H, dd, J = 9.7, 6.4 Hz), 3.40 (3 H, s), 3.02 (1 H, br s, exchanges with D_2O), 1.26 (3 H, d, J = 6.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 164.78, 164.63, 152.79, 151.04, 147.71, 146.29, 144.60, 140.42, 138.73, 128.31, 127.82, 127.73, 125.78, 125.41, 124.19, 110.07, 109.97, 105.75, 100.95, 84.07, 74.56, 74.14, 67.37, 61.08, 60.98, 60.82, 59.13, 56.28, 22.32. Anal. Calcd for $C_{29}H_{31}O_8N$: C, 66.91; H, 5.81; N, 2.69. Found: C, 66.87; H, 6.13; N, 2.53.

Biphenyl Allyl Ether Oxazolines 13a and 13b. To a stirred suspension of 130 mg (5.44 mmol) of NaH in 25 mL of anhydrous THF under an argon atmosphere was added 1.24 g (2.39 mmol) of the biaryl alcohol **12a** (R_f 0.31, ethyl acetate) in 10 mL of anhydrous THF at room temperature. The yellow suspension was stirred for 0.5 h and then 0.50 mL (5.46 mmol) of distilled allyl iodide was added and allowed to stir for 18 h. The yellow suspension was cautiously poured into 10 mL water and extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to afford a dark yellow oil that was flash chromatographed (ethyl acetate) to afford 1.15 g (85%) of **13a** (R_f 0.37, ethyl acetate) as a light yellow oil: $[\alpha]_{589}$ +84.3° (c 1.9; THF); IR (film) 3060, 3000, 2970, 2930, 2890, 2830, 1640, 1590, 1475, 1395, 1365, 1345, 1230, 1120, 1100, 1035, 920, 745 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.31 (1 H, s), 7.27–724 (3 H, m), 6.99 (1 H, s), 6.96–6.92 (2 H, m), 6.62 (1 H, s), 5.95 (1 H, d, J = 1.4 Hz), 5.92 (1 H, d, J = 1.4 Hz), 5.77–5.62 (1 H complex m), 5.14 (1 H, d, J = 7.5 Hz), 4.99–4.96 (1 H, m), 4.93–4.92 (1 H, m), 4.14 (2 H, apparent q, J = *ca.* 6.3 Hz), 3.97 (3 H, s), 3.94 (3 H, s), 3.64–3.50 (3 H, complex m) on which is superimposed 3.56 (3 H, s), 3.45 (1 H, dd, J = 9.7, 6.5 Hz), 3.38 (3 H, s), 1.34 (3 H, d, J = 6.3 Hz); ^{13}C-NMR (67.9 MHz, $CDCl_3$) δ 164.26, 152.53, 147.49, 145.76, 140.31, 137.61, 135.65, 128.28, 128.04, 127.74, 125.46, 123.18, 115.21, 109.87, 109.70, 105.38, 100.73, 84.02, 77.41, 74.35, 74.19, 69.11, 60.68, 60.62, 59.02, 56.10, 23.08.

Similar treatment of 1.23 g (2.36 mmol) of biaryl alcohol **12b** (R_f 0.20, ethyl acetate) as described for **13a** afforded 1.21 g (91%) of **13b** (R_f 0.48, ethyl acetate) as a light yellow oil: $[\alpha]_{589}$ +30.6° (*c* 1.90, THF); IR (film) 3060, 3030, 3010, 2970, 2930, 2890, 2830, 1735, 1642, 1590, 1560, 1475, 1455, 1420, 1400, 1365, 1345, 1230, 1115, 1033, 920, 862, 745, 690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.33–7.18 (4 H, m), 7.05 (1 H, s), 6.92–6.86 (2 H, m) 6.57 (1 H, s), 5.97–5.83 (1 H, complex m) on which is superimposed 5.96 (1 H, d, *J* = 1.4 Hz) and 5.86 (1 H, d, *J* = 1.4 Hz), 5.28–5.06 (3 H, complex m), 4.25 (1 H, q, *J* = 6.4 Hz), 4.17–4.10 (1 H, m), 3.95–3.85 (2 H, complex m) on which is superimposed 3.95 (3 H, s) and 3.94 (3 H, s), 3.63 (1 H, dd, *J* = 9.7, 4.4 Hz), 3.56 (3 H, s), 3.47 (1 H, dd, *J* = 9.7, 6.5 Hz), 3.39 (3 H, s), 1.19 (3 H, d, *J* = 6.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 164.28, 152.62, 150.82, 147.50, 145.84, 144.64, 140.37, 137.71, 135.81, 128.20, 127.96, 127.57, 125.24, 124.13, 115.12, 110.10, 109.79, 105.22, 100.67, 83.85, 77.41, 74.40, 74.07, 68.96, 60.68, 60.49, 58.95, 56.05, 23.13.

Biphenyl Carbinols 14a and 14b. To a stirred solution of 1.047 g (1.87 mmol) of biaryl oxazoline **13a** (R_f 0.37, ethyl acetate) in 50 mL of THF under an argon atmosphere at room temperature was added 5.0 g of powdered $NaHSO_4 \cdot H_2O$. The resultant yellow mixture was stirred for 3 h and then 25 mL of water was added and the yellow mixture stirred for 48 h at ambient temperature. The two layers were separated and the organic layer washed with saturated brine (2 × 20 mL) adjusted to pH 2. The organic layer was dried briefly over $MgSO_4$, filtered, and then quickly added (ca. 10 min) to a stirred mixture of 710 mg (18.7 mmol) of $LiAlH_4$ in 50 mL of anhydrous THF under argon at 0 °C. The reaction mixture was cautiously quenched with water and extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to afford a yellow oil. This was used immediately for the next step.

Malonates 15a and 15b. The product from above was dissolved in 50 mL of dry methylene chloride and then 525 mg (2.00 mmol) of triphenylphosphine was added to the stirred solution. The resultant yellow solution was cooled to 0 °C and a solution of 356 mg (2.00 mmol) of *N*-bromosuccinimide in 50 mL of dry dichloromethane was added and the solution stirred for 1.5 h at 0 °C. The dark yellow solution was poured into 20 mL of water and the layers separated. The aqueous layer was extracted with dichloromethane (50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to afford a dark yellow oil. This was filtered through a 4-in. silica plug [hexane:ethyl acetate (1:1)] and evaporated to afford 637 mg (73%) of the crude bromomethyl biphenyl. The latter was dissolved in 5 mL of anhydrous methanol and added to a stirred solution of 500 mg (21.7 mmol) of Na metal and 905 mg (6.85 mmol) of dimethyl malonate in 15 mL of anhydrous methanol. The resultant orange solution was stirred for 1 h, acidified with concentrated HCl, and then poured into 20 mL of water. This was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated to afford a yellow oil that was flash chromatographed [hexane:ethyl acetate (1:1)] to afford 588 mg (61%) of **15a** [R_f 0.52, hexane:ethyl acetate (1:1)] as a colorless oil: $[\alpha]_{589}$ +27.8° (*c* 2.2, THF); IR (film) 3080, 3000, 2970, 2950, 2930, 2900, 2840, 1750, 1732, 1592, 1565, 1492, 1478, 1452, 1430, 1398, 1340, 1318, 1230, 1135, 1100, 1030, 922, 745 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.09 (1 H, s), 6.56 (2 H, s), 6.02 (1 H, d, *J* = 1.4 Hz), 5.99 (1 H, d, *J* = 1.4 Hz), 5.93–5.78 (1 H, complex m), 5.27–5.25 (1 H, m), 5.21–5.18 (1 H, m), 4.02 (1 H, q, *J* =6.3 Hz), 3.95–3.81 (1 H, complex m) on which is superimposed 3.87 (3 H, s) and 3.86 (3 H, s), 3.76–3.60 (1 H, complex m) on which is superimposed 3.66 (3 H, s) and 3.64 (3 H, s), 3.55 (1 H, apparent dd, *J* = ca. 8.2, 7.3 Hz), 2.96 (1 H, d, *J* = 8.2 Hz), 2.94 (1 H, d, *J* = 7.3 Hz), 1.26 (3 H, d, *J* = 6.3 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 169.17, 168.91, 152.73, 151.89, 147.60, 146.29, 141.10, 136.88, 135.18, 131.34, 127.62, 126.88, 115.84, 109.92, 108.28, 105.79, 100.99, 74.24, 69.22, 60.71, 60.57, 55.90, 52.20, 32.11, 22.39.

Similar treatment of 1.50 g (2.67 mmol) of the biaryl oxazoline **13b** as described for **13a** afforded 771 mg (56%) of **15b** as a light yellow glass [R_f 0.58 hexane:ethyl acetate (1:1)]: $[\alpha]_{589}$ 8.8° (*c* 1.4, THF); IR (film) 3900, 3010, 2970, 2950, 2930, 2900, 2840, 1755, 1735, 1595, 1568, 1500, 1480, 1455, 1434, 1402, 1343, 1230, 1138, 1095, 1032, 995, 923 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.09 (1 H, s), 6.55 (1 H, s), 6.54 (1 H, s), 6.02 (1 H, d, *J* = 1.3 Hz), 6.00 (1 H, d, *J* = 1.3 Hz), 5.91–5.77 (1 H, complex m), 5.24–5.16 (1 H, m), 5.08–5.03 (1 H, m), 4.06 (1 H, q, *J* = 6.4 Hz), 3.95–3.80 (1 H, m) on which is superimposed 3.86 (6 H, s), 3.76–3.54 (2 H, m) on which is superimposed 3.68 (3 H, s) and 3.67 (3 H, s) and 3.62 (3 H, s), 2.94 (1 H, dd, *J* = 14.5, 9.0 Hz), 2.76 (1 H, dd, *J* = 14.5, 6.6 Hz) 1.20 (3 H, d, *J* = 6.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 169.06, 168.75, 152.89, 150.94, 147.66, 146.28, 141.26, 137.24, 135.61, 132.12, 127.89, 127.04, 115.21, 109.86, 108.28, 105.85, 100.93, 73.59, 68.96, 60.52, 55.95, 52.25, 52.13, 31.98, 22.92.

Biphenyl Carbinol Malonates 16a and 16b. To a stirred solution of 320 mg (0.62 mmol) of the allyl protected biaryl diester **15a** [R_f 0.52, hexane:ethyl acetate (1:1)] in 10 mL of 10% aqueous ethanol was added 15 mg (0.13 mmol) of diazabicyclo[2.2.2]octane and 40 mg (0.04 mmol) of tris(triphenylphosphine)rhodium(I) chloride. The resultant suspension was refluxed for 3 h and then poured into 10 mL of water. This mixture was extracted with ether (2 × 50 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated to afford a dark brown gum. The gum was dissolved in ethyl acetate and filtered through a 1-in. silica plug and the solvent evaporated to afford a brown oil. This was dissolved in 10 mL of 10% aqueous acetone and then 171 mg (0.63 mmol) of $HgCl_2$ added to the stirred mixture. A mixture of 180 mg (0.83 mmol) of yellow HgO in 10 mL of 10% aqueous ethanol was added to the mixture and the resultant orange suspension allowed to stir for 18 h at room temperature. The orange mixture was filtered through a Celite plug and the acetone evaporated. The residue was dissolved in ether (75 mL), rinsed with a saturated KI solution (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to afford a dark yellow oil which was flash chromatographed [hexane:ethyl acetate (1:1)] to afford 246 mg (83%) of **16a** as a light yellow foam [R_f 0.29, hexane:ethyl acetate (1:1)]: mp 47–49 °C; $[\alpha]_{589}$ +27.5° (*c* 1.2, THF): IR (film) 3640–3280, 3010, 2950, 2930, 2900, 2840, 1760, 1740, 1730, 1597, 1568, 1500, 1480, 1455, 1435, 1400, 1343, 1225, 1140, 1105, 1035, 930, 750 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.16 (1 H, s), 6.56 (1 H, s), 6.52 (1 H, s), 6.00 (1 H, d, *J* = 1.3 Hz), 5.98 (1 H, d, *J* = 1.3 Hz), 4.37 (1 H, q, *J* = 6.3 Hz), 3.87 (3 H, s), 3.86 (3 H, s), 3.67 (3 H, s), 3.63 (3 H, s), 3.56 (3 H, s), 3.51 (1 H, apparent dd, *J* = 8.1, 8.0 Hz), 3.24 (1 H, br s, exchanges with D_2O), 3.08 (1 H, dd, *J* = 14.4, 8.1 Hz,) 2.91 (1 H, dd, *J* = 14.4, 8.0 Hz), 1.34 (3 H, d, *J* = 6.3 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 169.44, 152.95, 152.10, 147.82, 146.50, 141.37, 139.68, 131.48, 127.47, 126.78, 109.65, 108.79, 106.33, 101.15, 66.68, 60.88, 60.71, 56.27, 52.58, 51.88, 32.43, 24.24. Anal. Calcd for $C_{24}H_{28}O_{10}$: C, 60.49; H, 5.92. Found: C, 59.55; H, 5.63.

Similar treatment of 296 mg (0.57 mmol) of the protected allyl biaryl diester **15b** [R_f 0.58, hexane:ethyl acetate (1:1)] as described for **15a** afforded 226 mg (83%) of **16b** as a light yellow glass following flash chroamtography [R_f 0,23, hexane:ethyl acetate (1:1)]: $[\alpha]_{589}$ +13.6° (*c* 2.0, THF); IR (film) 3660–3200, 3070, 3020, 2970, 2950, 2895, 2840, 1750, 1735, 1595, 1477, 1398, 1342, 1228, 1137, 1100, 1054, 1030, 922, 807 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.12 (1 H, s), 6.62 (1 H, s), 6.59 (1 H, s), 6.03 (1 H, d, *J* = 1.3 Hz), 6.01 (1 H, d, *J* = 1.3 Hz), 4.39 (1 H, q, *J* = 6.4 Hz), 3.89 (3 H, s), 3.87 (3 H, s), 3.64 (3 H, s), 3.62 (3 H, s), 3.53 (3 H, s), 3.27 (1 H, dd, *J* = 9.5, 6.4 Hz), 3.21 (1 H, br s, exchanges with D_2O), 3.08 (1 H, dd, *J* = 14.2, 6.4 Hz), 2.89 (1 H, dd, *J* = 14.2, 9.5 Hz), 1.40 (3 H, d, *J* = 6.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 168.79, 152.73, 150.93, 147.77, 146.718 141.32, 138.24, 131.69, 127.36, 109.71, 105.90, 101.04, 67.63, 66.26, 60.91, 60.71, 56.00, 52.14, 51.72, 32.22, 25.46, 21.66. Anal. Calcd for $C_{24}H_{28}O_{10}$: C, 60.49; H, 5.92. Found: C, 59.50; H, 5.73.

Dibenzocyclooctanone (19). To a stirred mixture of 9 mg (0.11 mmol) of sodium acetate and 104 mg (0.48 mmol) of pyridinium chlorochromate in 10 mL of dry dichloromethane at room temperature was added 100 mg (0.21 mmol) of the biaryl alcohol **16a** [R_f 0.29, hexane: ethyl acetate (1:1)] in 10 mL of dry dichloromethane. The mixture was stirred for 2 h and then poured into 10 mL of water. This was extracted with dichloromethane (2 × 25 mL), washed with brine (10 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to afford a dark brown gum, **17**. This was dissolved in ethyl acetate and filtered through a 1-in. silica plug and the ethyl acetate evaporated to afford a yellow oil. The yellow oil was dissolved in 10 mL of dry dichloromethane and 8 μL of trifluoroacetic acid was added to the stirred solution. Then 74 mg (0.23 mmol) of pyridinium bromide perbromide was slowly added over a 1-h period. The organic solution was stirred for an additional 0.5 h, washed with aqueous $NaHCO_3$ (5 mL), 10% HCl (5 mL), and brine (5 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to yield a yellow solid, **18**, which was dissolved in ethyl acetate and filtered through a 1-in silica plug. The solvent was evaporated to afford a light yellow solid which was dissolved in 1 mL of dry THF and added to a stirred mixture of 31 mg (0.27 mmol) of potassium *tert*-butoxide in 5 mL of dry THF under an argon atmosphere at ambient temperature. The mixture was stirried for 0.5 h and the mixture acidified with concentrated HCl. The reaction mixture was extracted with ethyl acetate (2 × 50 mL), washed with brine (25 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to afford a dark yellow oil that was flash chromatographed [hexane:ethyl acetate (1:1)] to afford 53 mg (54%) of **19** [R_f 0.35, hexane:ethyl acetate (1:1)] as a light yellow oil: $[\alpha]_{589}$ −62.4° (*c* 2.6, THF); ^1H NMR (270 MHz, $CDCl_3$) δ 7.56 (1 H, s), 6.64 (1 H, s), 6.44 (1 H, s), 6.08 (1 H, s), 6.05 (1 H, s), 3.91 (3 H, s), 3.85 (3 H, s), 3.79 (3 H, s), 3.74 (3 H, s), 3.56 (3 H, s), 3.32 (1 H, d, *J* = 13.8 Hz), 3.20 (1 H,

d, J = 13.8 Hz), 3.07 (1 H, d, J = 13.8 Hz), 2.76 (1 H, d, J = 13.8 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 196.34, 170.65, 170.28, 153.63, 151.86, 151.15, 147.97, 142.32, 132.75, 132.54, 130.64, 128.00, 112.57, 108.97, 108.24, 102.10, 61.19, 61.03, 59.18, 56.22, 52.99, 52.89, 45.37, 36.50.

Similar treatment of 164 mg (0.34 mmol) of biaryl alcohol **16b** [R_f 0.23, hexane:ethyl acetate (1:1)] as described for **16a** afforded 82 mg (51%) of **19** as a light yellow oil that had identical physical properties.

Dibenzocyclooctanone Carboxylates 20 and 21. To a stirred solution of 5 mL of 2.7 M KOH and 5 mL of ethanol was added a solution of 72 mg (0.15 mmol) of the biaryl diester **19** in 2 mL of ethanol and the resultant solution was refluxed for 2 h under argon. The solution was cooled to ambient temperature and the aqueous layer washed with ether (2 mL). The aqueous layer was acidified with concentrated HCl and this mixture extracted with ethyl acetate (2 × 20 mL), washed with brine (20 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to afford the crude diacid. This was heated to 205 °C under argon in a Kugelrohr oven for 15 min and then cooled to ambient temperature. The residue was esterified with excess diazomethane in ether (20 mL) to afford a 1:1 mixture of diasteromers (**20**, **21**) which were separated by flash chromatography [hexane:ethyl acetate (1:1)] to yield 18 mg (29%) of **20** [R_f 0.35, hexane:ethyl acetate (1:1)] which was recrystallized from methanol to afford white prisms followed by 19 mg (30%) of **21** [R_f 0.27, hexane:ethyl acetate (1:1)] as a clear glass.

20: mp 133–134 °C; $[\alpha]_{589}$ +5.2° (c 1.7, THF); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69 (1 H, s), 6.67 (1 H, s), 6.47 (1 H, s), 6.08 (1 H, s), 6.05 (1 H, s), 3.92 (3 H, s), 3.86 (3 H, s), 3.72 (3 H, s), 3.58 (3 H, s), 3.17–3.12 (1 H, m), 3.07–2.93 (1 H, m), 2.84–2.76 (2 H, m), 2.66–2.56 (1 H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 198.03, 173.77, 153.69, 151.62, 151.26, 147.93, 142.11, 133.50, 132.27, 131.33, 127.99, 113.25, 108.76, 108.54, 102.15, 61.29, 61.05, 56.28, 51.10, 43.63, 41.47, 33.33.

21: $[\alpha]_{589}$ −3.1° (c 1.3, THF); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.53 (1 H, s), 6.63 (1 H, s), 6.55 (1 H, s), 6.07 (1 H, d, J = 1.0 Hz), 6.04 (1 H, d, J = 1.0 Hz), 3.91 (6 H, s), 3.69 (3 H, s), 3.57 (3 H, s), 2.91–2.80 (4 H, m), 2.49–2.43 (1 H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 197.93, 173.77, 154.11, 152.00, 150.85, 147.87, 141.95, 133.23, 132.12, 127.84, 112.25, 109.08, 108.76, 107.38, 102.05, 61.24, 61.08, 56.43, 52.10, 45.07, 42.37, 33.85.

Interconversion of 21 to 20. According to the previous observations,[5d,f,15] pure **21** was heated for 12 h in xylene to give a 1:1 mixture of **20** and **21** which was separated by flash chromatography as above.

(−)-Steganone (1). To a stirred solution of 70 mg (0.17 mmol) of monoester **20** [R_f 0.35, hexane:ethyl acetate (1:1)] was added 1 mL of 5% KOH and 0.3 mL of 37% formaldehyde and the resultant clear solution stirred for 2 h at ambient temperature. The solution was then acidified with 3 N HCl and extracted with chloroform (3 × 20 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to afford a light yellow oil. The oil was dissolved in acetone (3 mL) and cooled to 0 °C and Jones reagent added slowly to the stirred solution until the orange color persisted. MeOH was added followed by water (5 mL) and this mixture extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with 1 N NaOH (5 mL), dried ($MgSO_4$), and filtered and the solvent removed to afford a clear yellow oil. Flash chromatography [hexane:ethyl acetate (1:1)] afforded 14 mg (20%) of a clear oil that was recrystallized from methanol to afford 8 mg (11%) of (−)-steganone (**1**): mp 161–163 °C [lit. mp 155–156 °C,[4] 155–158 °C,[6a] 155.5–157 °C,[6b] 154–156 °C[6c]]; $[\alpha]_D$ −161° (c 0.8, $CHCl_3$) [lit. $[\alpha]_D$ −202° (c 0.76, $CHCl_3$),[4] $[\alpha]_D$ −191° (c 0.76, $CHCl_3$),[6a] $[\alpha]_D$ −197° (c 0.77, $CHCl_6$),[6b] $[\alpha]_D$ −140° (c 1.16, $CHCl_3$)[6c]]: ^{1}H NMR (270 MHz, $CDCl_3$) 7.53 (1 H, s), 6.63 (1 H, s), 6.54 (1 H, s), 6.11 (1 H, d, J = 1.3 Hz), 6.09 (1 H, d, J = 1.3 Hz), 4.48 (1 H, apparent t, J = 9.7 Hz), 4.37 (1 H, dd, J = 9.3, 7.0 Hz), 3.89 (3 H, s), 3.88 (3 H, s), 3.61 (3 H, s), 3.26–3.09 (2 H, complex m), 2.84–2.76 (2 H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 195.39, 175.89, 154.38, 152.16, 151.62, 148.14, 141.95, 133.76, 132.28, 131.99, 127.10, 112.83, 108.81, 108.11, 102.36, 67.05, 61.13, 56.38, 50.14, 44.96, 30.48.

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Polynitro-Substituted Strained-Ring Compounds. Synthesis, Mechanism of Formation, and Structure of *trans*-Dinitrocyclopropanes

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Abstract: 1,2-Dinitrocyclopropane, 1,2-dimethyl-1,2-dinitrocyclopropane, and 1,2-diethyl-1,2-dinitrocyclopropane have been prepared in 23–36% yield by oxidative cyclization of the corresponding open-chain 1,3-dinitronate dianions with iodine in DMSO. In each case only the trans isomer of the dinitrocyclopropane was obtained. Treatment of 2,4-dibromo-2,4-dinitropentane with the lithium salt of 2-nitropropane gave *trans*-1,2-dimethyl-1,2-dinitrocyclopropane, suggesting the intermediacy of a halonitro nitronate intermediate in the oxidative cyclization process. Further mechanistic studies using *m*-dinitrobenzene suggest either an internal single-electron transfer, nonchain pathway or an internal S_N2 process leading to the dinitrocyclopropanes. An X-ray crystallographic study performed on *trans*-1,2-dinitrocyclopropane indicates substantially shortened distal C–C bonds (1.47 Å) and bisected conformations for each nitro group. Ab initio calculations using a 4-31G basis set are in agreement with the X-ray data, except longer distal C–C bonds (1.49 Å) are calculated. Ab initio calculations using a variety of basis sets were performed on nitrocyclopropane as a model.

Strained-ring compounds substituted with multiple nitro groups are of interest as potential new high-energy materials and as compounds that might possess unusual chemical reactivity. Several such compounds have recently been synthesized,[1] typically in milligram quantities. The simplest strained-ring nitro compound, nitrocyclopropane,[2] and a number of its simple analogues have long been known. However, dinitrocyclopropanes, except for one brief report[3] on 1,1-dimethyl-2,3-dinitrocyclopropane which we became aware of after this study was in progress, have not been discussed in the literature. Since dinitrocyclopropanes are the simplest example of strained-ring polynitro compounds, their

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