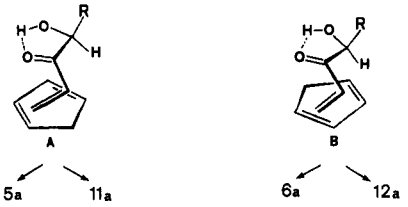
corresponding products **5a** and **6a** as shown below.



The above analysis suggests that the dienophile **9** with a *tert*-butyl substituent would exhibit even more enhanced diastereofacial selectivity than **1**. Molecular models indicate that (1) within the chelated framework the energy difference between the cisoid and transoid conformers of **9** is definitely greater than that in the case of **1** (because of the severe repulsion between vinylic hydrogens and the *tert*-butyl group of the transoid conformer of **9**), and (2) the steric interactions between the *tert*-butyl group of **9** and the approaching cyclopentadiene would be greater than that between the cyclohexyl group of **1** and the same diene. This prediction has indeed proven valid. The known (*S*)-2-hydroxy-3,3-dimethylbutyric acid, $[\alpha]^{20}_D$ +4.45° (*c* 4.0, H_2O),[12] resolved from its racemic mixture with (−)-1-phenylethylamine was converted to **9**, $[\alpha]^{20}_D$ +205.9° (*c* 2.64, $CHCl_3$), and compound (**9**) and its trimethylsilyl derivatives **10** $[\alpha]^{20}_D$ −58.8° (*c* 0.49, $CHCl_3$), were allowed to react with the diene in a manner analogous to that for **1** and **2**. As summarized in entries 8–11 in Table I, our expectations are fully realized, and at −20 °C the enone **9** attains a diastereofacial selectivity of >100:1 in the formation of the two endo diastereomers **11a** and **11b** (entry 10).[13] While there is room for further improvement in the endo/exo ratio, the design of reagents **1** and **9** has definitely demonstrated one rational approach to the asymmetric Diels–Alder reaction. Further work is underway.

Acknowledgment. We thank Professor W. Oppolzer for the written version of ref 6b and the National Institutes of Health (CA 28337) for financial support. High-resolution mass spectra were provided by the facility supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources, and infrared studies were performed with a Nicolet NIC-7199 FT-IR system purchased through an NIH grant (GM 27551).

Registry No. **1**, 85067-27-2; **2**, 85082-16-2; **3**, 85082-17-3; **9**, 85067-28-3; **10**, 85067-29-4; cyclopentadiene, 542-92-7.

Supplementary Material Available: Listing of spectral data (3 pages). Ordering information is given on any current masthead page.

(12) Tanabe, T.; Yajima, S.; Imaida, M. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2178. The reported specific rotation for this acid is $[\alpha]^{20}_C$ +4.50° (*c* 4, H_2O).

(13) The enantiomeric purity of all new compounds (except for the carboxylic acids) has been assessed by ^1H NMR spectroscopy, using $Eu(Hfbc)_3$, or by the Mosher acid chloride procedure [Dale, T. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.]

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The Nitrile Oxide Cycloaddition (NOC) Route to a Multipurpose *C*-Nucleoside Intermediate: A New Class of *C*-Nucleosides

Summary: A new route to the important class of antibiotic and antiviral agents, the *C*-nucleosides, has been developed. The nitrile oxide generated from a protected derivative of β-D-ribofuranosylnitromethane has been shown to react with ethoxyacetylene to deliver an isoxazole *C*-nucleoside. On hydrogenolytic cleavage of the N–O bond, a β-keto ester is formed that can be reacted with a bisnucleophile to yield a new *C*-nucleoside analogue.

Sir: In further extending the application of nitrile oxide cycloaddition chemistry to other molecules of Nature, it was reasoned that the generation of nitrile oxides bearing sugar units and their fragments could well prove to be of considerable importance to synthesis design.[1] As an example of this notion, we report herein a novel and very efficient route to a new class of *C*-nucleoside products containing ribose attached to an isoxazole. Furthermore, we show in one example how such *C*-nucleosides can in turn provide access to a host of related *C*-nucleoside structures.

Our work began with the known α- and β-D-ribofuranosylnitromethane derivatives **1α** and **1β**. These products are conveniently prepared by reacting a methanol solution of D-ribose with nitromethane in the presence of potassium carbonate (Scheme I). This procedure delivered the α-isomer in ~17% yield and the β-isomer in ~62% as described by Sudoh et al.[2] Each isomer was converted to its acetonide derivative (2,2-dimethoxypropane, THF, TsOH), and the remaining hydroxyl group was protected by silylation (t-Bu(Me)$_2$SiCl, imidazole). Since some epimerization of these isomers occurs during the protection process,[3] it has proven most convenient to carry out rigorous purification of each isomer after the silylation step rather than after the initial nitromethane condensation reaction.

With the pure D-ribofuranosylnitromethane derivatives **2α** and **2β** in hand, we were now ready to test the key nitrile oxide cycloaddition reaction. Since some initial concern did exist as to whether epimerization of the β-isomer to the α-isomer (the thermodynamically favored isomer)[4] might occur during the nitrile oxide forming step (PhNCO, Et_3N), care was taken to use very pure samples of **2α** and **2β** during the initial stages of the investigation.

On reaction of **2α** or **2β** with ethoxyacetylene[5] under the Mukaiyama conditions,[6] pure **3α** and **3β** were formed in high yield. Little, if any, epimerization was found to occur with either isomer, a fact that can be attributed to rapid interception of the nitronate anion by the phenyl isocyanate to generate the transient nitrile oxide without competing β-elimination of the tetrahydrofuranyl ring

(1) For some recent examples of such applications, see: Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788. Kozikowski, A. P.; Stein, P. D. *Ibid.* **1982**, *104*, 4023. Kozikowski, A. P.; Ishida, H. *Ibid.* **1980**, *102*, 4265. Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. Kozikowski, A. P.; Ghosh, A. K., manuscript in preparation. Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081.

(2) Sakakibara, T.; Takamoto, T.; Matsuzaki, T.; Omi, H.; Maung, U. W.; Sudoh, R. *Carbohydr. Res.* **1981**, *95*, 291.

(3) After acetonide formation using pure **1β**, an 84:16 mixture of the protected β- and α-products was obtained. Silylation of the acetonide derivative of **1β** gave a 9:1 mixture of the β- and α-products, respectively, after 12 h. If the silylation reaction was kept at room temperature for 6 days, a 45:55 mixture of the β- and α-products resulted.

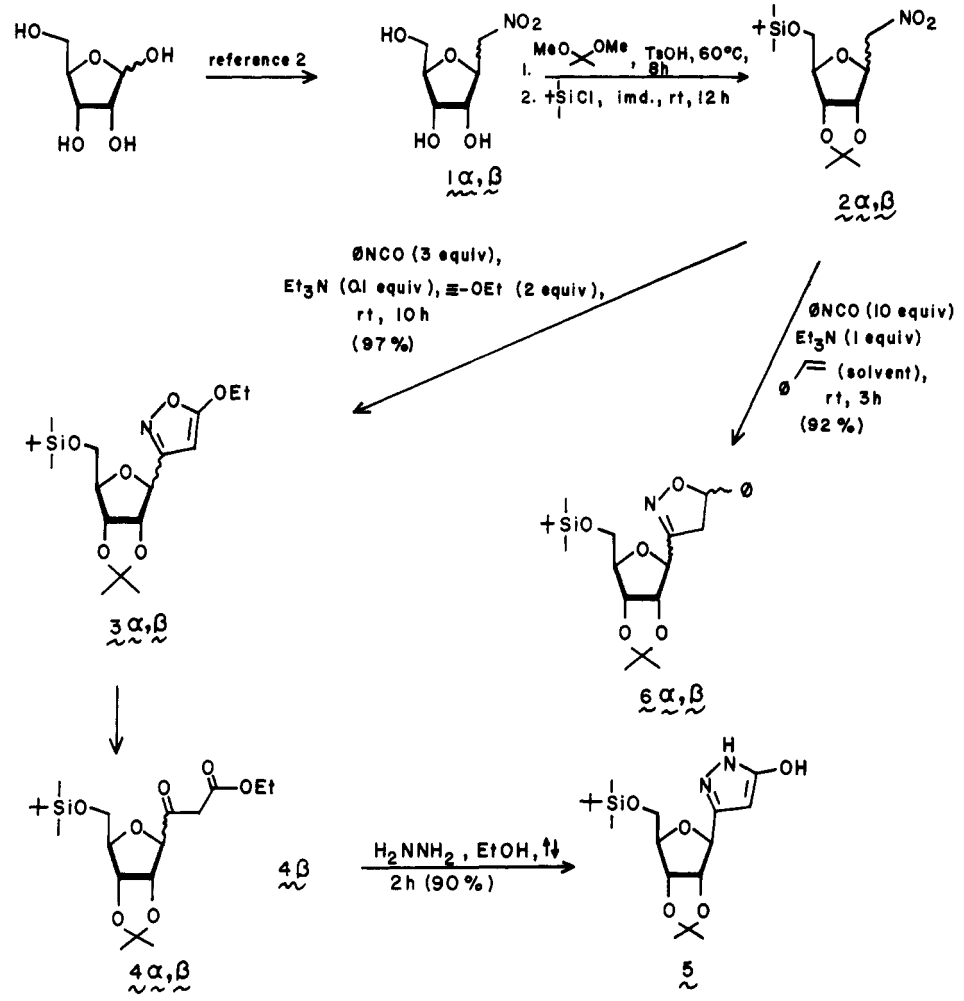
(4) Takamoto, T.; Omi, H.; Matsuzaki, T.; Sudoh, R. *Carbohydr. Res.* **1978**, *60*, 97.

(5) Jones, E. R. H.; Eglinton, G.; Whiting, M. C.; Shaw, B. L. "Organic Syntheses"; Wiley: New York, 1963; Vol. IV, p 404 (footnote 12).

(6) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

0022-3263/83/1948-1139$01.50/0

Scheme I. A New Strategy for C-Nucleoside Synthesis



oxygen. In addition, when a mixture of both isomers was used to generate nitrile oxide, more rapid disappearance of the β-isomer was noted.

Thus, in a single step it is possible to generate a new class of isoxazole C-nucleosides.[7] Moreover, when the relatively weak nature of the N–O bond of isoxazoles is taken into account,[8] it can be seen that **3** should itself serve as a versatile precursor to a host of other C-nucleoside derivatives.[9]

On exposure of **3β** to hydrogen and W-2 Raney nickel/BCl_3 in methanol/water,[10] a rapid reaction ensued to give the β-keto ester **4β** in 80% yield.[11] It should be noted here that such a derivative would be tedious to prepare by the application of any sort of acyl anion type chemistry to an activated ribose derivative. On exposing this β-keto ester in turn to a bisnucleophile, a ring-forming reaction was anticipated to occur with formation of a new C-nucleoside derivative. Indeed, treatment of **4β** with hydrazine gave the pyrazole nucleoside **5**,[12] a compound related structurally to pyrazofurin.

Olefins react equally well with the nitrile oxides generated from **2α** or **2β**. When styrene was employed as the

(7) An aminoisoxazole derivative of ribose has been generated previously as a key intermediate in the synthesis of oxazinomycin: De Bernardo, S.; Weigele, M. *J. Org. Chem.* **1977**, *42*, 109.

(8) Kochetkov, N. K.; Sokolov, S. D. *Adv. Heterocycl. Chem.* **1963**, *2*, 365.

(9) The use of dipolar cycloaddition chemistry in C-nucleoside construction in itself is not novel. However, in the majority of this foregoing work a ribose derivative serves as the dipolarophile rather than the dipole. See, for example: James, S. R. *J. Carbohydr. Nucleosides, Nucleotides* **1976**, *3*, 47. Tronchet, J. M. J.; Perret, F. *Carbohydr. Res.* **1974**, *38*, 169. Tronchet, J. M. J.; Perret, M. F. *Helv. Chim. Acta* **1971**, *54*, 683.

(10) This procedure for isoxazole cleavage was developed by A. K. Ghosh. Also, see: Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123. Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

(11) This new scheme for β-keto ester synthesis was developed by C. S. Li in these laboratories, and further applications of this process will be reported later. A product related structurally to **4** has been prepared previously from an acetylenic ester. See Tam, S. Y-K.; Klein, R. S.; de las Heras, F. G.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4854. Hydrogenation of **3α** likewise led to a single β-keto ester whose ^1H NMR characteristics were quite different from those of **4β**. Thus one may conclude that epimerization of the β-keto ester does not occur under the hydrogenation conditions.

(12) Representative spectral data for **3β**, **4β**, and **5** follow.

3β: $[\alpha]^{25}_D$ −36.2° (*c* 0.4, $CHCl_3$); IR (neat) 2980, 2950, 2920, 2850, 1725, 1600, 1500, 1470, 1450, 1380, 1290, 1260, 1215, 1080, 830, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.24 (s, 1 H), 4.94 (dd, 1 H, *J* = 6.3, 4.2 Hz), 4.90 (d, 1 H, *J* = 4.2 Hz), 4.73 (dd, 1 H, *J* = 6.1, 2.8 Hz), 4.21 (q, 2 H, *J* = 7.0 Hz), 4.17–4.21 (m, 1 H), 3.69 (dd, 1 H, *J* = 11.2, 4.2 Hz), 3.64 (dd, 1 H, *J* = 11.2, 4.6 Hz), 1.57 (s, 3 H), 1.44 (t, 3 H, *J* = 7.0 Hz), 1.36 (s, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); mass spectrum (70 eV), *m/z* 384, 342 (base), 284, 210, 184.

4β: $[\alpha]^{24}_D$ −1.00 (*c* 0.2, $CHCl_3$); IR (neat) 2980, 2950, 2925, 2850, 1730, 1600, 1535, 1500, 1460, 1440, 1380, 1370, 1310, 1260, 1220, 1160, 1120, 1090, 1060, 835, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.96 (dd, 1 H, *J* = 6.2, 2.6 Hz), 4.63 (br d, 1 H, *J* = 6.2 Hz), 4.51 (d, 1 H, *J* = 2.6 Hz), 4.30–4.35 (m, 1 H), 4.19 (q, 2H, *J* = 7.2 Hz), 3.86 (d, 1 H, *J* = 16.41 Hz), 3.81 (dd, 1 H, *J* = 11.5, 2.5 Hz), 3.68 (dd, 1 H, *J* = 11.5, 2.9 Hz), 3.45 (d, 1 H *J* = 16.4 Hz), 1.53 (s, 3 H), 1.36 (s, 3 H), 1.27 (t, 3 H, *J* = 7.2 Hz), 0.88 (s, 9 H), 0.06 (s, 6 H); mass spectrum (70 eV), *m/z* 402 (M^+), 387, 345 (base), 299, 291, 269.

5: $[\alpha]^{24}_D$ −27.5° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3450, 3300, 2950, 2850, 1720, 1580, 1520, 1460, 1380, 1200, 1080, 925 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.60 (br s, 1 H), 5.12 (d, 1 H, *J* = 2.8 Hz), 4.74 (dd, 1 H, *J* = 6.1, 3.2 Hz), 4.68 (dd, 1 H, *J* = 6.1, 2.8 Hz), 4.26 (ddd, 1 H, *J* = 3.6, 3.2, 3.2 Hz), 3.86 (dd, 1 H, *J* = 11.3, 3.2 Hz), 3.72 (dd, 1 H, *J* = 11.3, 3.6 Hz), 2.34 (br s, 1 H), 1.67 (br s, 1 H), 1.58 (s, 3 H), 1.36 (s, 3 H), 0.92 (s, 9 H), 0.13 (s, 6 H); mass spectrum (70 eV), *m/z* 370 (M^+), 355, 313 (base), 255, 237, 168.

dipolarophile, some diastereoselection was observed (6β, 2:1), using 2β as the nitrile oxide precursor. The nitrile oxide from 2α gave, on the other hand, a 1:1 mixture of separable diastereomers 6α.

In conclusion, when one considers all of the other known ways to manipulate isoxazoles, such as ring metalation, as well as the variety of ring-opening processes known for the isoxazolium salts (especially the 5-unsubstituted derivatives),[13] then numerous possibilities can be envisioned for the use of such nitrile oxides in the design of new C-nucleoside analogues. We further suggest that this general concept of constructing nitrile oxides containing sugars and sugar fragments should find broader applications in synthesis, for it is possible to effect carbon–carbon bond formation with creation of a masked β-hydroxy ketone from a chiral fragment containing an α-oxygen substituent.[14] This would, of course, be difficult to achieve through conventional carbanion chemistry because of competing β-elimination processes. Other reports concerning this situation will be forthcoming.

Acknowledgment. We are indebted to the National Institutes of Health (Grant No. HL-20579) for support of these investigations.

Registry No. 1α, 79698-06-9; 1β, 79733-40-7; 2α, 84987-81-5; 2β, 85027-42-5; 3α, 84987-82-6; 3β, 84987-83-7; 4α, 84987-84-8; 4β, 84987-85-9; 5, 84987-86-0; 6α, 84987-87-1; 6β, 84987-88-2; ethoxyethyne, 927-80-0; phenylethene, 100-42-5; hydrazine, 302-01-2.

(13) Wakefield, B. J.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 147.

(14) For a leading reference on the use of monosaccharide nitrones in synthesis, chemistry related in a sense to that described herein, see: Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134.

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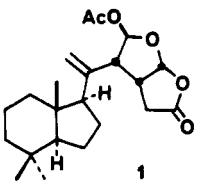
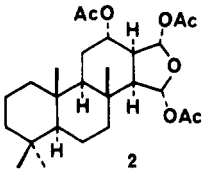
Norrisolide, a Novel Diterpene from the Dorid Nudibranch *Chromodoris norrisi*[1]

Summary: The dorid nudibranch *Chromodoris norrisi* contains an unusual rearranged diterpene, norrisolide (1). The structure of norrisolide was determined by X-ray diffraction analysis.

Sir: As part of a study of the chemical defense mechanism of nudibranch molluscs,[2] we have examined the chemical constituents of the common dorid nudibranchs from the Gulf of California. Most dorid nudibranchs contained metabolites either identical with or closely related to known sponge metabolites.[3] A notable exception to this observation was the discovery of the unusual diterpene norrisolide (1) from the brightly colored dorid nudibranch *Chromodoris norrisi* Farmer 1963.[4] In this paper we report the structural elucidation of norrisolide (1) by a single-crystal X-ray diffraction experiment.



1



2

Ten specimens of *Chromodoris norrisi* (average weight 0.2 g) were collected near San Carlos Bay, Sonora, Mexico, and were stored in acetone for 2 weeks. The dichloromethane-soluble material from the decanted acetone was twice chromatographed by LC on Partisil first with ether and then with 2:1 ether/hexane as eluants to yield norrisolide (1, 0.2 mg/animal) as small colorless crystals, mp 138–140 °C.

Norrisolide (1) had the molecular formula $C_{22}H_{32}O_5$. The mass spectrum showed a very weak molecular ion peak at m/z 376 with strong peaks at m/z 316 and 317, indicating facile loss of an acetate group. The infrared spectrum contained bands at 1800 (γ-lactone) and 1760 cm^{-1} (acetate). The ^{13}C NMR spectrum[5] contained two carbonyl signals at δ 173.6 (s) and 168.6 (s), two acetal carbon signals at δ 107.1 (d) and 101.8 (d), and signals for an α,α′-disubstituted olefin at δ 143.5 (s) and 116.8 (t). A series of ^1H NMR decoupling experiments defined the oxygen-containing portion of the molecule: a two-proton signal at δ 2.55 (d, 2 H, J = 7 Hz, C-13) was coupled to a signal at δ 3.36 (m, 1 H, J = 9.5, 7, 7, 6 Hz, C-12) that was in turn coupled to an acetal proton signal at δ 6.14 (1 H, d, J = 6 Hz, C-20) and a methine proton signal at δ 3.07 (dd, 1 H, J = 9.5, 3.5 Hz, C-11) that was further coupled to the second acetal proton signal at δ 6.44 (d, 1 H, J = 3.5 Hz, C-19). The chemical shift of the δ 3.07 signal and the absence of further coupling suggested that the α,α′-disubstituted olefin was located at C-10. Since the ^1H NMR spectrum[5] contained three methyl signals at δ 0.66 (s, 3 H), 0.84 (s, 3 H), and 0.86 (s, 3 H) and the molecular formula required an additional two carbocyclic rings from the nine remaining carbon atoms, these data indicated that norrisolide contained a novel diterpene ring system.

The structure of norrisolide (1) was determined by a single-crystal X-ray diffraction experiment.[6] A comput-

(1) Presented at the IUPAC Conference on Marine Natural Products, Tenerife, Spain, July 1982.

(2) Thompson, J. E.; Walker, R. P.; Wratten, S. J.; Faulkner, D. J. *Tetrahedron* **1982**, *38*, 1865 and references cited therein.

(3) Hochlowski, J. E.; Walker, R. P.; Ireland, C.; Faulkner, D. J. *J. Org. Chem.* **1982**, *47*, 88. Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1981**, *22*, 271 and unpublished data.

(4) Farmer, W. M. *Trans. San Diego Soc. Nat. Hist.* **1963**, *13*, 31.

(5) IR (CCl_4) 1800, 1760, 1370, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (s, 3 H), 0.84 (s, 3 H), 0.86 (s, 3 H), 2.07 (s, 3 H), 2.55 (2 H, d, J = 7 Hz), 3.07 (dd, 1 H, J = 9.5, 3.5 Hz), 3.36 (m, 1 H, J = 9.5, 7, 7, 6 Hz), 5.09 (br s, 1 H), 5.15 (br s, 1 H), 6.14 (d, 1 H, J = 6 Hz), 6.44 (d, 1 H, J = 3.5 Hz); ^{13}C NMR (C_6D_6) δ 173.6 (s), 168.6 (s), 143.5 (s), 116.8 (t), 107.1 (d), 101.8 (d), 58.8 (d), 57.8 (d), 50.1 (d), 45.1 (s), 41.8 (t), 40.6 (d), 38.7 (t), 33.5 (q), 33.3 (s), 30.5 (t), 24.3 (t), 21.2 (t), 20.7 (q), 20.5 (t), 19.9 (q), 14.2 (q); HRMS, obsd m/e 316.2047, $C_{20}H_{28}O_3$ (M − AcOH) required m/e 316.2038.

(6) Preliminary X-ray diffraction patterns showed monoclinic symmetry and accurate lattice constants of a = 12.691 (2) Å, b = 7.517 (2) Å, c = 22.531 (3) Å and β = 108.24 (7)°. Systematic extinctions and density were most plausibly accommodated by space group $C2$ with one molecule of $C_{22}H_{32}O_5$ in the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a four-circle diffractometer by using graphite monochromated Cu Kα radiation (1.541 78 Å) and 1° ω scans. A total of 1578 reflections was collected in this fashion, and after correction for Lorentz, polarization, and background effects 1447 (92%) were judged observed ($|F_o| \geq 3\sigma(R_o)$). A phasing model was deduced by standard multisolution direct methods and extended by tangent formula recycling.[7] This revealed the entire nonhydrogen structure, and 29 of the hydrogens were located by a difference synthesis after partial refinement. The remaining hydrogens were included at calculated positions, and block-diagonal least-squares refinement with anisotropic nonhydrogen atoms and isotropic hydrogens has converged to a standard residual of 0.058 for the observed reflections. Additional crystallographic details can be found in the supplementary material.

0022-3263/83/1948-1141$01.50/0