(calcd for $C_{15}H_{20}O_4$ m/e 264.1361).

Mexicanin I (12). A suspension of freshly prepared manganese dioxide (90 mg) and 9 mg (0.0378 mmol) of α-methylene lactone **30** in a solution of 2 mL of dry methylene chloride and 3 mL of benzene was stirred at room temperature for 30 min. The mixture was diluted with 20 mL of ether and filtered. The oxide cake was washed with ether (5 × 5 mL). The combined filtrate and washings were evaporated to dryness, and the residue was chromatographed on neutral silica gel (SilicAR CC-7). Elution with ether yielded 7 mg (78%) of crystalline mexicanin I: mp 244–247 °C; R_f 0.39 (ether); IR (KBr pellet) 3500, 2970, 2910, 2880, 2850, 1750, 1690, 1580, 1460, 1440, 1405, 1340, 1310, 1280, 1240, 1160, 1140, 1130, 1070, 1050, 1030, 1010, 985, 945, 890 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.66 (dd, 1 H, J = 6.1, 1.8 Hz), 6.41 (d, 1 H, J = 3.5 Hz), 6.16 (dd, 1 H, J = 6.1, 2.7 Hz), 5.67 (d, 1 H, J = 3.5 Hz), 4.81 (m, 1 H), 4.54 (dd, 1 H, J = 5.2, 2.7 Hz), 3.11 (m, 1 H), 2.68 (m, 1 H), 2.57 (m, 1 H), 2.42 (d, 1 H, J = 2.7 Hz), 2.22 (m, 1 H), 1.39 (m, 1 H), 1.25 (d, 3 H, J = 6.5 Hz), 1.24 (s, 3 H). Recrystallization from acetone–hexane provided analytically pure mexicanin I, mp 246–248 °C. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.50; H, 6.90.

Linifolin A (13). A solution of 5 mg (0.019 mmol) of mexicanin I, 0.5 mg of 4-(dimethylamino)pyridine, 0.5 mL of pyridine, and 0.1 mL of acetic anhydride was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure, leaving an oily residue which was chromatographed (ether elution) directly on neutral silica gel (SilicAR CC-7), providing 5 mg (86% yield) of crystalline linifolin A: mp 181–182 °C; R_f 0.42 (ether); IR ($CHCl_3$) 3020, 2950, 2870, 2850, 1765, 1755, 1710, 1585, 1460, 1400, 1380, 1320, 1290, 1250, 1160, 1150, 1130, 1060, 1015, 1000, 960, 930 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.59 (dd, 1 H, J = 6.0, 1.80 Hz), 6.29 (d, 1 H, J = 3.5 Hz), 6.12 (dd, 1 H, J = 6.0, 3.0 Hz), 5.96 (d, 1 H, J = 4.7 Hz), 5.70 (d, 1 H, J = 3.5 Hz), 4.81 (ddd, 1 H, J = 11.6, 9.2, 2.9 Hz), 3.26 (m, 1 H), 2.78 (dt, 1 H, J = 10.4, 2.2 Hz), 2.58 (ddd, 1 H, J = 13.3, 4.5, 2.9 Hz), 2.23 (m, 1 H), 2.08 (s, 3 H), 1.42 (m, 1 H), 1.26 (d, 3 H, J = 6.5 Hz), 1.23 (s, 3 H). Recrystallization from acetone–hexanes gave pure linifolin A, mp 182–182.5 °C. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.88; H, 6.60.

Acknowledgment. This investigation was supported by Public Health Service Research Grants CA 13689 and CA 28865 from the National Cancer Institute and the National Institutes of Health NMR Facility for Biomedical Studies (Grant RR-00292) located at Mellon Institute, Pittsburgh. We are indebted to Professors Werner Herz and T. J. Mabry for spectra of natural bigelovin. We are grateful to Professor Alfonso Romo de Vivar for a generous sample of linifolin A.

Methods for the Stereoselective Cis Cyanohydroxylation and Carboxyhydroxylation of Olefins

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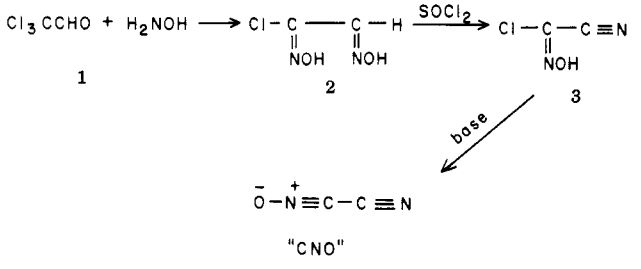
Two valuable reagents for the cis-specific vicinal cyanohydroxylation and carboxyhydroxylation of olefins are described. The cyanohydroxylation process is based on the decarboxylative ring opening of 3-carboxyisoxazolines prepared by the [3 + 2] cycloaddition reaction of carbethoxyformonitrile oxide with various alkenes. Fragmentation of the isoxazolines prepared from *cis*- and *trans*-2-butene has been found to occur without any crossover in stereochemistry. The carboxyhydroxylation process begins with the dipolar cycloaddition reaction of the nitrile oxide derived from the tetrahydropyranyl ether derivative of 2-nitroethanol. Deprotection, hydrogenation, and oxidative cleavage of the derived dihydroxy ketone yield the stereochemically pure β-hydroxy carboxylic acid.

In pursuit of new strategies for the stereospecific vicinal functionalization of alkenes, we have been inspired to investigate two old, yet relatively unappreciated reagents, carbethoxyformonitrile oxide (CEFNO)[1] and cyanogen *N*-oxide (CNO).[2] Since available literature evidence indicates that these reagents can be used to effect the vicinal cyanohydroxylation of olefins through decarboxylative ring opening,[3] such reactive dipoles might ideally serve to assemble useful part structures for natural product synthesis. Eventually one would want to be able to develop chiral variants of these or related products so that they could be used to prepare β-hydroxy nitriles in optically pure form. Additionally, one could hope to achieve the diastereoselective assembly of part structures through the cycloaddition of the achiral dipoles to optically pure alkenes.

Thus, in order to eventually probe the chiral-selective assembly of small molecules through dipolar cycloaddition

Scheme I



reactions, we first established the scope of reactivity of CEFNO and CNO with a variety of variously substituted olefins and then ascertained the level of stereoselectivity associated with the decarboxylative ring-opening process. Additionally, one other dipole, that prepared from the tetrahydropyranyl derivative of 2-nitroethanol,[4] has been used as a reagent for bringing about the cis carboxyhydroxylation of olefins. In this ancillary study, the nitrogen–oxygen bond of the isoxazoline is first cleaved by hydrogenation, and then the dihydroxy ketone which is

(1) Panizzi, L. *Gazz. Chim. Ital.* **1939**, *69*, 322. Musante, C. *Ibid.* **1939**, *69*, 523. Vaughan, W. R.; Spencer, J. L. *J. Org. Chem.* **1960**, *25*, 1160. Drefahl, G.; Hörhold, H.-H. *Chem. Ber.* **1964**, *97*, 159. Stache, W.; Fritsch, W.; Ruschig, H. *Justus Liebigs Ann. Chem.* **1965**, *685*, 228.

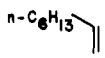
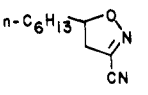
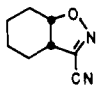
(2) Grundmann, C.; Frommeld, H.-O. *J. Org. Chem.* **1966**, *31*, 4235.

(3) Kalvoda, J.; Kaufmann, H. *J. Chem. Soc., Chem. Commun.* **1976**, 209. Kaufmann, H.; Kalvoda, J. *Ibid.* **1976**, 210.

(4) Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603.

0022-3263/83/1948-0366$01.50/0

Table I. Cycloadducts from CNO

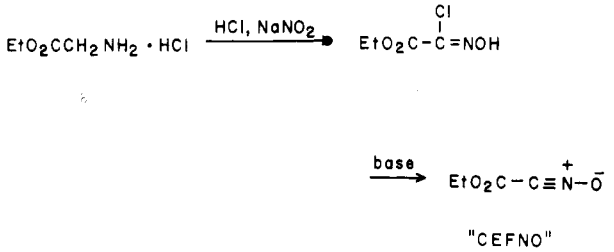
alkene	dipole/dipolarophile ratio	reaction temp, °C	product	yield, %
	1:3	0	 4	77
	1:3	−5	 5	62
	1:6	−5	 6	51
	1:3 1:30	−5	 7	37 56

unmasked is subjected to an oxidative cleavage process.[5]

Preparation and Reactions of CNO. Cyanogen *N*-oxide is conveniently generated from cyanoformhydroximic chloride (3) by base treatment[2] (Scheme I). The precursor to 3 is in turn prepared by the thionyl chloride promoted dehydration of chloroglyoxime (2) in ~50% yield,[6b] a compound synthesized readily from chloral hydrate (1) and hydroxylamine.[6a]

The dipolar cycloaddition reactions with CNO were examined with the four olefins displayed in Table I. The cyanoformhydroximic chloride and 3–30 equiv of the olefin were simply combined in ether and treated with 1 equiv of 0.1 N sodium carbonate added dropwise by syringe pump. While the formation of the 3-cyanoisoxazolines did take place in respectable yield, and these products could in turn be converted efficiently to their corresponding 3-carboxy-2-isoxazolines for use in the decarboxylative ring-opening studies (vide infra), the difficulty associated with procuring the chloral hydrate prompted us to investigate the chemistry of carbethoxyformonitrile oxide instead.[7]

Preparation and Reactions of CEFNO. The precursor of CEFNO is the nicely crystalline reagent ethyl chlorooximidoacetate (9). This chloro oxime is prepared



easily from glycine ethyl ester hydrochloride (8) by treatment with hydrochloric acid and sodium nitrite.[8] The original procedure of Skinner was followed strictly with but a slight modification in the isolation procedure (see Experimental Section). The yield of 9 is approximately 54%, and it can be stored on the shelf for months without noticeable decomposition.

Dipolar cycloaddition reactions with CEFNO were run by simply treating a mixture of ethyl chlorooximidoacetate and 1–40 equiv of the dipolarophile in diethyl ether dropwise with aqueous sodium carbonate or triethylamine in ether. The crude products isolated from these reactions were chromatographed on silica gel to furnish the adducts displayed in Table II. Due to the ready availability of chloro oxime 9, we were able to more easily examine the reactivity of CEFNO with a large number of alkenes. Since CEFNO generally gave higher yields of cycloadducts than did CNO and since its immediate precursor is more easily prepared, CEFNO is clearly the dipole of choice.

Perusal of Table II reveals several interesting facts. Even with cyclohexene, an 86% isolated yield of isoxazoline can be achieved if a 1:20 ratio of dipole to dipolarophile is employed. For comparison, we note that benzonitrile oxide has been reported to react with cyclohexene to deliver a 41% yield of the corresponding isoxazoline if a 1:18 ratio of dipole to dipolarophile is used.[9]

While a 70% yield of cycloadduct 19 was obtained from CEFNO and the trisubstituted olefin 1-methylcyclopentene, the tetrasubstituted olefin, 2,3-dimethyl-2-butene, reacted poorly even at high olefin concentrations to furnish at best a 7% isolated yield of cycloadduct 20.

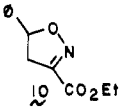
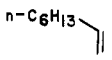
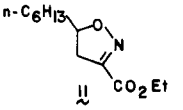
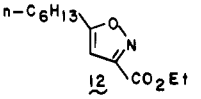
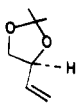
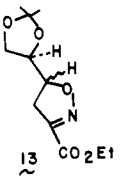
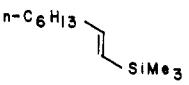
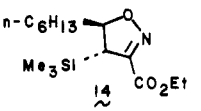
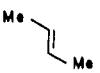
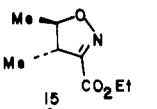
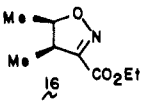
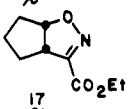
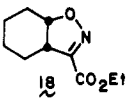
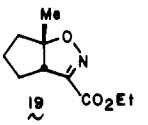
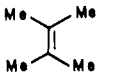
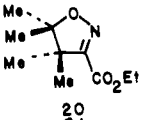
In regard to regiochemical issues, it is interesting to note here that although vinyltrimethylsilane has been reported to react with acetonitrile oxide to afford the expected 5-substituted isoxazoline,[10] (1-octenyl)trimethylsilane reacted so as to give the 5-*n*-hexyl-4-(trimethylsilyl)isoxazoline 14 exclusively. Thus in this case an alkyl group is shown to be a more powerful director of regiochemistry than the trimethylsilyl group.

With the optically active isopropylidene derivative of 3-butene-1,2-diol, diastereoface selection was observed for the intermolecular cycloaddition process. Chemical correlation studies are now in progress to identify the major product 13 (ratio = 80:20) of the reaction.[11] At this time we do call attention to the fact that such diastereoselection is not unexpected, especially in light of the theoretical calculations of Houk regarding this operation of the antiperiplanar effect in the addition of electrophiles to olefins,[12] a phenomenon which, of course, bears close similarities to Anh's work on the addition of nucleophiles to α-alkoxy ketones.[13] A related type of diastereoface selectivity has been observed by Kishi in the hydroboration of olefins possessing an allylic asymmetric center.[14]

Decarboxylative Ring-Opening Reactions. Huisgen had shown previously that triethylamine treatment of the isoxazoline 21 affords quantitatively methyl 3-cyano-2-hydroxypropionate (22)[15] (Scheme II). This reaction proceeds through removal of the C-3 proton followed by N–O bond heterolysis to deliver the hydroxy nitrile. Additionally, in a few steroidal systems, the isoxazoline-3-carboxylic acids have been pyrolyzed to the corresponding β-hydroxy nitriles.[16] Depending on the nature of the

(5) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
(6) (a) Hantzsch, A. *Chem. Ber.* **1892**, *25*, 705. (b) Kaufmann, H.; Houben, J. *Ibid.* **1913**, *46*, 2821.
(7) Chloral hydrate is a DEA schedule No. IV controlled substance.
(8) Skinner, G. S. *J. Am. Chem. Soc.* **1924**, *46*, 731.
(9) Zinner, G.; Günther, H. *Chem. Ber.* **1965**, *98* 1353.
(10) Cunico, R. F. *J. Organomet. Chem.* **1981**, *212*, C51.
(11) Ghosh, A., work in progress.
(12) Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. For a related observation in a Diels–Alder reaction, see: Franck, R. W.; John, T. V.; Olejniczak, K; Blount, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 1106.
(13) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(14) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259.
(15) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291.

Table II. Cycloadducts from CEFNO

alkene	dipole/dipolarophile ratio	reaction temp,[a] °C	product	yield, %
	1:1.2 1:8	rt rt	 10	80 89
	1:2	rt	 11	92
	1:1.5	rt	 12	90
	2:1	rt	 13	71
	1:1	rt	 14	70
	1:5	−6 to +3	 15	71
	1:5	−6 to +3	 16	68
	1:8	rt	 17	78
	1:20	rt	 18	86
	1:10	rt	 19	70
	1:40	35	 20	7

[a] rt = room temperature.

decarboxylation conditions, it is also possible to observe rupture of the 4,5-bond of a presumed isoxazoline carbanion (24) through a synchronous [$_{\sigma}2_{a} + {}_{\sigma}2_{a} + {}_{\omega}2_{s}$] fragmentation process.[3]

Mindful of this background information, we set about to examine the decarboxylative ring-opening reactions of the isoxazolines we had prepared, information which had to be garnered in order to better gauge the value of this [3 + 2] approach to the β-hydroxy nitrile synthesis.

The isoxazoline esters were thus saponified with 10% sodium hydroxide, and the free acids obtained on acidification were extracted with ethyl acetate and carefully dried. The 3-cyanoisoxazolines from Table I could be converted by base hydrolysis to the same carboxylic acid products.

The decarboxylation experiments were run by simply heating the acids without solvent at a temperature 5–10 °C above their melting point. Heating was continued until the evolution of carbon dioxide was no longer apparent. The crude reaction products were chromatographed on silica gel to give the β-hydroxy nitriles listed in Table III. In all cases, it was generally impossible to control the reaction so that the β-hydroxy nitrile was obtained completely free of the corresponding aldehyde (or ketone). The carbonyl side product could, however, be conveniently removed by extraction with sodium bisulfite. Apparently then, it is difficult to avoid the aforementioned synchro-

(16) Moersch, G. W.; Wittle, E. L.; Neuklis, W. A. *J. Org. Chem.* **1967**, *32*, 1387 and ref 3.

Scheme II

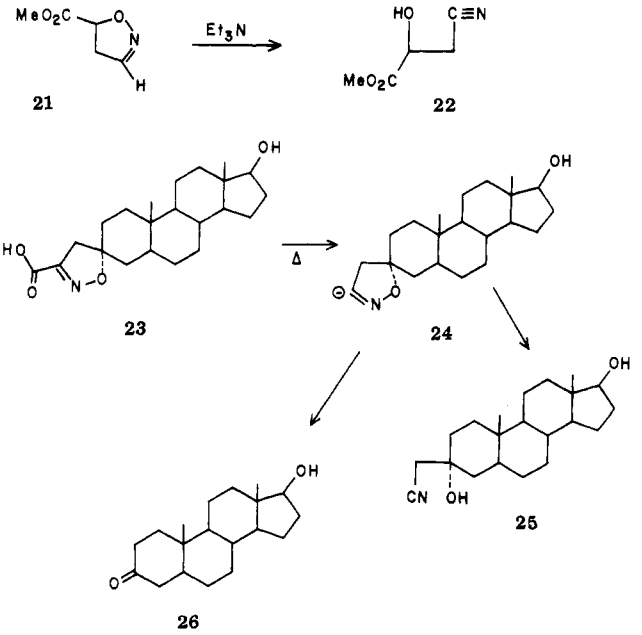
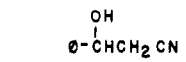
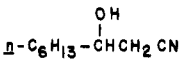
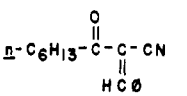
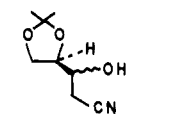
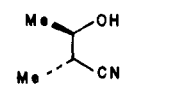
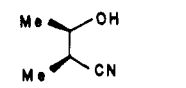
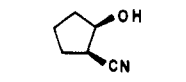
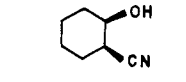
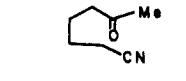
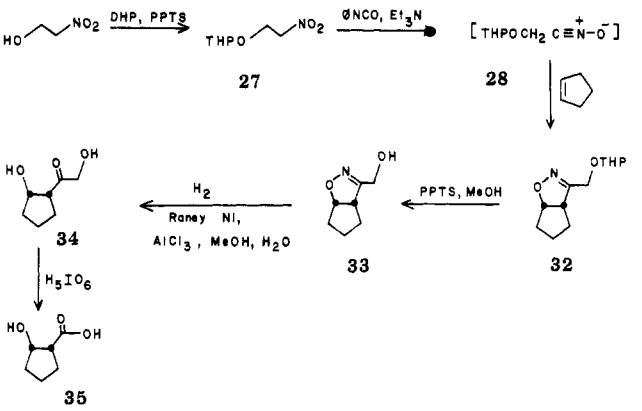


Table III. Decarboxylative Ring Opening of the CEFNO-Derived Isoxazolines

3-carboethoxyisoxazoline from which the acid was derived	product	yield, %
10		90
11		80
12		84
13		75
15		90
16		91
17		71
18		70
19		82

nous fragmentation involving rupture of the 4,5-bond regardless of the degree of olefin substitution. Pyrolysis of the isoxazoline acid prepared from 1-methyl-1-cyclopentene gave only the ring-opened keto nitrile. *None* of the β-hydroxy nitrile was isolated in this case. This latter

Scheme III



reaction does constitute a rather intriguing "nonoxidative" method for cleaving a carbon–carbon double bond with introduction of a single functionalized carbon atom.

The isoxazole acid **12** could also be pyrolyzed to obtain through decarboxylative ring opening an unstable β-keto nitrile. Since this product was very prone to polymerization, the pyrolysis was best carried out in the presence of benzaldehyde in order to intercept the β-keto nitrile as its benzylidene derivative.[17]

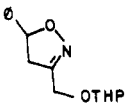
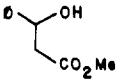
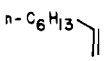
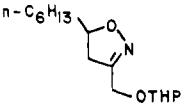
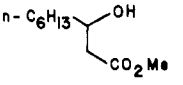
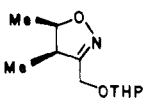
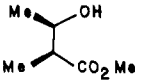
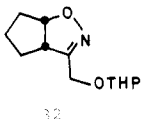
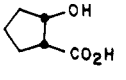
Most pertinent to the development of a stereoselective [3 + 2] approach to β-hydroxy nitriles (or acids) was the finding that pyrolysis of the isoxazoline acids prepared from *trans*- and *cis*-2-butene (**15** and **16**) occurred without any crossover in stereochemistry. Decarboxylative ring opening thus takes place without epimerization of the nitrile-bearing carbon. In these two cases it was interesting to observe that the amount of aldehyde byproduct formed was negligible.

Cis Carboxyhydroxylation. In further study of such methodology for olefin functionalization, we realized that the commercially available reagent 2-nitroethanol could provide a related (lower oxidation level) type of nitrile oxide which should be capable of functioning in a very similar fashion to CEFNO. The hydroxyl group of the 2-nitroethanol was thus protected as its tetrahydropyranyl ether,[4] and **27** was then reacted with phenyl isocyanate/triethylamine in the presence of several different olefins (Scheme III). Cycloaddition occurred in high yield to give the expected cycloadducts (Table IV). After removal of the THP group, the isoxazoline was subjected to hydrogenolysis by using a brew of Raney nickel, aluminum chloride, methanol, and water.[18] In the case of **33**, the dihydroxy ketone which resulted proved to be a single (cis) stereoisomer. Contrastingly, the hydrogenation of related compounds over Raney nickel in the presence of acetic acid has been found to give mixtures of both the cis and trans isomers. On subjection of **34** to aqueous periodic acid for 30 min at room temperature the β-hydroxy carboxylic acid **35** was formed in quantitative yield.

(17) Cusmano, S.; Giambrone, S. *Gazz. Chim. Ital.* **1950**, *80*, 702. Even on prolonged storage at room temperature, the 3-carboxyisoxazolines were found to undergo decomposition to β-hydroxy nitrile and aldehyde (or ketone).

(18) A full report on the hydrogenolysis reactions of isoxazolines as well as alternate ways to effect their conversion to β-hydroxy ketones is in preparation: Adamczyk, M., unpublished results. After preparation of this paper, it was discovered that subjection of the 3-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]isoxazolines to our Raney nickel/$AlCl_3$ reduction conditions resulted in both THP cleavage and N–O bond rupture to yield the dihydroxy ketones directly in high yield. It is also of interest to note that if a Wittig reaction is carried out on these dihydroxy ketones, the unsaturated diols so generated could be used to prepare α-methylene γ-lactones. See, for example: Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267.

Table IV. Cis Carboxyhydroxylation

alkene	isoxazoline	yield, %	β-hydroxy acid or ester	yield, %[a]
	 29	95		83
	 30	82		86
	 31	72		98
	 32	79		84

[a] Overall yield from the 3-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]isoxazoline.

The overall scheme thus defines a unique nonaldol route to β-hydroxy carboxylic acids. By protection of the hydroxyl group of 2-nitroethanol as its silyl ether, it should in fact be possible to further abbreviate the sequence, since α-trimethylsilyloxy ketones have been cleaved directly to β-hydroxy acids. We further note here that since it is possible to prepare optically active 2-nitroethanol derivatives possessing an asymmetric center β to the nitro group, the nitrile oxides derived from such reagents may be useful in preparing optically active β-hydroxy carboxylic acids.

Conclusions

We have described now two valuable reagents for the cis cyanohydroxylation[19] and cis carboxyhydroxylation of olefins. The first process is based upon the decarboxylative ring opening of 3-carboxyisoxazolines prepared from the dipolar cycloaddition of carbethoxyformonitrile oxide and an appropriate alkene. The latter process utilizes the nitrile oxide derived from a protected 2-nitroethanol derivative and requires a hydrogenation/oxidative cleavage sequence to transform the isoxazoline nucleus. The two procedures do thus differ significantly in the nature of the reaction conditions which a starting unsaturated molecule must survive from start to finish.

Further studies are not in progress to assess the possibility of achieving a chiral-selective synthesis of β-hydroxy acids through the use of optically active variants of **28**.

Experimental Section

Melting points were determined by a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 700 spectrophotometer with the polystyrene absorption at 1601 cm^{-1} as a reference. ^1H NMR spectra were recorded on a Varian EM-360, Varian EM-390, or Bruker WH-300 spectrometer with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained on an LKB 9000A gas chromatograph–mass spectrometer. Gravity column chromatography was performed on Merck Kieselgel 60 (70–230 mesh ASTM). Thin-layer chromatography was performed on Brinkmann MN Polygram 0.25-mm silica gel plastic plates with G/UV_{254} inorganic phosphar fluorescent indicator. TLC detection includes the use of I_2 vapor, 254 nm UV light and a 3% solution of vanillin in sulfuric acid/ethanol.

Chloroglyoxime [(Hydroxyimino)acetohydroximoyl Chloride, 2]. To a solution of 20.82 g (0.3 mol) of hydroxylamine hydrochloride in 50 mL of water was added sequentially 15.9 g (0.15 mol) of sodium bicarbonate in 100 mL of water and then dropwise with stirring 14.7 g (0.1 mol) of chloral. After 4 h, the reaction mixture was concentrated to half its original volume by rotary evaporation. A solution of 16 g (0.4 mol) of sodium hydroxide in 75 mL of water was added to the concentrate at 0 °C. After 5 min, this cold mixture was brought to a pH of about 3 with 25% sulfuric acid and was extracted with ethyl ether. The ethereal extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. The solid residue was chromatographed by using ethyl ether–hexanes to yield 6.8 g (56%) of **2**: mp 150 °C dec [lit.[6a] mp 150 °C (gas evolution)]; IR (Nujol) 3500–3100, 1710 (weak) cm^{-1}; mass spectrum (70 eV), *m/e* 122 (M^+).

Cyanoformhydroximoyl Chloride (3). To a solution of 3 g (24.5 mmol) of dry chloroglyoxime in 20 mL of anhydrous ether under a nitrogen atmosphere was added with stirring 7.5 mL of freshly distilled thionyl chloride (exothermic reaction). After 45 min the ethyl ether and excess thionyl chloride were removed by distillation. The residue was distilled under vacuum, and the fraction boiling at 71–73 °C (14 mm) was collected. The solid distillate was further purified by recrystallization from hexanes to yield 1.37 g (50%) of **3**: mp 56–57 °C (lit.[6b] mp 55–56 °C). The cyanoformhydroximoyl chloride was stored as an ether solution and used as such in further reactions.

General Procedure for the Preparation of 3-Cyanoisoxazolines from 3. To a vigorously stirred solution of 0.45 g (3.68 mmol) of cyanoformhydroximoyl chloride and 3–30 equiv of freshly distilled dipolarophile in 7 mL of ethyl ether was added by syringe pump over a 30-min period 1 equiv of a 1 N aqueous sodium carbonate solution. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel with ethyl acetate–hexanes to give the pure isoxazoline.

General Procedure for the Preparation of 3-Carboxyisoxazolines from 3-Cyanoisoxazolines. The cyanoisoxazoline (1 mmol) was refluxed in 4 mL of 20% aqueous sodium hydroxide for 30 min. Water (10 mL) and ethanol (10 mL) were then added, and refluxing was continued for an additional 1–2 h. The reaction mixture was concentrated to half its original volume by rotary evaporation, and the concentrate was cooled to 0 °C and acidified with 10% HCl. The resulting solution was saturated with sodium

(19) For another [3 + 2]-based approach for the syn cyanohydroxylation of olefins, see: Wade, P. A.; Hinney, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1319. Wade, P. A.; Pillay, M. K. *J. Org. Chem.* **1981**, *46*, 5425.

chloride and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated. The crude isolated acid could be used as such in the decarboxylation experiments. An analytical sample was prepared by dissolving the acid in benzene and precipitating it with hexanes.

Ethyl Chlorooximidoacetate (9). Glycine ester hydrochloride (69.7 g, 0.5 mol) was dissolved in 95 mL of water, and 41.5 mL of hydrochloric acid (d = 1.19) was added. The mixture was cooled to −5 °C, and a solution of 1 equiv of sodium nitrite in 50 mL of water was added dropwise. A second equivalent of hydrochloric acid and a second equivalent of sodium nitrite were then added in the same manner. The reaction mixture was extracted with ethyl ether, and the extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. The crude product was crystallized from hexanes to yield 41 g (54%) of **9**: mp 80 °C (lit.[8] mp 80 °C); IR (Nujol) 3500–3050, 1745, 1705, 1605 cm^{-1}; NMR ($CDCl_3$) δ 9.80–10.30 (br s, 1 H), 4.35 (q, 2 H, J = 7 Hz), 1.38 (t, 3 H, J = 7 Hz); mass spectrum (70 eV), m/e 151 (M^+).

General Procedure for the Preparation of 3-Carbethoxyisoxazolines from 9: To a vigorously stirred solution of 11.6 g (0.076 mol) of ethyl chlorooximidoacetate and 1–40 equiv of the freshly distilled dipolarophile in 170 mL of ether was added by syringe pump over a 5-h period either sodium carbonate (8.06 g, 0.076 mol) in 100 mL of water or triethylamine (10.6 mL, 0.076 mol) in 100 mL of ethyl ether. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel with ethyl acetate–hexanes to give the pure isoxazoline.

General Procedure for the Preparation of 3-Carboxyisoxazolines from 3-Carbethoxyisoxazolines. The 3-carbethoxyisoxazoline (10 mmol) in 20 mL of 10% sodium hydroxide was stirred for 1 h to give a clear solution (in some cases the addition of a few milliliters of ethyl alcohol was necessary). Stirring was continued until TLC analysis revealed the absence of starting material. The reaction mixture was cooled to 0 °C, acidified to a pH of 3 with 10% HCl, saturated with sodium chloride, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated to afford the 3-carboxyisoxazoline of a purity satisfactory for the decarboxylation step. An analytical sample was prepared by crystallization from benzene.

Thermal Decomposition of 3-Carboxyisoxazolines to β-Hydroxy Nitriles. The isoxazoline acid prepared as described above was heated without solvent at a temperature 5–10 °C above its melting point until the evolution of carbon dioxide ceased (~5–15 min). The crude product was chromatographed on silica gel with 20% ethyl acetate–hexanes. In cases where chromatography failed to remove the aldehyde side product, further purification was effected by stirring the aldehyde/nitrile mixture with a concentrated solution of sodium bisulfite overnight. This solution was then extracted with ethyl acetate, and the extracts were dried ($MgSO_4$) and concentrated to give the pure nitrile.

Thermal Decomposition of 5-*n*-Hexylisoxazole-3-carboxylic Acid in the Presence of Benzaldehyde. A mixture of the acid (197 mg, 1 mmol) prepared from ester **12** and benzaldehyde (424 mg, 4 mmol) was heated in a flask equipped with reflux condenser at 140 °C until carbon dioxide evolution ceased (10–15 min). The temperature was then raised to 175 °C for 5 min. The benzaldehyde was removed in vacuo, and the crude product was crystallized from 70% ethanol to afford 200 mg (84%) of the benzylidene derivative: mp 63–64 °C; IR (Nujol) 2252, 1700, 1595 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 8.20 (s, 1 H) 7.35–8.15 (m, 5 H), 2.91 (t, 2 H, J = 7 Hz), 0.75–2.05 (m, 11 H); mass spectrum (70 eV), m/e 241.

Preparation of the Tetrahydropyranyl Ether of 2-Nitroethanol. A solution of 2-nitroethanol (3 g, 21 mmol), dihydropyran (2.52 g, 30 mmol), and pyridinium p-toluenesulfonate (502 mg, 2 mmol) in 10 mL of dry methylene chloride was stirred at room temperature until the 2-nitroethanol was consumed (~25 h). The reaction mixture was diluted with 20 mL of ethyl ether and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel with 20% ethyl acetate–hexanes to yield 5.47 g (95%) of **27**: IR (thin film) 1550, 1380 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 4.48–4.85 (m, 3 H), 3.42–4.42 (m, 4 H), 1.20–1.90 (m, 6 H); mass spectrum (70 eV), m/e 175.

General Procedure for the Preparation of 3-[[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl]isoxazolines from 27. To a solution of 1.039 g (5.94 mmol) of **27** and the alkene (6 mmol) in 60 mL of dry benzene were added 1.41 g (11.88 mmol) of phenyl isocyanate and 3 drops of triethylamine. The reaction mixture was stired at room temperature until the nitro compound was consumed (8–48 h). The precipitate of diphenylurea was removed by filtration, the filtrate was diluted with 10 mL of water, and the mixture was stirred vigorously for 2 h. The mixture was filtered, and the organic layer was separated, dried ($MgSO_4$), and concentrated. The crude isoxazoline was purified by chromatography on silica gel with 25% ethyl acetate–hexanes as the eluent.

Preparation of the 3-(Hydroxymethyl)isoxazolines. A solution of the preceding tetrahydropyranyl ether derivative (3 mmol) and pyridinium p-toluenesulfonate (75.4 mg, 0.3 mmol) in 25 mL of dry methanol was stirred at 55 °C until deprotection was complete (~20 h). The reaction mixture was concentrated by rotary evaporation, and the residue was chromatographed on silica gel with 40% ethyl acetate–hexanes as the eluent to afford the title compound.

Hydrogenolysis of the 3-(Hydroxymethyl)isoxazolines. To the 3-(hydroxymethyl)isoxazoline (0.39 mmol) in 10 mL of a 5:1 methanol–water mixture was added aluminum chloride (208 mg, 1.56 mmol) and W-2 Raney nickel (1 mg). The reaction mixture was stirred under a hydrogen-filled balloon until TLC analysis revealed the absence of starting material (30 min to 4 h). The mixture was then filtered through Celite, and concentrated by rotary evaporation to a volume of approximately 1 mL. A saturated solution of sodium chloride was added, and the product was extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. The crude isolated product was chromatographed on silica gel with 50% ethyl acetate–hexanes as the eluent to provide the pure dihydroxy ketone.

Oxidative Cleavage of the Dihydroxy Ketones. A solution of the dihydroxy ketone (0.33 mmol) in 6 mL of methanol was treated with 3.8 mL of a 0.54 M solution of periodic acid in water. After 30 min, the reaction mixture was concentrated by rotary evaporation, and the residue was extracted with ethyl acetate (3×). The combined extracts were dried and concentrated to provide the β-hydroxy acid. The acid was converted to its methyl ester by treatment with diazomethane in ether. The methyl ester was further purified by chromatography on silica gel with 50% ethyl acetate–hexanes as the eluent.

***cis*-3a,5,6,6a-Tetrahydro-4*H*-cyclopent[*d*]isoxazole-3-carbonitrile (6)**: IR (thin film) 2260, 1560 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 4.63–5.03 (m, 1 H), 3.10–3.56 (m, 1 H), 0.96–2.06 (m, 6 H); mass spectrum (70 eV), m/e 136; exact mass calcd for $C_7H_8N_2O$ 136.0637, found 136.0637.

Ethyl *cis*-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazole-3-carboxylate (17): IR (thin film) 1720, 1585, 1270 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 5.05–5.51 (m, 1 H), 4.30 (q, 2 H, J = 7 Hz), 3.61–4.05 (m, 1 H), 1.31 (t, 3 H, J = 7 Hz), 0.98–2.35 (m, 6 H); mass spectrum (70 eV), m/e 183, 110; exact mass calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0896.

***cis*-3a,5,6,6a-Tetrahydro-4*H*-cyclopent[*d*]isoxazole-3-carboxylic acid**: mp 92–94 °C; IR (Nujol) 3300–2200, 1705, 1585 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 10.53–10.58 (br s, 1 H), 5.16–5.53 (m, 1 H), 3.63–4.06 (m, 1 H), 1.30–2.43 (m, 6 H); mass spectrum (70 eV) m/e 155; exact mass calcd for $C_7H_9NO_3$ 155.0582, found 155.0582.

***cis*-2-Hydroxycyclopentanecarbonitrile**: IR (thin film) 3650–3100, 2260 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 4.26–4.60 (m, 1 H), 3.16 (br s, 1 H, exchanges with D_2O), 2.78 (dt, 1 H, J = 7, 4.5 Hz), 1.36–2.23 (m, 6 H); mass spectrum (70 eV), m/e 112, 111; exact mass calcd for $C_6H_8N(C_6H_9NO–OH)$ 94.065 67, found: 94.065 40.

***cis*-3a,5,6,6a-Tetrahydro-3-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]-4*H*-cyclopent[*d*]isoxazole (32)**: IR (thin film) 3000–2700, 1715 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 4.86–5.20 (m, 1 H), 4.50–4.70 (m, 1 H), 4.23–4.43 (m, 2 H), 3.33–3.93 (m, 3 H), 1.23–2.20 (m, 12 H); mass spectrum (70 eV), m/e 180, 166, 141 (no parent ion).

***cis*-3a,5,6,6a-Tetrahydro-3-(hydroxymethyl)-4*H*-cyclopent[*d*]isoxazole (33)**: IR (thin film) 3600–3050, 3050–2800, 1700 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 5.00–5.28 (m, 1 H), 4.65–4.23

(m, 2 H), 3.55–3.98 (m, 1 H), 3.03 (br s, 1 H), 1.15–2.25 (m, 6 H); mass spectrum (70 eV), m/e 141; exact mass calcd for $C_7H_{11}NO_2$ 141.0790, found 141.0790.

***cis*-2-(Hydroxyacetyl)cyclopentanol (34)**: mp 62–64 °C; IR (Nujol) 3600–3050, 1710 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 4.50–4.60 (m, 1 H), 4.35 (AB q, 2 H, J = 19 Hz), 3.12 (br s, 1 H), 2.82 (dt, 1 H, J = 9.5, 4.85 Hz), 2.51 (br s, 1 H), 1.60–2.15 (m, 6 H); mass spectrum (70 eV), m/e 144, 126; exact mass calcd for $C_7H_{10}O_2$ ($C_7H_{12}O_3 - H_2O$) 126.0681, found 126.0681.

***cis*-2-Hydroxycyclopentanecarboxylic acid (35)**: mp 53 °C (lit.[20] mp 52–53.4 °C); IR (melt) 3600–2400, 1720 cm^{-1}; NMR ($CDCl_3/D_2O$, 90 MHz) δ 4.33–4.63 (m, 1 H), 2.60–3.00 (m, 1 H), 1.60–2.15 (m, 6 H); mass spectrum (70 eV), m/e 130, 112; exact mass calcd for $C_6H_8O_2$ ($C_6H_{10}O_3 - H_2O$) 112.0524, found 112.0524.

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Registry No. 1, 75-87-6; 2, 4732-58-5; 3, 4474-18-4; 4, 14442-22-9; 5, 83967-79-7; 6, 83967-80-0; 7, 83967-81-1; 8, 623-33-6; 9, 14337-43-0; 10, 7064-04-2; 10 acid, 10313-27-6; 11, 83967-82-2; 11 acid, 83967-83-3; 12, 83967-84-4; 12 acid, 83967-85-5; 13, 83967-86-6; 13 acid, 83967-87-7; 14, 83967-88-8; 15, 83967-89-9; 15 acid, 83967-90-2; 16, 83967-91-3; 16 acid, 83967-92-4; 17, 52482-08-3; 17 acid, 52482-09-4; 18, 83967-93-5; 18 acid, 83967-94-6; 19, 83967-95-7; 19 acid, 83967-96-8; 20, 83967-97-9; 27, 75233-61-3; 28, 77790-67-1; 29, 83967-98-0; 30, 83967-99-1; 31, 83968-00-7; 32, 83968-01-8; 33, 83670-84-2; 34, 83670-88-6; 35, 17502-28-2; CNO, 14442-19-4; CEFNO, 51983-62-1; hydroxylamine hydrochloride, 5470-11-1; styrene, 100-42-5; 1-octene, 111-66-0; cyclopentene, 142-29-0; cyclohexene, 110-83-8; 1-octyne, 629-05-0; 2,2-dimethyl-4-vinyl-1,3-dioxolane, 83968-02-9; (*E*)-1-(trimethylsilyl)-1-octene, 57365-47-6; (*E*)-2-butene, 624-64-6; (*Z*)-2-butene, 590-18-1; 1-methylcyclopentene, 693-89-0; 2,3-dimethyl-2-butene, 563-79-1; 3-hydroxy-3-phenylpropionitrile, 17190-29-3; 3-hydroxynonanenitrile, 30683-75-1; 2-benzylidene-3-oxononanenitrile, 83968-03-0; 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxypropionitrile, 83679-29-2; *erythro*-2-methyl-3-hydroxybutyronitrile, 83968-04-1; *threo*-2-methyl-3-hydroxybutyronitrile, 83968-05-2; *cis*-2-hydroxycyclopentanecarbonitrile, 70367-34-9; *cis*-2-hydroxycyclohexanecarbonitrile, 70367-35-0; 6-oxoheptanenitrile, 18458-15-6; 2-nitroethanol, 625-48-9; phenyl isocyanate, 103-71-9; methyl 3-hydroxy-3-phenylpropionate, 7497-61-2; methyl 3-hydroxynonanoate, 83968-06-3; methyl *erythro*-3-hydroxy-2-methylbutanoate, 39788-58-4.

(20) Pascual, J.; Castells, J. *J. Am. Chem. Soc.* **1952**, *74*, 2899.

Adducts of Anthrahydroquinone and Anthranol with Lignin Model Quinone Methides. 2. Dehydration Derivatives. Proof of Threo Configuration

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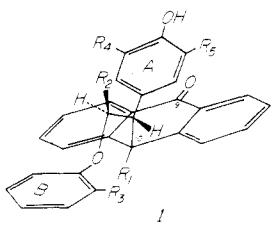
NMR studies of novel dehydration derivatives of anthrahydroquinone (AHQ)–lignin and anthranol–lignin model quinone methide adducts have confirmed the sole diastereomeric form of the adducts as "threo". Upon dehydration of the AHQ adduct 1-(3,4-dimethoxyphenyl)-1-(10-hydroxy-9-oxoanthracen-10-yl)-2-(2-methoxyphenoxy)propane with polyphosphoric acid, the spiro compound 3′-(3,4-dimethoxyphenyl)-2′,3′-dihydro-8′-methoxy-2′-methylspiro[anthracene-9(10*H*),4′-[4*H*-1]benzopyran]-10-one (**3b**) was obtained. Reduction of the anthranol adduct 1-(3-methoxy-4-hydroxyphenyl)-1-(9-oxoanthracen-10-yl)-2-(2-methoxyphenoxy)propane with $LiAlH_4$, followed by dehydration with BF_3·Et_2O gave the bicyclic compound 10,11-dihydro-2,3-dimethoxy-11-[1-(2-methoxyphenoxy)ethyl]-5,10-*o*-benzeno-5*H*-dibenzo[*a*,*d*]cycloheptene (**7d**). Coupling constants of the aliphatic protons in **3b** and **7d** are consistent only with the threo form. Therefore, by analogy, all other reported AHQ and anthranol adducts with asymmetry of Cα and Cβ are assigned the threo configuration.

A previous paper[1] describes the synthesis and characterization of adducts **1** formed by reaction of anthrahydroquinone (AHQ) or anthranol with lignin model quinone methides. Adducts of this type were postulated to be important intermediates in the catalytic delignification of wood. In the compounds where $R^2 \neq H$, both diastereomers are possible, although only one isomer has been found. Our tentative assignment of "threo"[1] is now confirmed by NMR studies of dehydration derivatives of **1** as reported here.



1

Synthesis of Derivatives

Dehydration reactions were performed with the methylated derivatives **2** (Scheme I) by utilizing either polyphosphoric acid (PPA) or boron trifloride etherate (BF_3·Et_2O). Dehydration of **2a** afforded an almost quantitative yield of the spiro product **3a**, presumably by an electrophilic attack of a transient benzylic carbonium ion at C-10 on ring B. Corresponding dehydration of **2b** (R_2 = CH_3) to **3b** was significantly less efficient (38%) perhaps

[†] Maintained at Madison, WI, in cooperation with the University of Wisconsin.

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