= 10, 11.1 Hz, CH_2Se), 4.61 (s, 1 H, =CH), 4.76 (s, 1 H, =CH), 7.20 (m, 3 H, ArH), 7.42 (m, 2 H, ArH).

(1*S*,3*S*,4*R*)- and (1*R*,3*R*,4*S*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-ethenylcyclohexanemethanol (1, Elemol). According to the method of Krief,[16] a mixture of 548 mg (1.31 mmol) of selenide **9a**, 1.01 g of basic alumina, and 0.6 mL of 90% *tert*-butyl hydroperoxide in 10 mL of THF was heated under nitrogen at 60 °C for 6.5 h. After gravity filtration, the solids were washed with ethyl acetate (50 mL) and the combined organic solutions concentrated to afford an oil that was purified by flash chromatography on silica gel to give 156 mg (53.7%) of a clear homogeneous oil. Analysis of this oil by TLC, GC, IR, and ^1H NMR (80 and 250 MHz) showed it to be identical spectroscopically to a sample of authentic elemol:[17] $[\alpha]_D$ ($CHCl_3$) 1.4–1.8°; ^1H NMR (250 MHz) δ 0.98 (s, 3 H, CH_3), 1.20 (s, 6 H, 2 CH_3), 1.2–1.7 (br d, 7 H), 1.71 (d, J = 0.7 Hz, 3 H, =CCH_3), 1.96 (dd, J = 8.5, 3.3 Hz, 1 H, =CCH), 4.58 (d, J = 0.7 Hz, 1 H, =CH), 4.82 (br s, 1 H, =CH), 4.87 (dd, J = 10.7, 1.6 Hz, 1 H, =CH), 4.88 (dd, J = 17.6, 1.6 Hz, 1 H, =CH), 5.80 (dd, J = 17.6, 10.7 Hz, 1 H, =CH); IR (film) 3085, 1638, 907, 890 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 80.88; H, 11.49.

(1*S*,3*R*,4*S*)- and (1*R*,3*S*,4*R*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-[2-(*p*-tolylsulfonoxy)ethyl]cyclohexanemethanol (8b). To a cooled solution (0 °C) of 0.54 g (2.2 mmol) of minor diol **7b** in 10 mL of pyridine was added 0.88 g (4.6 mmol) of tosyl chloride. After 24 h at 0 °C the reaction mixture was pured onto 10 g of ice and the resulting material estracted with ether (3 × 20 mL). The organic layers were then washed with 10% HCl (3 × 50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated to give 0.55 g (61.6%) tosylate **8b** which was used without further purification: ^1H NMR δ 1.16 (s, 6 H, 2 CH_3), 1.2–1.8 (br d, 9 H), 1.67 (s, 3 H, =CCH_3), 1.87 (m, 1 H, =CCH), 2.45 (s, 3 H, $ArCH_3$), 4.07 (t, J = 8 Hz, 2 H, CH_2OTs), 4.56 (br s, 1 H, =CH), 4.84 (br s, 1 H, =CH), 7.57 (AB, J_{AB} = 9 Hz, Δν = 37.2 Hz, 4 H, ArH).

(1*S*,3*R*,4*S*)- and (1*R*,3*S*,4*R*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-[2-(phenylselenyl)ethyl]cyclohexanemethanol (9b). In an adaptation of the procedure of Sjoberg,[15] 314 mg (1.00 mmol) of diphenyl diselenide in 15 mL of ethanol was treated with $NaBH_4$ until the solution became colorless. The reaction mixture was cooled to 0 °C, and 207 mg (0.53 mmol) tosylate **8b** in 10 mL of THF was added and the reaction mixture stirred at room temperature for 18 h whereupon it was quenced with 10% Na_2CO_3 (50 mL), the ethanol removed under vacuum, and the aqueous residue extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brime (50 mL), dried (Na_2SO_4), and concentrated to give an oil, which was purified by flash chromatography on silica gel to afford 131 mg (59%) of selenide **9b** used directly in the next reaction: ^1H NMR δ 0.90 (s, 3 H, CH_3), 1.12 (s, 6 H, 2 CH_3), 1.70 (s, 3 H, =CCH_3), 1.0–2.0 (br d, 10 H), 2.79 (m, 2 H, CH_2SeAr), 4.61 (br s, 1 H, =CH), 4.85 (br s, 1 H, =CH), 7.24 (m, 3 H, Ar*H*), 7.47 (m, 2 H, Ar*H*).

(1*S*,3*R*,4*S*)- and (1*R*,3*S*,4*R*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-ethenylcyclohexanemethanol (11, Isoelemol). According to the method of Krieg,[16] a mixture of 131 mg (0.31 mmol) of selenide **9b**, 1.3 mL of 90% *tert*-butyl hydroperoxide, and 247 mg of basic alumina in 5 mL of THF was heated at 60 °C for 4 h. The rection mixture was filtered, the solids were washed with ethyl acetate (20 mL), and the combined organics were concentrated to give an oil that was purified by flash chromatography on silica gel to give 47 mg (67.9%) of diene **11** as white crystals: mp 70–72 °C; ^1H NMr (250 MHz) δ 1.02 (s, 3 H, CH_3), 1.20 (s, 6 H, 2 CH_3), 1.69 (br s, 3 H, =CCH_3), 1.2–1.9 (br d, 7 H), 1.97 (dd, J = 11.0, 3.1 Hz, 1 H, =CCH), 4.64 (br s, 1 H, =CH), 4.77 (br s, 1 H, =CH), 4.96 (dd, J = 17.6, 1.5 Hz, 1 H, =CH), 5.01 (dd, J = 11.3, 1.5 Hz, 1 H, =CH), 6.26 (dd, J = 17.6, 11.1 Hz, 1 H, =CH); IR CCl_4) 3450 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 80.95; H, 11.83.

Synthesis of 4-Hydroxy-*N*-[5-(hydroxymethyl)-3-isoxazolyl]-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide and [(5-Methyl-3-isoxazolyl)amino]oxoacetic Acid. Major Metabolites of Isoxicam

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4-Hydroxy-*N*-[5-(hydroxymethyl)-3-isoxazolyl]-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (**2**), the major oxidative human metabolite of isoxicam (**1**), and [(5-methyl-3-isoxazolyl)amino]oxoacetic acid (**3**), the major rat metabolite of isoxicam (**1**), were synthesized. **2** was synthesized by condensation of the known benzothiazine ester **8** with the isoxazolamine **9b**. **9b** was synthesized via a nine-step sequence starting with 5-methyl-3-isoxazolecarboxylic acid (**14**). NBS bromination of **14** gave 5-(bromomethyl)-3-isoxazolecarboxylic acid, which was converted to the carbamate ester via a Curtius rearrangement of the acid azide. Displacement of bromine with silver acetate gave the acetoxy compound **21**. Hydrolysis of **21** gave the unstable 3-isoxazolamine derivative **9a**, which was converted to the $OSiMe_3$ derivative **9b**. The compound **3** was synthesized by reaction of ethyl oxalyl chloride with 5-methyl-3-isoxazolamine followed by base hydrolysis.

Isoxicam[1] (Maxicam, **1**) is a new nonsteroidal antiinflammatory agent which has been shown to be a clinically effective antiarthritic drug.[2] Pharmacokinetic[3,4] and metabolism studies in animals and man indicate **1** to have a long plasma half-life and to be metabolized via hy-

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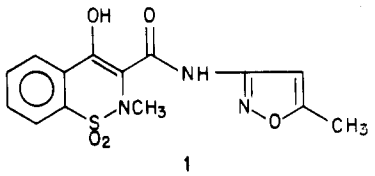
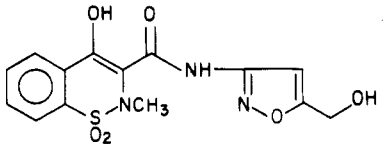


1



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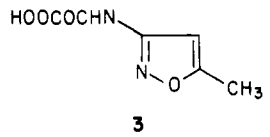
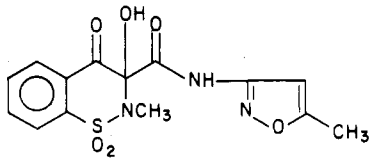


3

droxylation and oxidative cleavage of the drug. In humans,[3] the principal metabolite has been tentatively assigned the structure **2**, while both **2** and **3** are formed in the rat.[3] An alternate hydroxylated structure, **4**, was not considered on the basis of NMR data.[3]



4

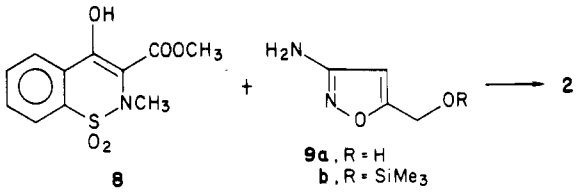
In order to confirm the structures of the metabolites, we undertook the synthesis of **2**, **3**, and **4**.

Initial attempts to directly brominate the active methine group of isoxicam (**1**) with bromine in acetic acid gave complex mixtures. Base-catalyzed (*n*-BuLi) bromination of the isoxicam C_3-methine group with NBS in THF followed by treatment with ammonium chloride solution gave **7** as the sole product. Formation of compound **7**, which is isomeric to the human metabolite **2**, probably resulted through a rearrangement of the 3-hydroxy compound **4** (Scheme I), which seems to be unstable under the reaction conditions.

The compound **7**, analyzed for $C_{14}H_{13}N_3O_6S$ (a gain of one oxygen atom over **1**), gave a negative ferric chloride test and had no UV absorption, indicating a loss of enolic character and conjugation. The compound **7** showed carbonyl bands at 1716, 1707, and 1618 cm^{-1} along with broad bands for OH and NH at 3460 and 3220 cm^{-1} unlike isoxicam (**1**). The NMR of compound **7** showed a *N*-methyl signal at 3.25 ppm similar to *N*-methylsaccharin and derivatives, whereas isoxicam had a *N*-methyl signal at 2.85 ppm.[1] It had two exchangeable protons, four aromatic protons as a multiplet at 7.8–8.3 ppm, a C_4-isoxazole proton singlet at 6.45 ppm, and a C_5-methyl group singlet at 2.3 ppm. The structure **7** was further confirmed by the mass spectrum, which showed the molecular ion at *m/e* 352 (M + 1 ion) and fragmentation ions at *m/e* 320 (M – $NHCH_3$), 258 (M – SO_2NHCH_3), 227 and 125 (β-cleavage), and 170 and 152 (Scheme I).

The attempted functionalization of the 5-Me group in **1**, under a variety of oxidative reaction conditions using protective groups for the 4-OH group gave no desired product. Thus, an alternate synthesis of **2** involving the condensation of ester **8**[5] with isoxazolamine **9a** was envisioned.

Attempted NBS bromination of 5-methyl-3-isoxazolamine (**10a**) or its derivatives (**10b,c**) gave only ring-brominated products (**11**) (Scheme II). No brominated compound, **12**, was isolated. The structure of **11a**[6] was



8

9a, R = H
b, R = $SiMe_3$

confirmed by NMR and synthesis of the authentic sample by direct bromination of **10b** with Br_2 in acetic acid followed by hydrolysis.

Attempted reduction of the known 3-nitro-5-isoxazolemethanol[7] (**13**) (Scheme II) under a variety of conditions gave ring-opened or decomposition products.

Since most direct modifications of **10** to **9a** were unsuccessful, a total synthesis of **9a** was required (Scheme III).

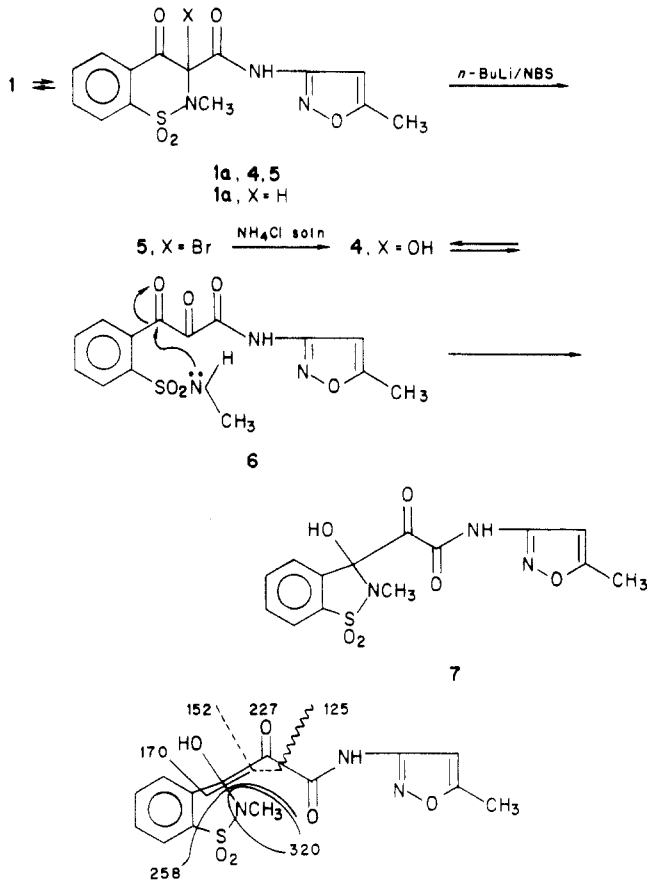
5-Methyl-3-isoxazolecarboxylic acid[8] (**14**) was prepared from acetonylacetone with 50% nitric acid. The acid **14** was converted to the trimethylsilyl ester **15**, with hexamethyldisilazane in carbon tetrachloride. Bromination of the crude ester **15** with NBS, high intensity light, and benzoyl peroxide as catalyst, gave a mixture of **15** and **16**, which was converted to the bromo acid **17** and unreacted acid **14** upon workup. The crude bromo acid **17** was reacted with oxalyl chloride in THF to give a 4:1 mixture of 5-(bromomethyl)- and 5-(chloromethyl)-3-isoxazolecarbonyl chloride (**18**) apparently by halogen exchange. The structure of **18** was confirmed by conversion to the acid **17**. The distilled acid chloride mixture **18** was converted to a mixture of acid azides **19**, which when refluxed with methanol in dioxane gave the 4:1 mixture of bromomethyl and chloromethyl carbamates **20**. The mixture of methyl carbamates **20** was reacted with silver acetate in acetic acid to give the acetate **21**, which was hydrolyzed with aqueous HCl and barium hydroxide solution in stepwise fashion to give **22** and **9a**, respectively. The compound **21** was also converted to **9a** via a one-step hydrolysis with barium hydroxide. Since the 3-amino-5-isoxazolemethanol (**9a**) is an unstable compound and decomposes on standing, it was immediately converted to the trimethylsilyl ether **9b** by reaction with hexamethyldisilazane in THF. The 3-isoxazolamine **9b** was reacted with the benzothiazine ester **8**[5] in refluxing xylene using 4A molecular sieves to remove the methanol that was formed. The trimethylsilyl ether **23** on treatment with methanol and aqueous HCl gave **2**, which was identical in all respects with the human metabolite of isoxicam.

The major rat metabolite, **3**, was synthesized according to Scheme IV. 5-methyl-3-isoxazolamine (**10a**) was reacted with ethyl oxalyl chloride in the presence of pyridine to give the oxamate ester **24**, which upon hydrolysis with sodium hydroxide gave the sodium salt **25**. Neutralization of **25** with aqueous HCl gave the metabolite **3**, which was identical in all respects with the identified rat metabolite of isoxicam.

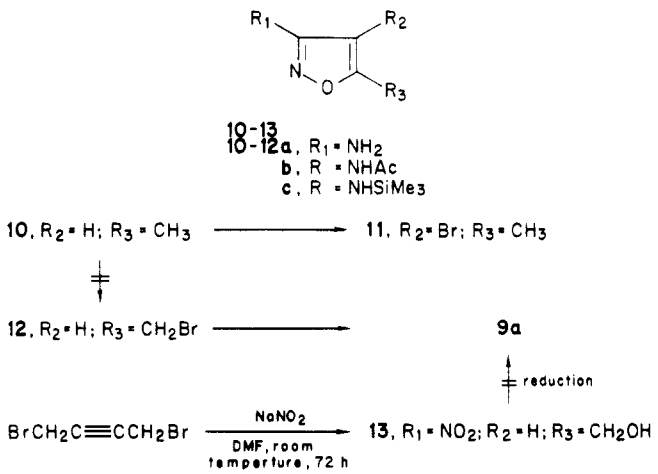
The metabolites **2** and **3** were tested in vitro cyclooxygenase[9] (bovine seminal vesicle) and lipoxygenase[10]

(4) Yakatan, G. J. *Semin. Arthritis Rheum.* **1982**, *12* (2), 154.
(5) Genzer, J. D.; Fontsere, F. C. U.S. Patent 3960856, 1976.
(6) Saito, N.; Kurihara, T.; Yamanaka, K.; Tsuruta, S.; Yasuda, S. *Yakugaku Zasshi* **1968**, *88*, 1289.
(7) Mechbov, T. D.; Sulimov, I. G.; Usik, N. V.; Mladenov, I.; Perlkalin, V. V. *Zh. Org. Khim.* **1980**, *16*, 1328.
(8) Gardner, T. S.; Lee, J.; Wenis, E. U.S. Patent 2908688, 1959.
(9) McNamara, D. B.; Boineau, F. G.; McMullen-Laird, M.; Lippton, H. L.; She, H. S.; Lewy, J. E.; Kadowitz, P. J. *Prostaglandins* **1982**, *24*, 585.
(10) Pugsley, T. A.; Spencer, C.; Boctor, A. M.; Gluckman, M. I. *Drug. Dev. Res.* **1985**, *5*, 171.
(11) In subsequent experiments the crude polysilylated **9** was used resulting in much better overall yield.

Scheme I



Scheme II



enzyme assay and were found to be inactive.

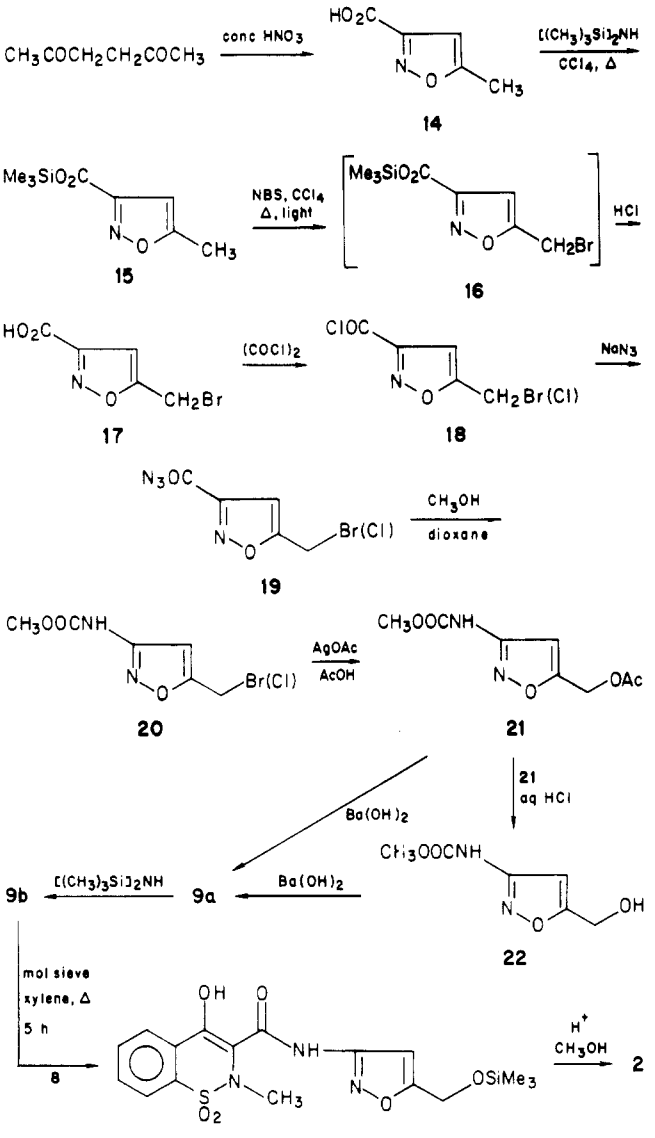
Experimental Section

Melting points are uncorrected. TLC analyses were run on E. Merck precoated silica gel 60 F-254 plates of 0.25-mm thickness. Compounds of interest were detected either by ultraviolet lamp (Mineralight, 254 nm) or by staining with iodine. ^1H NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as an internal standard. Ultraviolet spectra were determined as solution in methanol and infrared spectra as KBr plates or Nujol mulls. Solutions were dried with Na_2SO_4 or $MgSO_4$ and concentrated on a rotary evaporator at an ambient temperature at pressures of 10–20 mm. All moisture-sensitive reactions were performed under dry nitrogen.

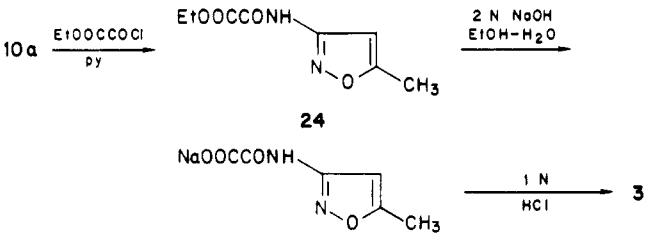
Reaction of 4-Hydroxy-2-methyl-*N*-(5-methyl-3-isoxazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (Isoxicam) with *N*-Bromosuccinimide (NBS). Isolation of Saccharin Derivative 7. Isoxicam (1) (3.35 g; 0.01 mol) was suspended in dry THF (250 mL) and was cooled to −70 °C under N_2. *n*-Butyllithium solution (0.5 mL; 1.05 mmol; 2.1 M in hexane) was added to the suspension and the mixture stirred for 30 min. A solution of NBS (freshly recrystallized and dried over P_2O_5) (2.14 g; 0.012 mol) in THF (50 mL) was added over a 5-min period to the suspension and the mixture stirred at −70 °C for 4 h. The reaction mixture was quenched with 20 mL of saturated NH_4Cl solution and allowed to stand at room temperature overnight.

The inorganic salts were filtered, and the yellow filtrate was evaporated to dryness, yielding a yellow oil, which was triturated with 2-propanol. Unreacted isoxicam (1.5 g) crystallized and was filtered. The filtrate was evaporated to dryness and then crystallized from ethyl acetate to give off-white crystals (1.61 g; 45.9%, negative $FeCl_3$ test). This solid was recrystallized from 2-propanol

Scheme III



Scheme IV



and EtOAc to a white solid. An analytical sample was obtained by using a preparative, centrifugally accelerated, radial, thin-layer chromatography (Chromatotron) and eluting with 3% MeOH–$CHCl_3$. The material obtained was recrystallized from EtOAc to give white crystals: mp 185–188 °C (negative $FeCl_3$ test); IR (KBr) 3460, 3220, 1716, 1707, 1618 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.38 (s, 3, CH_3), 3.28 (s, 3, NCH_3), 6.52 (s, 1, C_4-H), 7.77–8.06 (m, 4, Ar), 8.02 (s, 1, NH, D_2O exchangeable), 10.98 (s, 1, OH, D_2O exchangeable). Anal. Calcd for $C_{14}H_{13}N_3O_6S$: C, 47.87; H, 3.73; N, 11.96; S, 9.13. Found: C, 47.80; H, 3.52; N, 11.56; S, 9.46.

4-Bromo-5-methyl-3-isoxazolamine (11a). A solution of 5-methyl-3-isoxazolamine (**10a**) (31.3 g; 0.32 mol) in THF (300 mL) was cooled to −70 °C and was treated with *n*-BuLi solution (200 mL; 15.03%, 1.667 M; 0.33 mol) in heptane for 75 min. The resulting brown solution was stirred at −70 °C for 25 min. Trimethylsilyl chloride (35.95 g; 0.33 mol) was added to the anion solution at −70 °C over a 15-min period, and the solution was allowed to slowly come to room temperature (1.5 h). THF was distilled and the residue dissolved in small amount of heptane. The precipitated LiCl was filtered under N_2. The filtrate was recrystallized from *n*-pentane (500 mL) to give pale tan crystals (36.95 g) of **10c**: mp 77–83 °C; ^1H NMR ($CDCl_3$) δ 0.25 (s, 9, Me_3Si), 2.27 (s, 3, CH_3), 3.70 (br, 1, NH), 5.50 (s, 1, C_4-).

A solution of 5-methyl-*N*-(trimethylsilyl)-3-isoxazolamine (**10c**) (5.08 g; 0.03 mol) from above and 2,2′-azobis(isobutyronitrile) (AIBN) (200 mg) in CCl_4 (75 mL) was treated slowly (1 h) with NBS (6.23 g; 0.035 mol) at reflux temperature. After the addition was completed, the reaction mixture was heated at reflux temperature for an additional 2 h and then allowed to stand at room temperature overnight. The precipitated succinimide was filtered, and the orange filtrate was evaporated to dryness to give a pink oil. Crystallization from *n*-pentane gave white crystals (0.93 g, 17.5%). An analytical sample was obtained from a second crystallization from *n*-pentane as white crystals: mp 69–72 °C; IR (KBr) 3438, 3298, 3190, 1635, 1609, 1527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3, CH_3), 4.08 (br, 2, NH_2). Anal. Calcd for $C_4H_5BrN_2O$: C, 27.14; H, 2.85; N, 15.83; Br, 45.14. Found: C, 27.38; H, 2.79; N, 16.02; Br, 44.80.

4-Bromo-5-methyl-3-isoxazolamine (11a). A solution of bromine (4.6 g; 0.0576 mol) in glacial AcOH (10 mL) was added to a solution of *N*-(5-methyl-3-isoxazolyl)acetamide (**10b**) (4.0 g, 0.0285 mol) and anhydrous NaOAc (9.0 g, 0.115 mol) in glacial AcOH (40 mL). This reaction mixture was heated in an oil bath to 85–90 °C for 4.0 h. The solvent was evaporated, and the white residue was crystallized from water to give **11b**, yield 3.18 g (50.9%), mp 105–109 °C. The acetamidoisoxazole **11b** (2.56 g; 0.011 mol) was hydrolyzed with 50% aqueous HCl (50 mL) at reflux temperature until a solution was formed. The aqueous HCl solution was neutralized with 1 N KOH solution and extracted with CH_2Cl_2. Removal of CH_2Cl_2 gave a white solid **11a**,[6] mp 68–73 °C, which was identical in all respects with the product obtained from NBS reaction.

3-Nitro-5-isoxazolemethanol (13).[7] This was prepared from 1,4-dibromo-2-butyne (Fairfield Chemical Co.) and $NaNO_2$ by using a modified procedure.[7] Sodium nitrite (276 g; 4 mol) was added slowly portionwise to a cooled (0–5 °C) solution of 1,4-dibromo-2-butyne (42.4 g; 0.2 mol) in dry DMF (300 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 68 h. The dark brown mixture was poured into 1500 mL of ice-cooled water and then extracted with ether (3 × 300 mL), washed with brine (3 × 400 mL), and dried. Removal of solvent gave a dark yellow oil (4.4 g), which was chromatographed on a silica gel column. Elution with 1:1 toluene–methanol gave the desired product (2.6 g) contaminated with minor impurities. This material was rechromatographed over silica gel by eluting with $CHCl_3$ and with increasing amounts of MeOH. Fractions 40–44, eluted with 3% MeOH–$CHCl_3$, gave pure product (410 mg, 1.4%) by TLC and GC (OV-17 column). On cooling in dry ice–acetone bath, the product crystallized to a solid: mp 30–33 °C; IR (neat) 3400, 3160, 1560, 1480, 1340, 820 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 4.75 (br, 3, exchangeable 1, CH_2OH), 6.8 (s, 1, C_4H). Anal. Calcd for $C_4H_4N_2O_4$: C, 33.34; H, 2.80; N, 19.44. Found: C, 33.66; H, 3.02; N, 19.00.

5-(Bromomethyl)-3-isoxazolecarbonyl Chloride and 5-(Chloromethyl)-3-isoxazolecarbonyl Chloride (18). 5-methyl-3-isoxazolecarboxylic acid[8] (36.8 g, 0.29 mol) was suspended in 250 mL of CCl_4 and then treated with hexamethyldisilazane (27.5 g, 0.17 mol). The mixture was heated to reflux for 1 h, and the resulting yellow solution was evaporated to dryness to give an oil. The trimethylsilyl ester was dissolved in 300 mL of fresh CCl_4 and treated with *N*-bromosuccinimide (89 g, 0.5 mol) and 2.0 g of benzoyl peroxide. The reaction mixture was heated and illuminated by a Cole-Parmer Dynalume high-intensity lamp, so that moderate reflux was maintained. After 1 h of reaction, the mixture was charged with additional *N*-bromosuccinimide (10 g, 0.056 mol) and 0.5 g of benzoyl peroxide and maintained under reflux for an additional 0.5 h. The reaction mixture was cooled, and the succinimide was filtered. The red filtrate was evaporated to dryness, and the residue was dissolved in THF containing 5 mL of 4 N HCl. The solution was heated on a steam bath for 5 min and then evaporated to a red semisolid, which when triturated with Et_2O gave 30.6 g of crude bromo acid. The crude acid was dried under vacuum at room temperature for 15 h over P_2O_5.

The crude 5-(bromomethyl)-3-isoxazolecarboxylic acid **17** (18 g) was dissolved in 150 mL of dry THF and oxalyl chloride (36.38 g, 0.28 mol) was added. After the reaction mixture was heated at reflux for 2 h, the solvent and excess oxalyl chloride were removed under reduced pressure. The brown liquid was purified by distillation giving 6.27 g of product, bp 60–62 °C (0.1 mm), which was used without further purification. NMR and analysis indicated a mixture of 5-(chloromethyl)- and 5-(bromomethyl)-3-isoxazolecarbonyl chloride.

5-(Bromomethyl)-3-isoxazolecarboxylic Acid (17). A fraction [bp 75–80 °C (0.3 mm)] that was predominantly 5-(bromomethyl)-3-isoxazolecarbonyl chloride (1 g) was dissolved in 2 mL of acetone and cooled to 0 °C, and 3 mL of water was added to the solution. After the solution was allowed to stand at room temperature for 1 h, the solvent was removed under reduced pressure, giving 0.8 g of the acid. The acid **17** was dried over P_2O_5 for 3 days and had a mp 143–148 °C: IR (KBr) 3450, 1730, 1700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.8 (s, 2, CH_2Br), 6.8 (s, 1, C_4), 12.8 (br, 1, COOH); mass spectrum (70 eV), *m/e* 207, 206, 205, 126, 68. Anal. Calcd for $C_5H_4BrNO_3$: C, 29.15; H, 1.96; N, 6.80; Br, 38.79. Found: C, 29.39; H, 1.98; N, 6.81; Br, 38.54.

5-(Bromomethyl)-3-isoxazolecarbonyl Azide and 5-(Chloromethyl)-3-isoxazolecarbonyl Azide (19). A solution of 2.24 g (0.01 mol) of distilled acid chloride **18** in 5 mL of acetone was cooled in ice–water, and a solution of 0.68 g (0.0105 mol) of sodium azide in 2 mL of water was added rapidly and allowed to stand for 15 min. The solution was evaporated to dryness, and the white solid residue obtained was washed with cold water and dried under vacuum overnight over P_2O_5. The acid azide (1.82 g) was recrystallized from absolute EtOH, yielding white needles, mp 75–76.5 °C. Characterization of this material showed it to be a mixture of 5-(bromomethyl)isoxazole-3-carbonyl azide (77.5%) and 5-(chloromethyl)isoxazole-3-carbonyl azide (22.5%): IR (Nujol) 2120, 2150, 2170, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.5 (s, 1.55, CH_2Br), 4.65 (s, 0.45, CH_2Cl), 6.75 (s, 1, C_4H). Anal. Calcd for $C_5H_3H_4O_2Br$ and $C_5H_3N_4O_2Cl$ (77.5:22.5): C, 27.17; H, 1.37, N, 25.35; Br, 28.02; Cl, 3.61. Found: C, 27.35; H, 1.53; N, 25.63; Br, 28.20; Cl, 3.35.

Methyl [5-(Bromomethyl)-3-isoxazolyl]carbamate and Methyl [5-(Chloromethyl)-3-isoxazolyl]carbamate (20). A solution of 1.16 g (~5.0 mmol) of a mixture of 5-(bromomethyl)-3-isoxazolecarbonyl azide and 5-(chloromethyl)-3-isoxazolecarbonyl azide (**19**) in 10 mL of MeOH and 25 mL of 1,4-dioxane was heated to reflux in an atmosphere of nitrogen for 6 h and allowed to stand overnight at 25 °C. The reaction mixture was evaporated to dryness to give 1.23 g of an off-white solid, which was recrystallized from isopropyl ether, mp 140–143 °C. This was characterized as a 80:20 mixture of (bromomethyl)- and (chloromethyl)isoxazole derivative **20**: IR (Nujol) 3200, 1730, 1640, 1565 cm^{-1}; ^1H NMR (5:1 $CDCl_3$ + Me_2SO-d_6) δ 3.75 (s, 3, CH_3), 4.45 (s, 1.6, CH_2Br), 4.6 (s, 0.4, CH_2Cl), 6.85 (s, 1, C_4H), 10.2 (br, 1, NH). Anal. Calcd for $C_6H_7N_2O_3Br$ and $C_6H_7N_2O_3Cl$ (80:20): C, 31.87; H, 3.12; N, 12.39; Br, 28.27; Cl, 3.14. Found: C, 31.94; H, 3.22; N, 12.74; Br, 28.33; Cl, 3.01.

Methyl [5-((Acetyloxy)methyl)-3-isoxazolyl]carbamate (21). A mixture of **20** (4.7 g; 0.02 mol), AcOH (50 mL), and silver acetate (3.7 g; 0.022 mol) was heated to reflux for 3.5 h. The reaction mixture was cooled to 25 °C, and the silver salts were filtered. The filtrate was evaporated to dryness, and the crude

solid was recrystallized from isopropyl ether–*n*-pentane to give an off-white crystalline solid (2.73 g, 63.8%). An analytical sample was prepared by two additional crystallizations from isopropyl ether as white crystals, **21**: mp 126–128 °C; IR (Nujol) 3220, 1750, 1730, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.15 (s, 3, CH_3CO), 3.85 (s, 3, CH_3O), 5.15 (s, 2, CH_2), 6.9 (s, 1, C_4H), 8.4 (br, 1, NH, D_2O exchangeable). Anal. Calcd for $C_8H_{10}N_2O_5$: C, 44.86; H, 4.71; N, 13.08. Found: C, 44.53, 44.45; H, 4.69, 4.71; N, 13.51, 13.39.

Methyl [5-(Hydroxymethyl)-3-isoxazolyl]carbamate (22). A solution of crude **21** (4.0 g; 0.0187 mol) in MeOH (20 mL) and 4 N HCl (20 mL) was heated on a steam bath for 5 min, and the MeOH was evaporated. A white solid byproduct (AgCl) precipitated and was removed by filtration. The filtrate was evaporated to dryness to give an oil, which upon standing, slowly crystallized. The crude product was washed with Et_2O–*n*-pentane and then recrystallized from Et_2O, giving **22** (0.80 g, 24.9%) as tan crystals: mp 115–117 °C; IR (KBr) 3460, 3260, 3220, 1740, 1720, 1635 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.65 (s, 3, CH_3) 4.5 (d, 2, CH_2, J = 5.4 Hz), 5.6 (t, 1, OH, J = 5.4 Hz, D_2O exchangeable), 6.55 (s, 1, C_4H), 10.55 (s, 1, NH, D_2O exchangeable). Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.28. Found: C, 42.12; H, 4.41; N, 16.30.

5-[((Trimethylsilyl)oxy)methyl]-3-isoxazolamine (9b). A mixture of **21** (0.5 g, 2.3 mmol) in 50% aqueous ethanol (10 mL) and barium hydroxide (0.79 g, 4.6 mmol) was heated to reflux for 18 h (in subsequent experiments it was found that a 1-h reaction time was sufficient). After the mixture was cooled to room temperature, a few pieces of dry ice were added. The resulting barium carbonate was filtered, and the filtrate was evaporated to a residue, which was extracted with THF. The THF extract was treated with hexamethyldisilazane, and the mixture was heated to reflux for 1 h. The reaction mixture was evaporated to dryness and extracted with boiling *n*-pentane. The *n*-pentane solution was concentrated and cooled to give off-white platelet crystals (140 mg; 32.7%): mp 70–75 °C; IR (Nujol) 3400, 3300, 3200, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 9, Me_3Si), 4.1 (br, 2, NH_2), 4.6 (s, 2, CH_2), 5.8 (s, 1, C_4H). Anal. Calcd for $C_7H_{14}N_2O_2Si$: C, 45.13; H, 7.58; N, 15.04. Found: C, 44.95; H, 7.48; N, 15.43.

4-Hydroxy-*N*-[5-(hydroxymethyl)-3-isoxazolyl]-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (2). A mixture of **9b**[11] (559 mg; 3 mmol) and the benzothiazine ester 8[5] (807 mg; 3 mmol) in xylene (125 mL) was heated at reflux for 5 h in a Soxhlet apparatus, the thimble of which contained 20 g of Linde type 4A molecular sieves. The reaction mixture was evaporated to dryness, and the residue was dissolved in 75 mL of MeOH and 2 mL of 2 N HCl. The solution was concentrated with heating, and 2-propanol was added periodically maintaining a volume of ca. 35 mL. The solution was allowed to cool to give white crystals (465 mg, 44.1%): mp 240–244 °C dec; IR (KBr) 3450, 1630, 1610 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.85 (s, 3, NCH_3), 3–4 (br, OH, H_2O), 4.5 (s, 2, CH_2), 6.8 (s, 1, C_4H), 7.9 (m, 4, Ar), 11.5 (s, 1, NH); UV (MeOH) λ_{max} 323 (ϵ 12770), 239 (11650) nm; mass spectrum, *m/e* 351 (M^+), 173, 145, 117. Anal. Calcd for $C_{14}H_{13}N_3O_6S$: C, 47.87; H, 3.73; N, 11.96; S, 9.13. Found: C, 48.13; H, 3.90; N, 11.84; S, 9.32.

Ethyl [(5-Methyl-3-isoxazolyl)amino]oxoacetate (24). A solution of 5-methyl-3-isoxazolamine (5.8 g; 0.051 mol) in CH_2Cl_2 (195 mL) and pyridine (8.1 g; 0.102 mol) was cooled to 5 °C and was treated slowly with ethyl oxalyl chloride (7.3 g; 0.0535 mol). The solution was stirred at 25 °C for 2 h and then at 40 °C for 15 min. The solvent was evaporated, and the residue was treated with 150 mL of water, stirred, and filtered. The residue was washed with Et_2O and dried to give **24** as a white solid (8.83 g; 87.3%): mp 130–134 °C; IR (KBr) 3211, 3080, 1747, 1718, 1626, 1546 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.28 (t, 3, CH_3), 2.40 (s, 3, CH_3), 4.25 (q, 2, CH_2), 6.58 (s, 1, C_4H), 11.75 (s, 1, NH). Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.37; H, 5.03; N, 14.17.

[(5-Methyl-3-isoxazolyl)amino]oxoacetic Acid (3). A mixture of **24** (7.23 g, 0.037 mol), EtOH (37 mL), water (37 mL), and 1 N NaOH (37 mL) was stirred at 25 °C for 40 min and then heated to 55 °C until a clear solution was obtained. The solution was filtered, diluted with absolute EtOH and allowed to crystallize. The white solid was filtered and dried to give 4.75 g (66.9%) of the sodium salt **25**: mp 275–280 °C dec; IR (KBr) 3354, 3184, 1701, 1649, 1557 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.4 (s, 3, CH_3), 6.6 (s, 1, C_4H). Anal. Calcd for $C_6H_5N_2O_4Na$: C, 37.51; H, 2.62; N, 14.58. Found: C, 37.39; H, 2.74; N, 14.73.

The mother liquor from the above crystallization was evaporated to dryness, and the residue was dissolved in water (38 mL) and acidified with 1 N HCl (38 mL) to give a white precipitate. The crude acid was recrystallized from aqueous HCl to give an analytical sample of **3** (220 mg): mp 215–219 °C dec; IR (KBr) 3288, 1763, 1718, 1700, 1619, 1549 cm^{-1}. Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.26; H, 3.60; N, 16.33.

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Total Synthesis of Modhephene

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A new approach to the natural propellane modhephene is described. Critical to the success of this synthesis was a dianion-mediated cyclopentannulation procedure, a heteroatom-assisted stereoselective hydrogenation, a regioselective lactonization, and a dimethylation of a carbonyl.

Modhephene (**1**), isolated from the Rayless Goldenrod, has been the target of several innovative syntheses.[1] In a recent paper[2] we described the stero- and regiospecific synthesis of the Smith intermediate (**2**)[3], thus constituting

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