Synthesis of Racemic Brevioxime and Related Model Compounds

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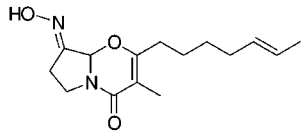
The synthesis, in racemic form, of the insect juvenile hormone inhibitor brevioxime (**1**) is described, as well as exploratory studies that led to the related model compounds **14** and **15a**. The route to **1** involves Ag^+-mediated coupling of the amine derived from **20** with the β-keto thioester **32**. Acid treatment of the coupled product **33** led by acetal hydrolysis, cyclization, and desilylation to **34a**,**b**, from which **1** was reached by oxidation and conversion into the oxime. In the synthesis of the amino component **20**, a known, but unusual, reduction was used for converting a nitrile into an amine hydrochloride.

We report full details of our model studies and total synthesis of racemic brevioxime (**1**).[1] This compound was



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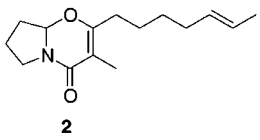

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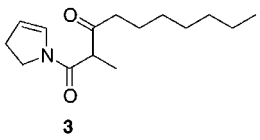

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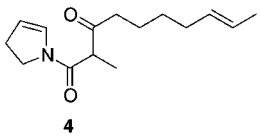

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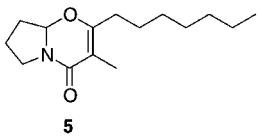

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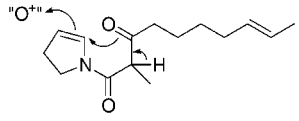
isolated[2,3] from a strain of the fungus *Penicillium brevicompactum*, and its structure was reported a few years ago.[2] The substance was found to be a potent inhibitor of juvenile hormone III biosynthesis,[3] and it appears to block those enzymatic steps of the isoprenoid pathway that are specific for insects.[3] These properties make it a potential lead compound for the development of insecticides. The related compounds **2**,[4] **3**,[5] and **4**[4] have also been isolated from the same fungus and their biological properties examined. Compounds **3** and **4** both inhibit formation of juvenile hormone, but the mode of action of **2**, which is also an insecticide, does not appear to have been established.

The structure of brevioxime is an unusual one and, although a number of benzo-fused substances containing a similar ring system are known, those lacking a fused benzene ring are rare,[6,7] and the only other unsaturated examples we know of are compounds made in this laboratory and described below, as well as model compounds, such as the totally synthetic **5**, prepared[5] by the discoverers of brevioxime.

Our initial thoughts on synthetic approaches dwelt on the possibility of generating an enamide, so that cyclization, as indicated by the arrows in structure **6**, could be induced by some type of epoxidizing agent. While many



6

enamides (and enecarbamates) are known,[8] the one required by the above plan would be part of a β-dicarbonyl system, and we were unable to make such a species—at least within the time we were prepared to spend on the problem. Accordingly, we reanalyzed the synthesis in terms of the double cyclization **7** → **8** → **9** summarized in Scheme 1.[9] This approach which, in the event, proved successful was initially tried with model compounds. We prepared first of all **14** (see Scheme 2) from the two components **10**[10] and **11**.[11] Both of these

(1) Clive, D. L. J.; Hisaindee, S. *Chem. Commun.* **1999**, 2251−2252.
(2) Moya, P.; Castillo, M.; Primo-Yúfera, E.; Couillaud, F.; Martínez-Máñez, R.; Garcerá, M.-D.; Miranda, M. A.; Primo, J.; Martínez-Pardo, R. *J. Org. Chem.* **1997**, *62*, 8544−8545.
(3) Castillo, M.; Moya, P.; Couillaud, F.; Garcerá, M.-D.; Martínez-Pardo, R. *Arch. Insect Biochem. Physiol.* **1998**, *37*, 287−294.
(4) Cantín, Á.; Moya, P.; Castillo, M.-A.; Primo, J.; Miranda, M. A.; Primo-Yúfera, E. *Eur. J. Org. Chem.* **1999**, 221−226.
(5) Moya, P.; Cantín, Á.; Castillo, M.-A.; Primo, J.; Miranda, M. A.; Primo-Yúfera, E. *J. Org. Chem.* **1998**, *63*, 8530−8535.
(6) (a) Boehme, H.; Boeing, H. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1961**, *294*, 556−562. (b) Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1968**, *33*, 2402−2407.
(7) Cf.: (a) Baldwin, J. E.; Hulme, C.; Schofield, C. J.; Edwards, A. J. *J. Chem. Soc., Chem. Commun.* **1993**, 935−936. (b) Claridge, T. D. W.; Hulme, C.; Kelly, R. J.; Lee, V.; Nash, I. A.; Schofield, C. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 485−490.
(8) E.g.: (a) Lenz, G. R. *Synthesis* **1978**, 489−518. (b) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237−1241. (c) Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605−1608. (d) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324−4330. (e) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353−365. (f) Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 4791−4792. (g) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646−6652 and references therein.
(9) Cf.: (a) Reference 7. (b) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393−396. (c) Baldwin, J. E.; Adlington, R. M.; Bryans, J. S.; Lloyd, M. D.; Sewell, T. J.; Schofield, C. J.; Baggaley, H. K.; Cassels, R. *J. Chem. Soc., Chem. Commun.* **1992**, 877−879. (d) Clive, D. L. J.; Coltart, D. M.; Zhou, Y. *J. Org. Chem.* **1999**, *64*, 1447−1454.
(10) Kadota, I.; Kawada, M.; Saya, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 2109−2112.

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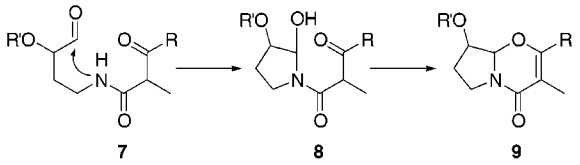
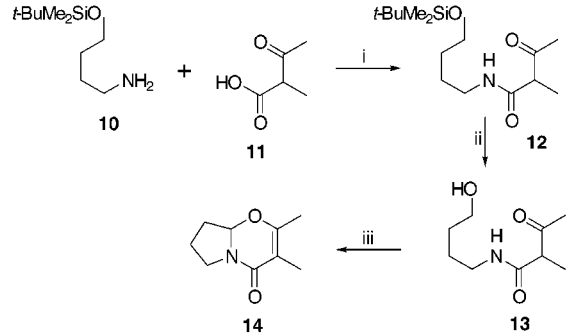
Scheme 1



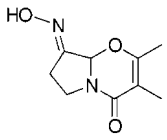
Scheme 2[a]



[a] Legend: (i) DCC, DMAP, 3 equiv of the β-keto acid, 62-92%; (ii) Bu_4NF, AcOH, THF, 40 °C, overnight, 80%; (iii) Pr_4NRuO_4, *N*-methylmorpholine *N*-oxide, silica gel chromatography, 33%.

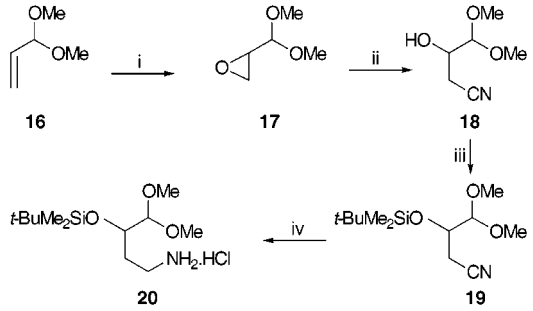
are known compounds, and they were obtained by the literature methods. Ethyl acetoacetate was methylated via its pyrrolidine enamine[12] and hydrolyzed under carefully controlled conditions,[11] to afford the sensitive acid **11**. 4-Aminobutanol was best prepared in three steps from tetrahydrofuran[13] (AcCl, heat, 66%; phthalimide, DMF, NaI, heat, 88%; aqueous KOH, heat, 64%), and silylation then gave the protected amine **10**.[10] Coupling of **10** and **11** was achieved using DCC (62−92%), and then desilylation (Bu_4NF) gave alcohol **13**. From that point, oxidation with Pr_4NRuO_4−*N*-methylmorpholine *N*-oxide[14] led directly to the simple model compound **14** (33%).

Formation of **14** served to validate the approach based on amide closure onto an aldehyde, followed by a second cyclization involving the β-dicarbonyl system. We therefore next sought to prepare **15a** by an analogous route,



so as to gain experience in generating the oxime function. In the present case, compound **20** proved to be a suitable amine segment,[15] and it was prepared as shown in Scheme 3. Acrolein dimethyl acetal (**16**[16]) was epoxidized by a general literature procedure,[17] and the resulting epoxide **17** was treated with KCN in aqueous EtOH at room temperature,[18] so as to form hydroxy nitrile **18**. This was silylated under standard conditions (**18** → **19**). Reduction of the nitrile was initially troublesome, until we tried catalytic hydrogenation in the presence of

Scheme 3[a]



[a] Legend: (i) HOCl, NaOH, 72%; (ii) KCN, H_2O, EtOH, 62%; (iii) *t*-$BuMe_2SiCl$, DMAP, Et_3N, CH_2Cl_2, 81%; (iv) PtO_2, H_2, 50 psi, $CHCl_3$, EtOH, 64−100%.

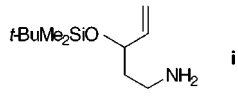
several equivalents of $CHCl_3$, which serves as a controlled source of HCl.[19] That method gave the required amine as its hydrochloride salt **20** in yields varying from 64 to 100%.[20]

Having found a convenient route to **20**, the next task was to prepare the β-keto amide **22**. Formation of β-keto amides can be a far from simple task; in the present case, direct DCC-mediated coupling with acid **11** gave material that was difficult to purify, but the general method of Ley et al.,[21] which involves Ag^+-mediated coupling with a β-keto thioester, worked well. The required thioester **21**[22] was made by methylation[22] (NaH, DME, MeI, 90%) of *S*-*tert*-butyl 3-ketobutanethioate,[23] and reaction between **20** and **21**, in the presence of Et_3N and $AgOSO_2CF_3$, gave the desired amide **22** in 79% yield (Scheme 4).

When amide **22** was exposed to the action of aqueous TFA in $CHCl_3$, the acetal hydrolysis, cyclization, and desilylation steps occurred, giving a mixture of products **23a**,**b**, epimeric at the hydroxyl-bearing carbon. The chromatographically less polar alcohol (**23a**) was isolated in 37% yield and the more polar (**23b**) in 36% yield. X-ray analysis of the former established that the hydroxyl and adjacent angular hydrogen are syn. The material was converted (42%) into ketone **24** by the action of the Dess−Martin reagent (Pr_4NRuO_4 did not work[24]), and the more polar isomer was oxidized by the action of Pr_4NRuO_4 (46%, or 84% after correction for recovered starting

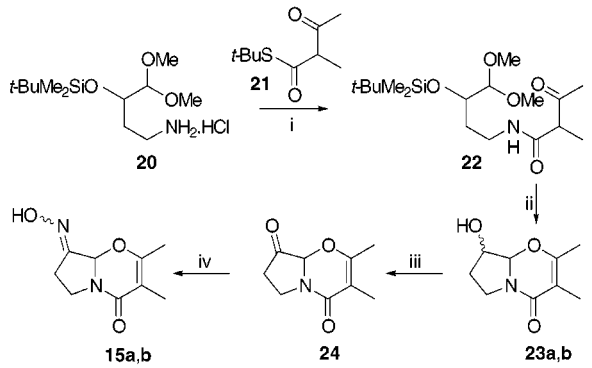
(11) Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896−1901.
(12) Baron, M.; De Cointet, P.; Bauduin, G.; Pietrasanta, Y.; Pucci, B. *Bull. Soc. Chim. Fr.* **1982**, *7*−*8*, *II*, 249−256.
(13) Maxfield, F. R.; Alter, J. E.; Taylor, G. T.; Scheraga, H. A. *Macromolecules* **1975**, *8*, 479−491.
(14) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(15) We initially used amine **i**, in which the eventual aldehyde function is masked as a carbon−carbon double bond. Unfortunately, after coupling with acid **11**, we were unable to isolate characterizable products from attempts to cleave the double bond.



(16) (a) Cf.: Childs, R. F.; Hagar, M. E. *Can. J. Chem.* **1980**, *58*, 1788−1794. (b) We prepared the compound, although it is commercially available.
(17) Cf.: Weisblat, D. I.; Magerlein, B. J.; Myers, D. R.; Hanze, A. R.; Fairburn, E. I.; Rolfson, S. T. *J. Am. Chem. Soc.* **1953**, *75*, 5893−5896.
(18) Cf.: Effenberger, F.; Null, V. *Liebigs Ann. Chem.* **1992**, 1211−1212.
(19) Secrist, J. A., III.; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335−336.
(20) We noticed that in runs giving a very high yield, the spent catalyst was inflammable.
(21) Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 3019−3020.
(22) López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *Synthesis* **1998**, 186−194.
(23) Sakaki, J.; Kobayashi, S.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 2262−2264.
(24) No starting material was recovered.

Scheme 4[a]



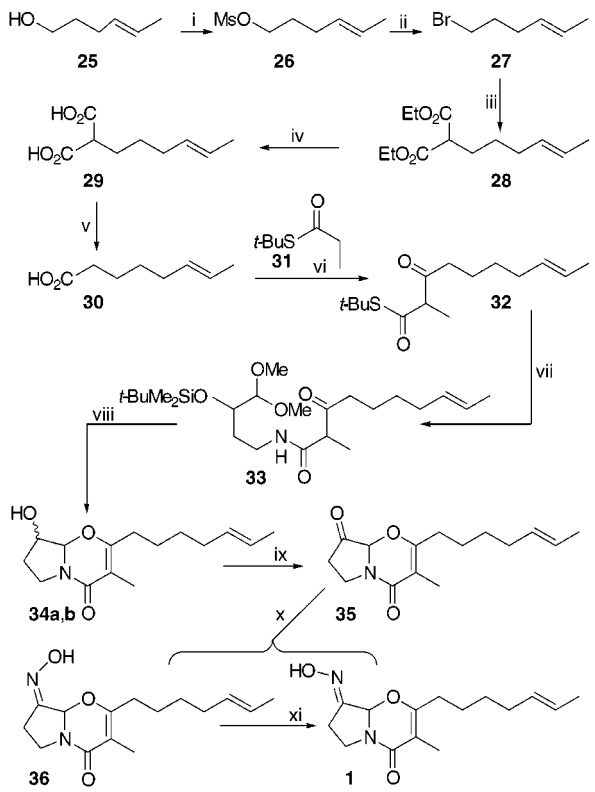
[a] Legend: (i) Et_3N, $AgOSO_2CF_3$, 79%; (ii) 50% aqueous CF_3CO_2H, $CHCl_3$, 36% of more polar isomer (**23b**), 37% of less polar isomer (**23a**); (iii) Dess−Martin periodinane on less polar isomer, 42%, Pr_4NRuO_4, CH_2Cl_2, MeCN on more polar isomer, 46% (84%, corrected for recovered starting material); (iv) $H_2NOH{\cdot}HCl$, H_2O, AcONa, 73% *E*, 6% *Z*.

material). Curiously, this compound was inert to the Dess−Martin reagent under conditions that were satisfactory with the other isomer.

Finally, ketone **24** was converted into its separable *E* (**15a**) and *Z* (**15b**) oximes, under standard conditions.[25] The (*E*)-oxime was by far (>12:1) the major product.

We were now in a position to apply the experience gained from our model studies to the synthesis of brevioxime itself. To this end, we needed to couple the amino component **20** with the *β*-keto thioester **32** (see Scheme 5), and our first task was to prepare that ester. Since ester **21** was available from our model studies, we naturally attempted to alkylate it by double deprotonation[26] and treatment with (*E*)-6-iodo-2-hexene,[27] but this approach gave a very poor yield (33%). Likewise, alkylation of *S*-*tert*-butyl 3-ketobutanethioate with the same iodide was also inefficient (ca. 37% yield), and we eventually made the required thioester **32** by acylation of **31** (**30** + **31** → **32**; Scheme 5). The acid **30** was best made from (*E*)-4-hexenol (**25**[28a]) by the classical method shown in Scheme 5. Each of the compounds **25**−**30** has been reported before, but some of the preparations probably contained a small amount of *Z* isomer, as the best route to **25** gives material contaminated with the *Z* alcohol (<5%[28a]). In our work, spinning band distillation of **25**, derived[28] from readily available 3-chlorotetrahydro-2-methylpyran,[28b,c] afforded isomerically pure alcohol. This was mesylated, converted into the bromide, and used to alkylate diethyl malonate (**25** → **26**[29] → **27**[29] → **28**[30,31]). Hydrolysis, and thermal decarboxylation, then

Scheme 5[a]



[a] Legend: (i) MsCl, Et_3N, THF, ca. 100%; (ii) LiBr, THF, heat, 3.5 h, 87%; (iii) $CH_2(CO_2Et)_2$, EtONa, 72%; (iv) aqueous KOH, room temperature, 24 h, 99%; (v) heat (160 °C), 5 h, 94%; (vi) Im_2CO, then add mixture of LDA (3 equiv) and **31** (3 equiv), 64%; (vii) **20**, $AgOSO_2CF_3$, Et_3N, 90%; (viii) 50% aqueous TFA, $CHCl_3$, ca. 100%; (ix) Dess−Martin for less polar isomer, ca. 57% (100% after correction for recovered starting material), Pr_4NRuO_4, CH_2Cl_2, MeCN for more polar isomer, 21% (28% after correction for recovered starting material); (x) $NH_2OH{\cdot}HCl$, AcONa, EtOH−H_2O, 81% *E* isomer, 13% *Z* isomer; (xi) $CDCl_3$, 51 h, 44% *E* isomer, 42% *Z* isomer.

gave the key carboxylic acid **30** (**29**[31] → **30**[31]). This was converted into its imidazolide[32,33] and used to acylate the enolate derived from thioester **31**.[35] In this way, *β*-keto thioester **32** was obtained in 64% yield. Coupling of **32** with the amino component **20** under conditions that had served well in the model study ($AgOSO_2CF_3$, Et_3N) was again successful and gave *β*-keto amide **33** in 90% yield. Exposure to a mixture of 50% aqueous TFA and $CHCl_3$ resulted in the desired series of transformations (hydrolysis, cyclization, and desilylation), giving rise to **34a**,**b**, as a 1:1 mixture of epimers in almost quantitative yield. As in the model series, the next step—oxidation of the hydroxyl to a ketone—was not straightforward. The less polar alcohol (isolated in 45% from **33**) gave ketone **35** in 57% yield (or 100%, corrected for recovered starting material) with the Dess−Martin reagent. Pr_4NRuO_4 destroyed the alcohol. The more polar alcohol (42% from

(25) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: London, 1989; p 1259.

(26) Cf.: (a) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082−1087. (b) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121−129.

(27) Krief, A.; Kenda, B.; Barbeaux, P.; Guitlet, E. *Tetrahedron* **1994**, *50*, 7177−7192.

(28) (a) Crombie, L.; Wyvill, R. D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1983−1995. (b) Crombie, L.; Harper, S. H. *J. Chem. Soc.* **1950**, 1707−1722. (c) In the preparation of 3-chlorotetrahydro-2-methylpyran by the literature procedure,[28b] use of a mechanical stirrer is essential because, if the mixture is not stirred vigorously, the reaction becomes violent after two-thirds of the Grignard reagent has been added. The initial chlorination of dihydropyran was done in CCl_4 instead of Et_2O.

(29) Becker, D.; Nagler, M.; Sahali, Y.; Haddad, N. *J. Org. Chem.* **1991**, *56*, 4537−4543.

(30) Jacobson, M.; Keiser, I.; Chambers, D. L.; Miyashita, D. H.; Harding, C. *J. Med. Chem.* **1971**, *14*, 236−239.

(31) Ansell, M. F.; Brown, S. S. *J. Chem. Soc.* **1957**, 1788−1795.

(32) Cf.: Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Tetrahedron Lett.* **1987**, *28*, 2837−2840.

(33) Instead of the imidazolide, the corresponding derivative of 2,2′-carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) can be used (cf. ref 34).

(34) Jouin, P.; Poncet, J.; Dufour, M.-N.; Maugras, I.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1988**, *29*, 2661−2664.

(35) Footnote 36 in: Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288−3300. We used DMAP and pyridine in CH_2Cl_2 instead of Et_3N and Et_2O in the preparation of the thioester.

33) could be oxidized by Pr_4NRuO_4 in 21% yield (or 28%, after correction for recovered starting material). This alcohol was inert to the Dess−Martin reagent. Thus, the total yield of ketone **35** is about 39%. Comparison of the ^{1}H NMR spectra of the two alcohols with those of the model compounds **23a** and **23b** suggests[36] that, once again, the less polar isomer has the hydroxyl and angular hydrogen syn, but we did not establish the reasons—steric or stereoelectronic—for the different behaviors of the two compounds toward oxidizing agents.[37]

Ketone **35** was converted into a 4.3:1 (^{1}H NMR) mixture of separable oximes **1** and **36**. The major isomer (81% yield) proved to have the natural *E* geometry. When the minor isomer (13% yield) was stored for 2 days in $CDCl_3$, it was converted into a mixture of the (*E*)- and (*Z*)-oximes, which were isolated in yields of 44% and 42%, respectively. Our racemic brevioxime was crystalline, and its spectral properties were identical (within experimental error) with reported[2] values.

The above route illustrates the utility of the cyclization of an amide nitrogen onto an aldehyde carbonyl for generating certain nitrogen heterocycles. The method we have used is convergent and is clearly suitable the synthesis of analogues.

Experimental Section

General Procedures. Unless stated to the contrary, the general procedures used previously[38] were followed. The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively.

***N*-[4-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]butyl]-2-methyl-3-oxobutanamide (12).** A cold (−78 °C) solution of *β*-keto acid **11**[11] (310 mg, 2.66 mmol) in dry CH_2Cl_2 (0.50 mL) was added dropwise (ca. 5 min) to a stirred and cooled (−78 °C) solution of the *O*-protected amino alcohol **10**[10] (300 mg, 1.48 mmol), DCC (335 mg, 1.62 mmol) and DMAP (30 mg, 0.24 mmol) in dry CH_2Cl_2 (1 mL). Stirring was continued overnight, but the cold bath was not recharged. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (2 × 22 cm), using 1:1 EtOAc−hexanes, gave **12** (411 mg, 92%) as a colorless oil: FTIR ($CDCl_3$ cast) 3500−3150, 1724, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 0.04 (s, 6 H), 0.88 (s, 9 H), 1.37 (d, *J* = 7.0 Hz, 3 H), 1.47−1.60 (m, 4 H), 2.23 (s, 3 H), 3.20−3.30 (m, 2 H), 3.36 (q, *J* = 7.2 Hz, 1 H), 3.62 (t, *J* = 5.9 Hz, 2 H), 6.28 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) *δ* −5.3 (q′), 14.7 (q′), 18.4 (s′), 26.0 (q′), 26.1 (t′), 28.6 (q′), 30.0 (t′), 39.5 (d′), 55.1 (t′), 62.7 (t′), 169.3 (s′), 207.6 (s′); exact mass *m*/*z* calcd for $C_{15}H_{31}NO_3Si$ 301.2073, found 301.2074. This experiment was done several times; the yields varied between 67% and 92%.

***N*-[4-Hydroxybutyl]-2-methyl-3-oxobutanamide (13).** Bu_4NF (1.0 M in THF, 0.81 mL, 0.81 mmol) was added to a stirred solution of *β*-keto amide **12** (222 mg, 0.74 mmol) and glacial AcOH (0.09 mL, 1.47 mmol) in dry THF (2.50 mL). The mixture was warmed to 45 °C (oil bath) for 14 h and then evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:9 MeOH−Et_2O, gave **13** (110 mg, 80%) as a colorless oil: FTIR ($CDCl_3$ cast) 3650−3150, 1720, 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 1.37 (d, *J* = 7.3 Hz, 3 H), 1.54−1.66 (m, 4 H), 2.24 (s, 3 H), 2.20−2.28 (br s, 1 H), 3.22−3.32 (m, 2 H), 3.38 (q, *J* = 7.2 Hz, 1 H), 3.66 (t, *J* = 5.8 Hz, 2 H), 6.54 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) *δ* 14.7 (q′), 26.1 (t′), 28.6 (q′), 29.7 (t′), 39.4 (t′), 55.0 (d′), 62.3 (t′), 169.6 (s′), 207.7 (s′); exact mass *m*/*z* calcd for $C_9H_{17}NO_3$ 187.1209, found 187.1212.

6,7,8,8a-Tetrahydro-2,3-dimethyl-4*H*-pyrrolo[2,1-*b*][1,3]-oxazin-4-one (14). *N*-Methylmorpholine *N*-oxide (24.0 mg, 0.20 mmol), Pr_4NRuO_4 (2.4 mg, 0.007 mmol), and crushed 4 Å molecular sieves (68 mg) were added to a stirred solution of alcohol **13** (25.5 mg, 0.14 mmol) in dry CH_2Cl_2 (0.8 mL). Stirring was continued for 2 h, and the mixture was then loaded onto a silica gel column (0.8 × 14 cm). Flash chromatography, using 99:1 EtOAc−hexanes, gave **14** (8.2 mg, 33%) as an unstable, colorless oil: FTIR ($CDCl_3$ cast) 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) *δ* 1.80 (s, 3 H), 1.81−1.92 (m, 1 H), 1.93 (s, 3 H), 1.94−2.16 (m, 2 H), 2.22−2.35 (m, 1 H), 3.38−3.48 (m, 1 H), 3.70−3.78 (m, 1 H), 5.24 (t, *J* = 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) *δ* 10.3 (q′), 16.7 (q′), 21.9 (t′), 31.6 (t′), 44.3 (t′), 87.4 (d′), 106.6 (s′), 160.2 (s′) (one of the olefinic signals was not observed); exact mass *m*/*z* calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0946.

1,1-Dimethoxy-2,3-epoxypropane (17). The method[17] for the corresponding diethyl acetal was followed. Ice-cold HOCl[39] (79.0 mL) was added in three portions to a stirred and cooled (0 °C) emulsion of acrolein dimethyl acetal (**16**) (7.36 g, 72.06 mmol) in water (30.0 mL). The temperature of the mixture was kept below 14 °C, and cooling and stirring were continued for 25 min after the end of the addition. The cold bath was removed, and $NaHCO_3$ (4.5 g, 42.4 mmol) and 1 M aqueous $Na_2S_2O_3$ (3.0 mL, 3.0 mmol) were added to the mixture, which was then saturated with NaCl and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the crude chlorohydrin, which was used directly in the next step.

Powdered NaOH (5.50 g, 137.5 mmol) was tipped into a stirred solution of the crude chlorohydrin in dry PhH (80.0 mL) (protection from moisture by $CaSO_4$ guard tube). The mixture was refluxed for 30 min, removed from the oil bath, stirred for 1 h, and filtered. Spinning band distillation of the filtrate gave **17** (6.171 g, 72%) as a pale yellow oil: FTIR ($CDCl_3$ cast) 2998, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 2.71−2.79 (m, 2 H), 3.04−3.10 (m, 1 H), 3.40 (s, 3 H), 3.42 (s, 3 H), 4.23 (d, *J* = 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) *δ* 43.6 (t′), 51.2 (d′ or q′), 53.8 (d′ or q′), 54.5 (d′ or q′), 103.0 (d′); exact mass *m*/*z* calcd for $C_5H_9O_3$ (M − H) 117.0552, found 117.0553.

3-Hydroxy-4,4-dimethoxybutanenitrile (18). A solution of KCN (414 mg, 6.36 mmol) in water (4 mL) was added to a stirred solution of epoxide **17** (501 mg, 4.24 mmol) in EtOH (10 mL).[18] Stirring was continued for 24 h, by which time all the starting material had reacted (TLC control, silica, 1:3 EtOAc−hexanes). The solvent was evaporated and the residue was filtered through a pad (5 × 4 cm) of silica gel, using CH_2Cl_2. Evaporation of the filtrate gave **18** (469 mg, 76%) as a thick, colorless oil: FTIR (neat film) 3700−3200, 2252 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 2.49−2.68 (m, 2 H), 3.10 (br s, 1 H), 3.45 (s, 3 H), 3.46 (s, 3 H), 3.83−3.86 (m, 1 H), 4.25 (d, *J* = 5.6, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) *δ* 20.8 (t′), 55.2 (q′), 56.1 (q′), 67.5 (d′), 105.4 (d′), 117.6 (s′); exact mass *m*/*z* calcd for $C_6H_{10}NO_3$ 144.0661 (M − H), found 144.0660.

3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4-dimethoxybutanenitrile (19). *t*-$BuMe_2SiCl$ (2.252 g, 14.9 mmol) and DMAP (36.5 mg, 0.30 mmol) were tipped into a stirred and cooled (0 °C) solution of nitrile **18** (1.083 g, 7.469 mmol) and Et_3N (1.35 mL, 10.4 mmol) in dry CH_2Cl_2 (15 mL). Stirring at 0 °C was continued for 15 min; the mixture was warmed to room temperature and was then refluxed for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 × 20 cm), using 1:3 EtOAc−hexanes, gave **19** (1.272 g, 65% (or 81%, after correction for recovered **18** (0.214 g)) as a colorless oil: FTIR ($CDCl_3$ cast) 2250 cm^{-1}; ^{1}H NMR

(36) The characteristic signals are as follows: **23a**, *δ* 5.07 (d, *J* = 3.8 Hz, 1 H); **23b**, *δ* 5.24 (d, *J* = 3.5 Hz, 1 H); **34a**, *δ* 5.03 (d, *J* = 3.7 Hz, 1 H); **34b**, *δ* 5.20 (d, *J* = 3.5 Hz, 1 H).

(37) (a) Mechanistic studies of oxidations with TPAP: Tony, K. J.; Mahadevan, V.; Rajaram, J.; Swamy, C. S. *React. Kinet. Catal. Lett.* **1997**, *62*, 105−116. (b) Lee, D. G.; Congson, L. N. *Can. J. Chem.* **1990**, *68*, 1774−1779. (c) Mechanistic studies on the Dess−Martin reagent: De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272−9279 and references quoted therein.

(38) Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426−7437.

(39) Footnote 8 in: Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1980**, *21*, 1117−1120.

($CDCl_3$, 360 MHz) δ 0.12 (s, 3 H), 0.15 (s, 3 H), 0.92 (s, 9 H), 2.50−2.63 (m, 2 H), 3.45 (s, 3 H), 3.48 (s, 3 H), 3.87 (q, J = 4.7 Hz, 1 H), 4.19 (d, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.5 MHz) δ −5.0 (q′), −4.6 (q′), 18.0 (s′), 21.8 (t′), 25.6 (q′), 56.5 (q′), 56.6 (q′), 69.8 (d′), 106.7 (d′), 118.0 (s′); exact mass (HR electrospray) m/z calcd for $C_{12}H_{25}NNaO_3Si$ 282.1501, found 282.1496.

3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4-dimethoxybutanamine Hydrochloride (20). Adam's catalyst (82 mg) was suspended in dry EtOH (40 mL, distilled from Mg/I_2), and a solution of nitrile **19** (934 mg, 3.60 mmol) in dry EtOH (10 mL) was added to the suspension, followed by bench $CHCl_3$ (1.85 mL). The mixture was shaken under H_2 (50 psi, Parr bottle) at room temperature for 24 h. The catalyst was filtered off, and the filtrate was evaporated. The residue was kept under oil-pump vacuum for 24 h to give **20** (1.08 g, 100%). Recrystallization from CH_2Cl_2−petroleum ether (bp 60−70 °C) gave **20** as white flakes in quantitative yield. The following data were obtained for the material: mp 118−122 °C; FTIR (USCOPE) 3460, 3300−2500, 2049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.10 (s, 3 H), 0.11 (s, 3 H), 0.89 (s, 9 H), 1.72 (br s, 2 H), 1.93−2.14 (m, 2 H), 3.10−3.23 (m, 2 H), 3.44 (s, 3 H), 3.52 (s, 3 H), 3.87 (q, J = 4.3 Hz, 1 H), 4.18 (d, J = 3.9 Hz, 1 H), 8.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −4.7 (q′), 18.0 (s′), 25.8 (q′), 29.4 (t′), 36.0 (t′), 56.4 (q′), 57.4 (q′), 71.0 (d′), 107.6 (d′); exact mass (HR electrospray) m/z calcd for $C_{12}H_{30}NO_3Si$ 264.1995, found 264.1990.

The yield in this experiment varied between 60% and 75%. In the above case, the recovered catalyst appeared to be very active and burned on exposure to air.

***N*-[3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4-dimethoxybutyl]-2-methyl-3-oxobutanamide (22).** Et_3N (0.26 mL, 1.88 mmol) was added to a stirred solution of amine hydrochloride **20** (282 mg, 0.94 mmol) and thioester **21**[22] (177 mg, 0.94 mmol) in dry THF (2 mL). $AgOSO_2CF_3$ (488 mg, 1.88 mmol) was tipped into the mixture. After 40 min, the reaction was complete (TLC control, silica, 1:1 EtOAc−hexanes). The brown mixture was poured into a small volume of hexanes above a column of silica gel (2 × 15 cm), and the column was developed in the standard manner for flash chromatography, using 1:1 EtOAc−hexanes, to give **22** (251 mg, 79%) as a pale yellow oil: FTIR ($CDCl_3$ cast) 3500−3150, 1722, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 1.36 (d, J = 7 Hz, 3 H), 1.68−1.83 (m, 2 H), 2.22 (s, 3 H), 3.28−3.38 (m, 3 H), 3.42 (d, J = 0.6 Hz, 3 H), 3.44 (d, J = 0.7 Hz, 3 H), 3.70−3.76 (m, 1 H), 4.15 (dd, J = 7.0, 0.7 Hz, 1 H), 6.45 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) (mixture of rotamers) δ −4.9 (q′), −5.0 (q′), 14.2 (q′), 14.3 (q′), 18.1 (s′), 25.8 (q′), 28.35 (q′), 28.39 (q′), 31.5 (t′), 36.1 (t′), 55.25 (q′), 55.30 (q′), 56.0 (q′), 56.2 (q′), 71.68 (d′), 71.73 (d′), 107.6 (d′), 169.1 (s′), 169.2 (s′), 207.0 (s′); exact mass (HR electrospray) m/z calcd for $C_{17}H_{35}NNaO_5Si$ 384.2182, found 384.2187.

(8α,8aα)-6,7,8,8a-Tetrahydro-8-hydroxy-2,3-dimethyl-4*H*-pyrrolo[2,1-*b*][1,3]oxazin-4-one (23a) and (8α,8a*β*)-6,7,8,8a-Tetrahydro-8-hydroxy-2,3-dimethyl-4*H*-pyrrolo-[2,1-*b*][1,3]oxazin-4-one (23b). Aqueous TFA (50%, 2.0 mL) was added to a stirred solution of β-keto amide **22** (187.5 mg, 0.518 mmol) in $CHCl_3$ (4 mL). Stirring was continued for 48 h, and the solvent was then evaporated. The residue was kept under oil-pump vacuum for 24 h, after which time a white solid was obtained. Flash chromatography over silica gel (1.2 × 20 cm), using 1:1 EtOAc−Et_2O and then 2:9:9 MeOH−EtOAc−Et_2O, gave the less polar isomer **23a** (38.4 mg, 37%) and the more polar isomer **23b** (36.3 mg, 35%) as white crystalline solids. The following data were obtained for compound **23a**: mp 104−106 °C; FTIR ($CDCl_3$ cast) 3600−3100, 1645, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (d, J = 0.5 Hz, 3 H), 1.87−1.98 (m, 1 H), 1.95 (d, J = 0.6 Hz, 3 H), 2.21−2.29 (m, 2 H), 3.59−3.71 (m, 2 H), 4.45−4.52 (m, 1 H), 5.07 (d, J = 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.2 (q′), 16.7 (q′), 30.0 (t′), 41.7 (t′), 75.3 (d′), 92.1 (d′), 106.7 (s′), 159.8 (s′), 163.1 (s′); exact mass m/z calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0897.

The following data were obtained for compound **23b**: mp 118−120 °C; FTIR ($CDCl_3$ cast) 3600−3100, 1651, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (d, J = 0.8 Hz, 3 H), 1.94−2.14 (m including d at δ 1.98 (J = 0.9 Hz), 5 H in all), 2.44−2.48 (m, 1 H), 3.52−3.60 (m, 1 H), 3.68−3.78 (m, 1 H), 4.42−4.47 (m, 1 H), 5.24 (d, J = 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.2 (q′), 16.8 (q′), 29.3 (t′), 41.7 (t′), 70.6 (d′), 87.6 (d′), 106.9 (s′), 159.0 (s′), 162.9 (s′); exact mass m/z calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0896.

6,7-Dihydro-2,3-dimethyl-4*H*-pyrrolo[2,1-*b*][1,3]oxazine-4,8(8a*H*)-dione (24) from Less Polar Alcohol. Dess−Martin periodinane (17.8 mg, 0.04 mmol) was added to a solution of the less polar isomer **23a** (5.9 mg, 0.032 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred for 2 h and then applied directly to a silica gel column (0.8 × 13 cm) made up with 99:1 EtOAc−hexanes. Flash chromatography, using the same solvent, gave **24** (2.5 mg, 42%) as a colorless oil: FTIR ($CDCl_3$ cast) 1772, 1659 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.79 (d, J = 0.8 Hz, 3 H), 2.00 (d, J = 0.9 Hz, 3 H), 2.60−2.78 (m, 2 H), 3.52−3.62 (m, 1 H), 4.00−4.10 (m, 1 H), 5.06 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 10.3 (q′), 16.9 (q′), 34.1 (t′), 38.3 (t′), 82.2 (d′), 107.5 (s′), 160.0 (s′), 163.4 (s′), 204.9 (s′); exact mass m/z calcd for $C_9H_{11}NO_3$ 181.0739, found 181.0738.

6,7-Dihydro-2,3-dimethyl-4*H*-pyrrolo[2,1-*b*][1,3]oxazine-4,8(8a*H*)-dione (24) from More Polar Alcohol. *N*-Methylmorpholine *N*-oxide (8.64 mg, 0.074 mmol), Pr_4NRuO_4 (0.9 mg, 0.0026 mmol), and crushed 4 Å molecular sieves (25 mg) were added in succession to a stirred solution of the more polar isomer **23b** (9.0 mg, 0.049 mmol) in dry 1:1 CH_2Cl_2−MeCN (0.5 mL). Stirring was continued for 1.5 h, and the mixture was then loaded onto a silica gel column (0.8 × 14 cm) made up with 99:1 EtOAc−hexanes. Flash chromatography, using the same solvent, gave **24** (4.2 mg, 46% or 84% after correction for recovered starting material (4.0 mg)) as a colorless oil, spectroscopically identical with the compound obtained from the other isomer.

6,7-Dihydro-2,3-dimethyl-4*H*-pyrrolo[2,1-*b*][1,3]oxazine-4,8(8a*H*)-dione 8-Oxime (15a,b). A solution of $NH_2OH\cdot HCl$ (8.8 mg, 0.127 mmol) and AcONa (17.6 mg, 0.129 mmol) in water (0.2 mL) was added to a stirred solution of ketone **24** (4.4 mg, 0.024 mmol) in EtOH (0.2 mL). Stirring was continued for 3.5 h, and the solvent was then evaporated. Flash chromatography of the residue over silica gel (0.8 × 20 cm), using 99:1 EtOAc−hexanes, gave the less polar (*E*)-oxime **15a** (3.5 mg, 74%) and the more polar (*Z*)-oxime **15b** (0.3 mg, 6.3%) as white solids. The following data were obtained for compound **15a**: mp 176−178 °C, the compound then solidifies but does not melt again; FTIR (CH_2Cl_2 cast) 3600−2950, 1643 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.79 (d, J = 0.8 Hz, 3 H), 1.98 (d, J = 0.9 Hz, 3 H), 2.74−2.98 (m, 2 H), 3.41−3.50 (m, 1 H), 3.94−4.04 (m, 1 H), 5.59 (d, J = 1.5 Hz, 1 H), 8.40 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 10.3 (q′), 16.9 (q′), 23.9 (t′), 41.9 (t′), 84.5 (d′), 107.4 (s′), 158.3 (s′), 160.7 (s′), 163.3 (s′); exact mass m/z calcd for $C_9H_{12}N_2O_3$ 196.0848, found 196.0843.

The following data were obtained for compound **15b**: FTIR (CD_2Cl_2 cast) 3500−3000, 1640 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.78 (d, J = 0.9 Hz, 3 H), 1.98 (d, J = 0.8 Hz, 3 H), 2.62−2.71 (m, 1 H), 2.78−2.90 (m, 1 H), 3.26−3.34 (m, 1 H), 4.00−4.08 (m, 1 H), 5.87 (d, J = 1.4 Hz, 1 H), 7.56 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 10.4, 17.0, 27.4, 41.7, 80.1, 107.2, 157.5, 160.5, 162.8; exact mass m/z calcd for $C_9H_{12}N_2O_3$ 196.0848, found 196.0849. The melting point was not measured.

(*E*)-4-Hexenol (25).[28] Freshly cut Na (2.43 g, 105 mmol) was powdered by heating in xylenes (dried over 4 Å molecular sieves, 75 mL) at 120 °C with stirring. The resulting suspension was cooled, and the Na powder was washed with dry Et_2O under N_2 and then covered with dry Et_2O (20 mL). A few drops of a solution of 3-chloro-2-methyltetrahydropyran[28b,c] (*Caution!* hazard warning) (6.00 g, 42.3 mmol) in dry Et_2O (20 mL) was added to the Na with vigorous magnetic stirring. After a few minutes, a vigorous reaction occurred and a purple mixture was formed. The remaining pyran solution was added at such a rate as to maintain gentle reflux. The blue mixture was left for 28 h at room temperature, and the excess Na was carefully destroyed (N_2 atmosphere) with wet Et_2O, followed by water. The ether layer was separated, and the aqueous layer was

extracted with Et_2O. The combined organic extracts were washed successively with 5% aqueous HCl (50 mL) and brine and then dried ($MgSO_4$). The solvent was removed by distillation at 1 atm, and the oily residue was distilled to yield **25** (3.99 g, 94%) as a 95:5 mixture of *E* and *Z* isomers, bp 85−90 °C (water-pump vacuum). Spinning band distillation at 158−159 °C (1 atm) gave pure (GC-MS) (*E*)-4-hexenol as a colorless liquid in 20% yield: FTIR (neat film) 3600−3100 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56−1.66 (m containing d at δ 1.63 (J = 6.2 Hz), 5 H in all), 1.90 (s, 1 H), 2.01−2.09 (m, 2 H), 3.61 (t, J = 6.5 Hz, 2 H), 5.37−5.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.8 (q′), 28.8 (t′), 32.4 (t′), 62.4 (t′), 125.4 (d′), 130.6 (d′); exact mass *m*/*z* calcd for $C_6H_{12}O$ 100.0888, found 100.0887.

Methanesulfonic Acid (*E*)-4-Hexenyl Ester (26).[29] $MeSO_2Cl$ (1.81 mL, 23.3 mmol) was added dropwise to a stirred and cooled (0 °C) solution of (*E*)-4-hexenol (**25**; 1.915 g, 19.2 mmol) and Et_3N (3.33 mL, 23.2 mmol) in dry THF (40.0 mL). Stirring at 0 °C was continued for 40 min, the cold bath was removed, and stirring was continued for 30 min. The mixture was quenched with water (25 mL) and diluted with CH_2Cl_2 (100 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude **26** (3.409 g, 100%) as a pale yellow oil, suitable for the next step. Pure mesylate, obtained by flash chromatography over silica gel (3.5 × 16 cm) using 1:4 EtOAc−hexanes, had the following data: FTIR ($CDCl_3$ cast) 1352, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.63 (dq, J = 5.6, 1.1, 1.1 Hz, 3 H), 1.78 (quintet, J = 6.9 Hz, 2 H), 2.08 (q, J = 7.0 Hz, 2 H), 2.98 (d, J = 0.9 Hz, 3 H), 4.19 (t, J = 6.5 Hz, 2 H), 5.31−5.41 (m, 1 H), 5.42−5.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.8 (q′), 28.2 (t′), 28.8 (t′), 37.3 (q′), 69.5 (t′), 126.6 (d′), 129.1 (d′); exact mass *m*/*z* calcd for $C_7H_{14}O_3S$ 178.0664, found 178.0663.

(*E*)-6-Bromo-2-hexene (27).[29] Anhydrous LiBr (dried overnight at 110 °C under oil-pump vacuum; 2.94 g, 33.8 mmol) was tipped into a stirred solution of crude mesylate **26** (2.008 g, 11.28 mmol) in dry THF (40.0 mL). The resulting solution was refluxed for 3.5 h, by which time all starting material had been consumed (TLC control, silica gel, 1:4 EtOAc−hexanes). The mixture was cooled and added to pentane (200 mL), washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled to give **27** (1.605 g), as a colorless, acrid liquid: bp 165 °C (760 mmHg); FTIR ($CDCl_3$ cast) 1779, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (dq, J = 6.3, 1.3, 1.3 Hz, 3 H), 1.90 (quintet, J = 6.9 Hz, 2 H), 2.10−2.70 (m, 2 H), 3.40 (t, J = 6.8 Hz, 2 H), 5.32−5.42 (m, 1 H), 5.45−5.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.9 (q′), 30.9 (t′), 32.5 (t′), 33.3 (t′), 126.4 (d′), 129.2 (d′); exact mass *m*/*z* calcd for $C_6H_{11}{}^{79}Br$ 162.00446, found 162.0044.

Diethyl (*E*)-2-[4-Hexenyl]propanedioate (28).[30,31] (*E*)-6-Bromo-2-hexene (**27**; 1.515 g, 9.30 mmol) in dry EtOH (5.0 mL) was added dropwise to a stirred solution of $NaCH(CO_2Et)_2$ (prepared from $CH_2(CO_2Et)_2$ (1.53 mL, 11.2 mmol) and Na (257 mg, 11.6 mmol) in dry EtOH (6.0 mL) at 50 °C). The resulting mixture was refluxed under Ar for 3 h and then cooled. Most of the solvent was evaporated, and the residue was taken up in pentane (100 mL), washed with water, dried ($MgSO_4$), evaporated, and fractionally distilled to give **28** (1.636 g, 72%) as a colorless oil: bp 172 °C (water-pump vacuum); FTIR ($CDCl_3$ cast) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.24 (t, J = 7.2 Hz, 6 H), 1.31−1.40 (m, 2 H), 1.61 (d, J = 4.8 Hz, 3 H), 1.87 (q, J = 7.9 Hz, 2 H), 1.94−2.02 (m, 2 H), 3.29 (t, J = 7.6 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 4 H), 5.30−5.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.1 (q′), 17.9 (q′), 27.2 (t′), 28.2 (t′), 32.1 (t′), 51.9 (d′), 61.2 (t′), 125.5 (d′), 130.5 (d′), 169.5 (s′); exact mass *m*/*z* calcd for $C_{13}H_{22}O_4$ 242.1518, found 242.1516.

(*E*)-2-[4-Hexenyl]propanedioic Acid (29).[31] Diethyl (*E*)-2-[4-hexenyl]propanedioate (**28**; 1.64 g, 6.76 mmol) was added to a stirred and cooled (0 °C) solution of KOH (1.51 g, 27.3 mmol) in water (26 mL), followed by sufficient EtOH (12 mL) to produce homogeneity. After 24 h, the solution was washed with CH_2Cl_2 and the aqueous layer was cooled (0 °C) and acidified to pH ca. 2 (universal indicator) with concentrated HCl. The precipitated diacid **29** was extracted with Et_2O, and the combined extracts were dried ($MgSO_4$) and evaporated to give crude **29** (1.248 g, 99%), which was recrystallized from PhH to give pure **29** (739 mg, 59% recovery) as a white solid: mp 110−112 °C (lit.[31] mp 115−116 °C); FTIR (USCOPE) 3400−2400, 1709 cm^{-1}; ^1H NMR (DMSO-d_6, 360 MHz) δ 1.40−1.51 (m, 2 H), 1.65 (d, J = 5.5 Hz, 3 H), 1.95 (q, J = 7.8 Hz, 2 H), 2.03 (q, J = 6.6 Hz, 2 H), 3.44 (t, J = 7.4 Hz, 1 H), 5.33−5.51 (m, 2 H), 10.3−11.0 (br s, 2 H); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 17.7 (q′), 26.7 (t′), 27.9 (t′), 31.7 (t′), 51.4 (d′), 124.8 (d′), 130.8 (d′), 170.9 (s′); exact mass *m*/*z* calcd for $C_9H_{14}O_4$ 186.0892, found 186.0888.

(*E*)-6-Octenoic Acid (30).[31] A round-bottomed 50 mL flask containing (*E*)-2-[4-hexenyl]propanedioic acid (**29**; 943 mg, 5.07 mmol) was lowered into a preheated (155−160 °C) oil bath. After 5.5 h, the flask was cooled and its contents were dissolved in saturated aqueous $NaHCO_3$ (15 mL). The resulting solution was washed with Et_2O, and the aqueous layer was acidified with concentrated HCl. The precipitated acid was extracted with Et_2O, and the combined extracts were dried ($MgSO_4$) and evaporated to give the crude acid. Flash chromatography over silica gel (2 × 20 cm), using 1:1 Et_2O−hexanes, gave **30** (676 mg, 93%) as a colorless oil: FTIR ($CDCl_3$ cast) 3600−2300, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35−1.48 (m, 2 H), 1.58−1.68 (m, 5 H), 1.96−2.04 (m, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 5.33−5.50 (m, 2 H) (acidic H not observed); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.9 (q′), 24.1 (t′), 28.9 (t′), 32.1 (t′), 33.8 (t′), 125.3 (d′), 130.8 (d′), 179.5 (s′); exact mass *m*/*z* calcd for $C_8H_{14}O_2$ 142.0994, found 142.0991.

***S*-1,1-Dimethylethyl (*E*)-2-Methyl-3-oxo-8-decenethioate (32).** 1,1′-Carbonyldiimidazole (293 mg, 1.81 mmol) was tipped into a stirred and cooled (0 °C) solution of (*E*)-6-octenoic acid (**30**; 233 mg, 1.64 mmol) in dry THF (0.8 mL). Brisk evolution of gas occurred. When the reaction had subsided, the cold bath was removed and stirring was continued for 30 min.

In the meantime the lithium enolate of thioester **31**[35] was prepared by slow addition of LDA (made by dropwise addition of BuLi (2.5 M in hexanes, 1.97 mL, 4.92 mmol) to *i*-Pr_2NH (0.69 mL, 4.92 mmol) in dry THF (1.0 mL) at −78 °C, followed by warming to 0 °C (transfer to an ice bath) for 5 min, and recooling to −78 °C) to a stirred and cooled (−78 °C) solution of **31** (719 mg, 4.92 mmol) in THF (1 mL). After 15 min a yellow solution was obtained.

The imidazolide solution made in the first part of this experiment was cooled to −78 °C and transferred by cannula over 10 min into the stirred and cooled (−78 °C) enolate solution. Stirring at −78 °C was continued for 30 min, the cold bath was removed, and stirring was continued for a further 5 min. The reaction was quenched with saturated aqueous NH_4Cl (2 mL), and the mixture was diluted with Et_2O (30 mL). The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and evaporated to give a yellow oil. Flash chromatography over silica gel (2 × 24 cm), using 1:24 Et_2O−petroleum ether (bp 60−70 °C), gave **32** (287.2 mg, 64%) as a colorless oil: FTIR ($CDCl_3$ cast) 1725, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.28−1.37 (m, containing d at δ 1.31 (J = 7.0 Hz), 5 H in all), 1.47 (s, 9 H), 1.51−1.63 (m, 2 H), 1.63 (d, J = 4.6 Hz, 3 H), 1.92−2.02 (m, 2 H), 2.41−2.62 (m, 2 H), 3.64 (q, J = 7.0 Hz, 1 H), 5.32−5.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.5 (q′), 17.9 (q′), 23.1 (t′), 28.9 (t′), 29.6 (q′), 32.2 (t′), 41.1 (t′), 48.8 (s′), 62.1 (d′), 125.1 (d′), 130.9 (d′), 197.1 (s′), 204.9 (s′); exact mass *m*/*z* calcd for $C_{15}H_{26}O_2S$ 270.1653, found 270.1645.

(*E*)-*N*-[3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-4,4-dimethoxybutyl]-2-methyl-3-oxo-8-decenamide (33). $AgOSO_2CF_3$ (224 mg, 0.864 mmol) was tipped into a stirred mixture of amine hydrochloride **20** (129 mg, 0.432 mmol), dry Et_3N (0.12 mL, 0.864 mmol), and β-keto thioester **32** (116.6 mg, 0.432 mmol) in dry THF (5 mL). The reaction was over in ca. 20 min (TLC control, silica, 1:1 EtOAc−hexanes). The mixture was loaded onto a dry silica gel column (2 × 18 cm) and flash chromatography, using 1:1 EtOAc−hexanes, gave **33** (147.4 mg, 90%) as a thick, pale yellow oil: FTIR ($CDCl_3$ cast) 3450−3150, 1720, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 1.24−1.33 (m, 2 H),

1.35 (dd, J = 7.1, 0.6 Hz, 3 H), 1.52−1.61 (m, 2 H), 1.63 (dt, J = 3.4, 1.3 Hz, 3 H), 1.67−1.83 (m, 2 H), 1.94−1.99 (m, 2 H), 2.47−2.61 (m, 2 H), 3.31−3.40 (m, 3 H), 3.43 (s, 3 H), 3.44 (d, J = 1.3 Hz, 3 H), 3.72 (ddd, J = 6.3, 4.9, 1.4 Hz, 1 H), 4.12 (d, J = 4.8 Hz, 1 H), 5.34−5.46 (m, 2 H), 6.47 (d, J = 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (mixture of rotamers) δ −4.8 (q′), −4.5 (q′), 14.7 (q′), 14.8 (q′), 17.9 (q′), 18.2 (s′), 22.9 (t′), 25.9 (q′), 28.9 (t′), 31.7 (t′), 32.3 (t′), 36.1 (t′), 41.26 (t′), 41.29 (t′), 54.58 (q′), 54.64 (q′), 55.94 (d′), 56.2 (q′), 71.66 (d′), 71.71 (d′), 107.6 (d′), 125.2 (d′), 130.9 (d′), 126.29 (s′), 169.35 (s′), 209.4 (s′); exact mass m/z calcd for $C_{23}H_{45}NO_5Si$ 443.3067, found 443.3060.

(*E*)-2-(5-Heptenyl)-6,7,8,8a-tetrahydro-8-hydroxy-3-methyl-4*H*-pyrrolo[2,1-*b*][1,3]oxazin-4-one (34a,b). Aqueous TFA (50%, 1.0 mL) was added to a stirred solution of β-keto amide **33** (224 mg, 0.50 mmol) in $CHCl_3$ (2 mL). Stirring was continued for 36 h, by which time the starting material had been consumed (TLC control, silica, 1:1 EtOAc−hexanes). The solvent was evaporated, and the residue was left under oil-pump vacuum for 24 h, to obtain a mixture of diastereoisomers **34a**,**b** (133.5 mg, ca. 100%) as a white solid. Flash chromatography over silica gel (2 × 20 cm), using 1:24 MeOH−Et_2O, gave the less polar diastereoisomer **34a** (61.4 mg, 45%) and the more polar diastereoisomer **34b** (56.4 mg, 42%) as colorless liquids. The following data were obtained for compound **34a**: FTIR ($CDCl_3$ cast) 3600−3100, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30−1.43 (m, 2 H), 1.53 (quintet, J = 7.6 Hz, 2 H), 1.61−1.66 (m, 3 H), 1.78 (s, 3 H), 1.87−2.01 (m, 3 H), 2.15−2.33 (m, 3 H), 2.97 (br s, 1 H), 3.56−3.71 (m, 2 H), 4.42−4.46 (m, 1 H), 5.03 (d, J = 3.7 Hz, 1 H), 5.35−5.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.0 (q′), 17.9 (q′), 26.3 (t′), 29.1 (t′), 30.1 (t′), 30.5 (t′), 32.2 (t′), 41.8 (t′), 75.2 (d′), 92.3 (d′), 106.4 (s′), 125.2 (d′), 130.9 (d′), 163.4 (s′), 163.5 (s′); exact mass m/z calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1675.

The following data were obtained for compound **34b**: FTIR ($CDCl_3$ cast) 3600−3050, 1737, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34−1.44 (m, 2 H), 1.54 (quintet, J = 7.6 Hz, 2 H), 1.65 (d, J = 4.9 Hz, 3 H), 1.79 (s, 3 H), 1.92−2.13 (m, 4 H), 2.23 (quintet, J = 7.2 Hz, 1 H), 2.34 (quintet, J = 7.3 Hz, 1 H), 2.50 (br s, 1 H), 3.55−3.64 (m, 1 H), 3.66−3.78 (m, 1 H), 4.30−4.90 (m, 1 H), 5.20 (d, J = 3.5 Hz, 1 H), 5.33−5.49 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.0 (q′), 17.9 (q′), 26.3 (t′), 29.1 (t′), 29.3 (t′), 30.5 (t′), 32.2 (t′), 41.7 (t′), 70.6 (d′), 87.7 (d′), 106.8 (s′), 125.3 (d′), 130.8 (d′), 162.5 (s′), 163.1 (s′); exact mass m/z calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1670.

(*E*)-2-(5-Heptenyl)-6,7-dihydro-3-methyl-4*H*-pyrrolo-[2,1-*b*][1,3]oxazine-4,8(8a*H*)-dione (35) from Less Polar Alcohol. Dess−Martin periodinane (68.8 mg, 0.16 mmol) in dry CH_2Cl_2 (1 mL) was added to a stirred solution of the less polar alcohol **34a** (28.8 mg, 0.11 mmol) in dry CH_2Cl_2 (0.5 mL). Stirring was continued for 2 h (TLC control, silica, 3:1 EtOAc−hexanes), and the mixture was diluted with EtOAc (4 mL) and stirred for 5 min with saturated aqueous $NaHCO_3$ (2 mL) containing $Na_2S_2O_3$ (250 mg). More EtOAc (8 mL) was added, followed by water (4 mL). The aqueous layer was extracted with EtOAc, and the combined organic extracts were evaporated. Flash chromatography of the oily residue over silica gel (1 × 20 cm), using 3:1 EtOAc−hexanes, gave **35** (15.6 mg, 54%, or 99% after correction for recovered starting material (13.0 mg, 45%)) as a colorless liquid: FTIR ($CDCl_3$ cast) 1774, 1664 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.32−1.42 (m, 2 H), 1.51−1.61 (m, 2 H), 1.64 (d, J = 3.84 Hz, 3 H), 1.84 (s, 3 H), 1.94−2.06 (m, 2 H), 2.21−2.42 (m, 2 H), 2.62−2.83 (m, 2 H), 3.57−3.66 (m, 1 H), 4.08−4.17 (m, 1 H), 5.03 (s, 1 H), 5.32−5.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 10.0 (q′), 17.9 (q′), 26.2 (t′), 29.1 (t′), 30.5 (t′), 32.2 (t′), 33.7 (t′), 38.0 (t′), 81.7 (d′), 107.1 (s′), 125.3 (d′), 130.8 (d′), 163.3 (s′), 163.5 (s′), 204.4 (s′); exact mass m/z calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1514.

(*E*)-2-(5-Heptenyl)-6,7-dihydro-3-methyl-4*H*-pyrrolo-[2,1-*b*][1,3]oxazine-4,8(8a*H*)-dione (35) from More Polar Alcohol. *N*-Methylmorpholine *N*-oxide (12.3 mg, 0.105 mmol), Pr_4NRuO_4 (1.23 mg, 0.00350 mmol), and crushed 4 Å molecular sieves (35.0 mg) were added in succession to a stirred solution of the more polar alcohol **34b** (18.6 mg, 0.07 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred for 2 h and then loaded onto a silica gel column (1 × 15 cm) made up with 3:1 EtOAc−hexanes. Flash chromatography, using 3:1 EtOAc−hexanes, gave **35** (3.5 mg, 18% (23% after correction for recovered starting material (3.7 mg)) as a colorless liquid, spectroscopically identical with material obtained from the other isomer.

(*E*,*E*)- and (*E*,*Z*)-2-(5-Heptenyl)-6,7-dihydro-3-methyl-4*H*-pyrrolo[2,1-*b*][1,3]oxazine-4,8(8a*H*)-dione 8-Oxime (1 and 36). A solution of $H_2NOH{\cdot}HCl$ (29.9 mg, 0.43 mmol) and AcONa (60.8 mg, 0.44 mmol) in water (0.25 mL) was added to ketone **35** (22.6 mg, 0.09 mmol). EtOH (0.25 mL) was added to the mixture until turbidity disappeared, and the mixture was stirred for 3 h, by which time the starting material had been consumed (TLC control, silica, 3:1 EtOAc−hexanes). The solvent was evaporated, and the residue was washed through a silica pad (1 × 4 cm), using EtOAc (15 mL). Evaporation of the filtrate gave a mixture of oxime isomers (23.8 mg, 99%) as a pale yellow solid. Flash chromatography over silica gel (1 × 20 cm), using 3:1 EtOAc−hexanes, gave the less polar isomer **1** (17.9 mg, 74%) and the *Z* isomer **36** (4.9 mg, 20%) as white solids. The ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100.6 MHz) spectra of **1** were the same as those reported; the compound had mp 146-149 °C.

The following data were obtained for compound **36**: mp 138.5−140 °C; FTIR (CH_2Cl_2 cast) 3600−3050, 1641 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.35−1.44 (m, 2 H), 1.55−1.60 (m, 2 H), 1.63 (d, J = 3.6 Hz, 3 H), 1.78 (s, 3 H), 1.96−2.02 (m, 2 H), 2.21 (quintet, J = 7.2 Hz, 2 H), 2.67 (ddd, J = 9.1, 7.5, 1.9 Hz, 1 H), 2.79−2.90 (m, 2 H), 3.26−3.36 (m, 1 H), 3.98−4.07 (m, 1 H), 5.38−5.45 (m, 2 H), 5.81 (d, J = 1.3 Hz, 1 H), 7.66 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.1 (q′), 17.9 (q′), 26.3 (t′), 27.1 (t′), 29.0 (t′), 30.5 (t′), 32.2 (t′), 41.4 (t′), 79.8 (d′), 106.9 (s′), 125.2 (d′), 130.9 (d′), 156.9 (s′), 163.2 (s′), 164.0 (s′) (the spectrum showed a trace of the *E* isomer **1**); exact mass m/z calcd for $C_{15}H_{22}N_2O_3$ 278.1631, found 278.1624.

A sample (4.9 mg) of the (*Z*)-oxime **36** was stored for 51 h in $CDCl_3$. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 3:1 EtOAc−hexanes, gave **1** (2.2 mg, 44%) and **36** (2.1 mg, 42%).

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Supporting Information Available: Figures giving NMR spectra of **12**−**15a**,**b**, **17**−**20**, **22**−**30**, **32**−**36**, and racemic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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