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A New Method for Preparation of 3,6-Dihydro-*2H*-1,3-oxazines and Explorations of Their Use in Stereoselective Synthesis of 1,3-Amino Alcohol Derivatives

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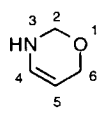
Abstract: Condensation of β-hydroxy aldehydes with *N*-sulfonyl aldimines produces 3,6-dihydro-*2H*-1,3-oxazines in moderate to excellent yields. The process is stereoselective, with the C-2 and C-6 substituents having a *trans* relationship in these heterocycles. Some transformations of these oxazines as potential acyclic 1,3-amino alcohol synthons are described.

Among the four possible dihydro-1,3-oxazine isomers, the 3,6-dihydro-*2H*-1,3-oxazine structure **1** is the rarest, and few examples of this heterocyclic ring system exist.[1,2] In addition, virtually nothing is known about the transformation chemistry of these heterocycles. During the past few years, we have been exploiting the reaction of an aldehyde with an *N*-sulfinyl sulfonamide to produce an *N*-sulfonyl imine.[3] While engaged in this work, we inadvertently found a method for synthesis of 3,6-dihydro-*2H*-1,3 oxazines, and in this paper describe some initial studies in this area.[4]



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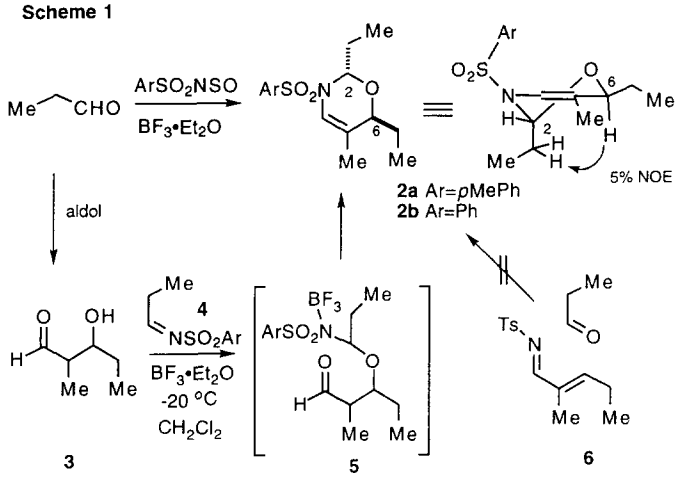
In our original experiments, it was observed that treatment of *N*-sulfinyl *p*-toluenesulfonamide with an excess of propionaldehyde and boron trifluoride etherate yielded a 1:3 adduct characterized as 3,6-dihydro-*2H*-1,3-oxazine **2a** (Scheme 1).[4b] We initially believed that this compound had probably arisen via a hetero Diels-Alder process involving the derived *N*-tosyl imine **6** of the propionaldehyde aldolization product and an equivalent of propionaldehyde. However, imine **6** was independently synthesized and it was found that this azadiene did not react under any conditions with propionaldehyde to afford oxazine **2a**.[4b]

Scheme 1



Alternatively, it seemed feasible that the dihydrooxazine could have arisen from condensation of the aldol **3** with *N*-tosyl imine **4** (Ar=*p*MePh). In fact, treatment of preformed β-hydroxyaldehyde **3**[5] with the *N*-tosyl imine [3] did afford heterocycle **2a** in good yield. 3,6-Dihydro-*2H*-1,3-oxazine **2a** proved to be a single stereoisomer which has been assigned the *trans* configuration on the basis of ^{1}H NMR NOE experiments. In particular, a significant integral enhancement was seen between the proton at C-6 and one of the diastereotopic methylene protons of the C-2 ethyl group.

We have been able to obtain an X-ray crystal structure of the closely related 3,6-dihydro-*2H*-1,3-oxazine **2b** which supports the stereochemical assignment of **2a** made by NMR methods. An ORTEP plot of 3,6-dihydrooxazine **2b** is shown in Fig. 1. It appears that the heterocyclic ring of **2b** exists in approximately a flattened "sofa" conformation, as has been previously found for the related 4*H*-1,3-dioxin system by NMR analysis.[6] In addition, the aromatic ring of the sulfonyl group is in a pseudoaxial position, thus blocking one face of the olefinic double bond contained within the dihydrooxazine ring. This unique feature of the molecule has a significant effect on the stereoselectivity of reactions at this olefinic site (*vide infra*). It might also be noted that two crystal structures recently reported by Burgess[7] and two determined by us (*vide infra*) on tetrahydro-1,3-oxazines show the same preference for a pseudoaxial *N*-arylsulfonyl moiety.

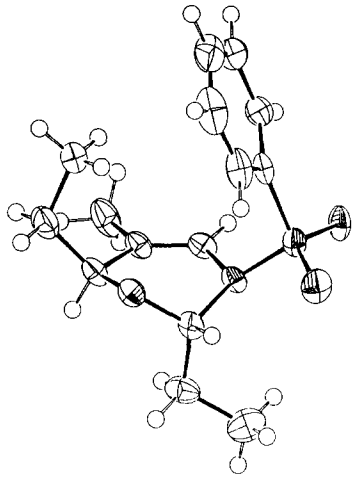
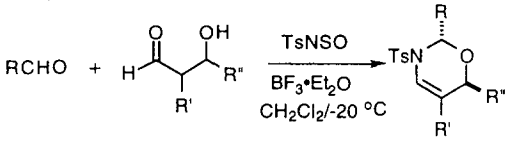


Fig 1. ORTEP drawing of 3,6-dihydrooxazine **2b**

It seems reasonable that oxazines **2a/b** are produced via intermediate **5** (Scheme 1), which one would expect to be a complex mixture of stereoisomers. The C-2,6 stereochemistry in **2a/b** is presumably set in the cyclodehydration step. The *trans* dihydrooxazine stereochemistry is probably the thermodynamically more stable one, and this configuration may be established by some type of acid catalyzed amido acetal equilibration process in the transformation of compound **5** to **2a/b**.

The condensation of a β-hydroxy aldehyde with an *N*-sulfonyl aldimine to produce a 3,6-dihydro-2*H*-

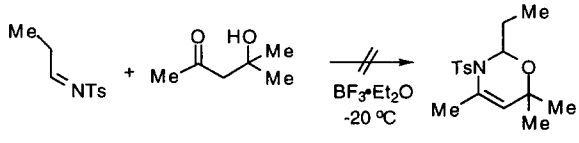
Scheme 2



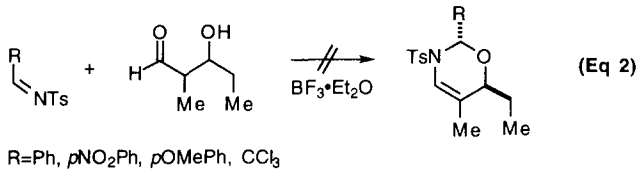
7a R=nPr, R'=Et, R"=nPr	83%
7b R=Et, R'=Et, R"=nPr	75%
7c R=Me, R'=Et, R"=nPr	73%
7d R=nPr, R'=Me, R"=Et	87%
7e R=Me, R'=Me, R"=Et	71%
7f R=nPr, R'=H, R"=Me	40%
7g R=Et, R'=H, R"=Me	51%
7h R=nPr, R'=H, R"=2-Pr	47%
7i R=nPr, R'=H, R"=n$C_{14}H_{29}$	42%

1,3-oxazine is a general one. Thus, a variety of aldols were combined with *in situ*-formed *N*-tosyl imines in moderate to excellent yields as shown in Scheme 2. In all cases, only single stereoisomers were produced, which by analogy with dihydrooxazines **2a/b** were assumed to be *trans*.

A few additional related condensations were attempted unsuccessfully. For example, the β-hydroxy ketone diacetone alcohol did not react with the *N*-tosyl imine of propionaldehyde (Eq. 1). Moreover, less reactive *N*-tosyl imines as the ones derived from benzaldehyde, *p*-nitrobenzaldehyde, *p*-anisaldehyde and chloral did not produce oxazines in this type of reaction (Eq. 2).



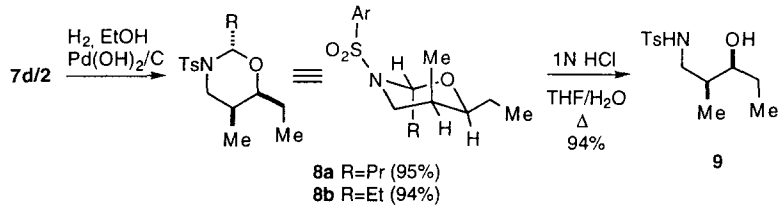
(Eq 1)



R=Ph, *p*NO_2Ph, *p*OMePh, CCl_3

We have begun to explore the possibility of utilizing these readily prepared heterocycles in stereoselective synthesis of 1,3-amino alcohols.[8] Towards this goal, catalytic hydrogenation of dihydro-1,3-oxazine **7d** (Scheme 3) was investigated and found to afford a single stereoisomeric tetrahydrooxazine in excellent yield having the stereochemistry shown in **8a**. The configuration and conformation of this reduction product was

Scheme 3

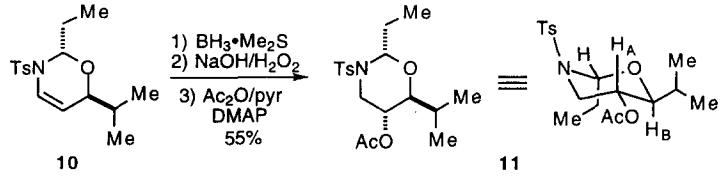


8a R=Pr (95%)
8b R=Et (94%)

established by ^{1}H NMR NOE experiments (for data, see Experimental Section). Assuming 3,6-dihydro-2*H*-1,3-oxazine **7d** has the same conformation shown for **2b** (Fig. 1), hydrogenation thus occurs from the face of the molecule opposite the large pseudoaxial arylsulfonamide moiety. The NOE data indicate that the aryl group is also pseudoaxial in the hydrogenation product, tetrahydro-1,3-oxazine **8a**. Similarly, hydrogenation of dihydrooxazine **2** afforded tetrahydrooxazine **8b**. Mild acidic hydrolysis of **8b** could be smoothly effected to provide acyclic 1,3-amino alcohol derivative **9** in high yield.

A second transformation of these oxazines which was investigated involved hydroboration of the double bond.[9] Treatment of 3,6-dihydro-2*H*-1,3-oxazine **10** with borane-dimethyl sulfide complex, followed by

Scheme 4



hydrogen peroxide, and then acetylation of the resulting alcohol, yielded acetate **11** as a single regio- and stereoisomer (Scheme 4). The stereochemistry of **11** was established by ^{1}H NMR (J_{AB}=9.5 Hz). Once again in this case, hydroboration occurs on the face of oxazine **10** opposite to the pseudoaxial tosyl group.

We have also investigated the oxidation of the ring double bond in these heterocycles. Reaction of oxazine **2a** with a catalytic amount of osmium tetraoxide and trimethylamine-N-oxide[10] was stereoselective,

affording only diol **12** (Scheme 5). The stereochemistry of this diol was firmly established by X-ray crystallography.[11] An ORTEP drawing of this compound is shown in Fig. 2. As can be seen, the arylsulfonyl

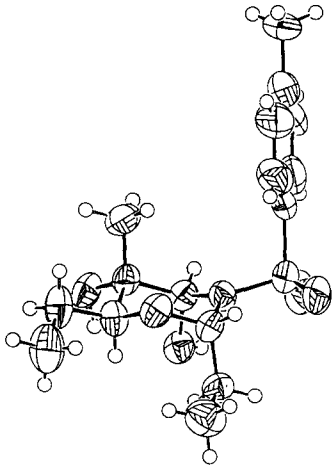
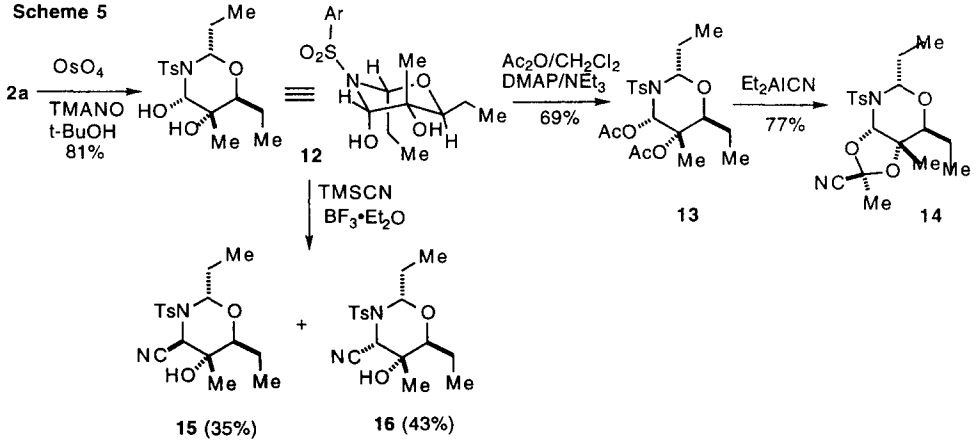


Fig 2. ORTEP drawing of tetrahydrooxazine **12**

group is in a pseudoaxial position in the molecule. This conformation and configuration was confirmed by NOE studies (see Experimental Section). The hydroxylation of oxazine **2a** by OsO_4 is consistent with the hydrogenation and hydroboration experiments described above, in that reagent attack occurs opposite to the bulky pseudoaxial tosyl group.

Some further transformations of diol **12** have also been investigated. Compound **12** could be converted to the diacetate **13** in good yield. An attempt was then made to replace the acetate group with cyano via an *N*-

Scheme 5

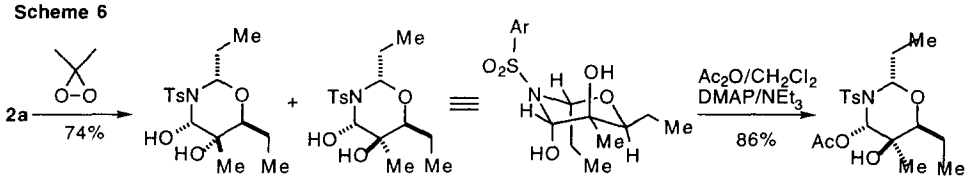


tosyl iminium ion intermediate.[12] Thus, acetate **13** was treated with diethylaluminum cyanide, but we were surprised to find only cyano acetal **14** was produced. This compound is a single stereoisomer assigned the structure indicated by NOE studies (see Experimental Section). It was found, however, that diol **12**, when

exposed to trimethylsilyl cyanide and boron trifluoride etherate gave the desired hydroxy nitrile. Unfortunately, about a 1:1 mixture of stereoisomers **15** and **16** was obtained in this case.

The oxidation of dihydrooxazine **2a** with dimethyldioxirane (DMD)[13] was also examined and led to some surprising results (Scheme 6). Although considerable effort was made to produce the epoxide derived

Scheme 6



from **2a**, in all attempts only diol could be isolated, presumably resulting from epoxide opening by adventitious water. The diol proved to be predominantly stereoisomer **17**, along with a small amount of **12**, shown to be identical to the diol from osmium tetraoxide catalyzed oxidation of **2a**. The structure of the major isomer **17** was proven by X-ray crystallography,[11] and an ORTEP drawing of the molecule is shown in Fig. 3.

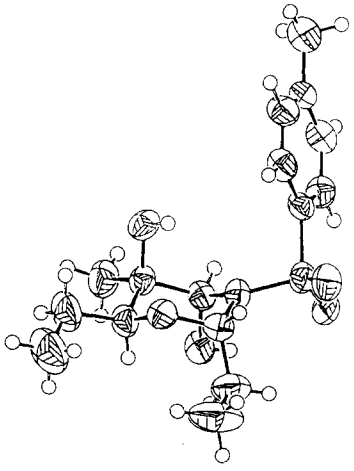


Fig 3. ORTEP drawing of tetrahydrooxazine **17**

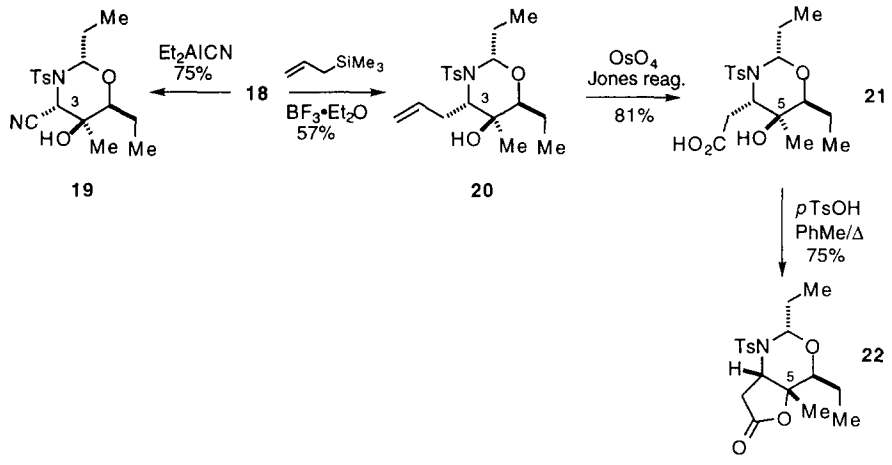
Unexpectedly, diol **17** results from epoxidation by DMD on the olefin face opposite to that with OsO_4 (*i.e.*, *syn* to the *N*-tosyl moiety). It might also be noted that oxidation of dihydrooxazine **2a** with *m*-chloroperbenzoic acid gave the same stereochemical result as DMD. At this point, we are unable to satisfactorily rationalize the stereochemical discrepancy between the chemistry of these oxazines described above and the DMD and *m*CPBA epoxidation results.

Some further reactions of diol **17** have been examined. Acetylation of **17** afforded monoacetate **18**. The diacetate could not be formed even under forcing conditions, perhaps due to shielding of the C-5 axial

hydroxyl group by the tosyl moiety (*cf* Fig. 2). The stereochemistry of acetate **18** was confirmed by NOE methodology (see Experimental Section).

The acetate **18** could be converted stereoselectively to hydroxy nitrile **19** with diethylaluminum cyanide (Scheme 7). It appears that cyanide attack on the intermediate *N*-tosyliminium ion derived from **18** occurs from

Scheme 7



an axial direction *anti* to the pseudoaxial arylsulfonyl group. The stereochemistry of nitrile **19** was proved by ^{1}H NMR NOE studies (see Experimental Section). In addition, acetate **18** could be allylated at C-3 to stereoselectively afford **20**. The allyl group was then oxidized[14] to produce acid **21**. The configurations of these compounds were again established by NOE experiments (see Experimental Section). Finally, lactonization of hydroxy acid **21** was effected with *p*-toluenesulfonic acid in refluxing toluene to give **22**. Interestingly, this bicyclic lactone was shown by NOE results to have the *cis*-fused stereochemistry. Therefore, ring closure at C-5 occurs with inversion.

The work described here indicates that 3,6-dihydro-2*H*-1,3-oxazines are easily prepared in one step from aliphatic *N*-tosyl aldimines and β-hydroxy aldehydes. In these preliminary experiments it has been demonstrated that these heterocycles are potentially useful synthons for stereoselective construction of acyclic 1,3-amino alcohol derivatives. We intend to further explore the scope and some applications of this synthetic methodology.

EXPERIMENTAL SECTION

General Procedure: 3,6-Dihydro-2,6-dipropyl-5-ethyl-3-tosyl-2*H*-1,3-oxazine (7a). To an oven dried 25 mL round bottomed flask fitted with a syringe cap and an argon inlet was added *N*-sulfinyl-*p*-toluenesulfonamide[15] (0.18 g, 0.83 mmol) and 5 mL of anhydrous CH_2Cl_2. Butyraldehyde (0.074 mL, 0.83 mmol) was added and the reaction mixture was stirred for 1 h at rt. The reaction mixture was cooled to -20 °C,

BF_3•OEt_2 (0.15 mL, 1.2 mmol) was added immediately, followed by the freshly distilled 2-ethyl-3-hydroxyhexanal[5,15] (0.24 g, 1.7 mmol). The resulting solution was stirred for 2 h at -20 °C and 10 mL of saturated $NaHCO_3$ solution was added. The mixture was diluted with 40 mL of saturated $NaHCO_3$ solution and extracted with three 50 mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.30) to yield 0.24 g (83%) of oxazine. IR (film) 3060, 2950, 2920, 2860, 1660, 1590, 1160, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (2 H, d, J = 8.1 Hz), 7.21 (2 H, d, J = 8.2 Hz), 6.24 (1 H, s), 5.28 (1 H, t, J = 6.9 Hz), 4.01 - 3.98 (1 H, m), 2.33 (3 H, s), 1.89 - 1.78 (2H, m), 1.75 - 1.62 (2 H, m), 1.45 - 1.18 (4 H, m), 0.99 - 0.88 (6 h, m), 0.72 - 0.63 (1 H, m), 0.58 (3 H, t, J = 6.4 Hz), 0.53 - 0.45 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 135.3, 129.8, 129.0, 127.5, 116.8, 82.1, 68.2, 33.1, 23.3, 21.1, 17.9, 16.1, 16.0, 13.6, 13.4, 11.8; EIMS *m/z* (relative intensity) 351 (51), 308 (45), 279 (38), 155 (12), 124 (100), 108 (7), 91 (35), 55 (11); exact mass calcd for $C_{19}H_{29}NO_3S$ 351.1868, found 351.1884.

2,5-Diethyl-3,6-dihydro-6-propyl-3-tosyl-2*H*-1,3-oxazine (7b). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.19 g, 0.89 mmol), propionaldehyde (0.064 mL, 0.89 mmol), BF_3•OEt_2 (0.16 mL, 1.3 mmol) and 2-ethyl-3-hydroxyhexanal[5,16] (0.26 g, 1.8 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.32) to yield 0.22 g (75%) of oxazine. IR (film) 3050, 2960, 2860, 1645, 1590, 1150, 970, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (2 H, d, J = 8.3 Hz), 7.24 (2 H, d, J = 8.0 Hz), 6.23 (1 H, s), 5.21 (1 H, t, J = 6.9 Hz), 4.03 - 4.00 (1 H, m), 2.36 (3 H, s), 1.88 - 1.79 (2H, m), 1.76 - 1.67 (2 H, m), 1.40 - 1.19 (2 H, m), 1.00 - 0.92 (6 H, m), 0.71 - 0.63 (1 H, m), 0.59 (3 H, t, J = 6.4 Hz), 0.48 - 0.36 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 135.3, 129.9, 129.2, 127.6, 116.9, 83.8, 68.2, 33.1, 24.3, 23.5, 21.3, 16.1, 13.8, 12.0, 9.2; EIMS *m/z* (relative intensity) 337 (20), 308 (7), 294 (12), 279 (12), 124 (100), 91 (40), 43 (13); exact mass calcd for $C_{18}H_{27}NO_3S$ 337.1712, found 337.1701.

3,6-Dihydro-5-ethyl-2-methyl-6-propyl-3-tosyl-2*H*-1,3-oxazine (7c). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.17 g, 0.80 mmol), acetaldehyde (0.045 mL, 0.80 mmol), BF_3•OEt_2 (0.15 mL, 1.2 mmol) and 2-ethyl-3-hydroxyhexanal[5,16] (0.23 g, 1.6 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.33) to yield 0.19 g (73%) of oxazine. IR (film) 3050, 2950, 2910, 2860, 1650, 1590, 1160, 975, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (2 H, d, J = 8.3 Hz), 7.23 (2 H, d, J = 8.4 Hz), 6.26 (1 H, s), 5.50 (1 H, t, J = 6.1 Hz), 4.08 - 4.04 (1 H, m), 2.35 (3 H, s), 1.90 - 1.81 (2H, m), 1.39 (3 H, d, J = 6.1 Hz), 1.35 - 1.21 (1 H, m), 0.99 (3 H, t, J = 7.4 Hz), 0.94 - 0.81 (2 H, m), 0.59 (3 H, t, J = 6.4 Hz), 0.50 - 0.40 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 135.2, 129.4, 129.1, 127.5, 116.5, 78.8, 68.0, 33.0, 23.4, 21.2, 18.0, 16.0, 13.7, 11.9; EIMS *m/z* (relative intensity) 323 (10), 308 (2), 280 (35), 199 (89), 171 (40), 155 (36), 127 (100), 91 (74); exact mass calcd for $C_{17}H_{25}NO_3S$ 323.1555, found 323.1549.

3,6-Dihydro-6-ethyl-5-methyl-2-propyl-3-tosyl-2*H*-1,3-oxazine (7d). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.19 g, 0.89 mmol), butyraldehyde (0.080 mL, 0.89 mmol), BF_3•OEt_2 (0.16 mL, 1.3 mmol) and 3-hydroxy-2-methylpentanal[5,16] (0.21 g, 1.8 mmol).

The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.32) to yield 0.25 g (87%) of oxazine. IR (film) 3060, 2950, 2920, 2860, 1655, 1590, 1365, 1345, 1240, 1220, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.69 (2 H, d, J = 8.4 Hz), 7.27 (2 H, d, J = 8.1 Hz), 6.32 (1 H, s), 5.34 (1 H, t, J = 6.9 Hz), 3.99 - 3.97 (1 H, m), 2.39 (3 H, s), 1.71 - 1.63 (2 H, m), 1.50 (3 H, s), 1.49 - 1.33 (3 H, m), 1.18 - 1.04 (1 H, m), 0.92 (3 H, t, J = 7.4 Hz), 0.16 (3 H, t, J = 7.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.3, 135.3, 129.3, 127.5, 123.5, 118.3, 82.5, 69.9, 33.3, 23.7, 21.3, 18.0, 16.2, 13.6, 6.7; CIMS *m/z* (relative intensity) 324 (M^+ + 1, 33), 252 (100); EIMS, *m/z* (relative intensity) 323 (1), 309 (5), 280 (5), 252 (5), 155 (9), 96 (100), 91 (39), 57 (18); exact mass calcd for $C_{17}H_{25}NO_3S$ 323.1555, found 323.1553.

2,6-Diethyl-3,6-dihydro-5-methyl-3-tosyl-2*H*-1,3-oxazine (2a). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.18 g, 0.84 mmol), propionaldehyde (0.061 mL, 0.84 mmol), BF_3•OEt_2 (0.16 mL, 1.3 mmol) and 3-hydroxy-2-methylpentanal[5,16] (0.20 g, 1.7 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.31) to yield 0.21 g (82%) of oxazine. IR (film) 3060, 2980, 2940, 2880, 1660, 1600, 1170, 815 cm^{-1}; ^1H NMR (300, $CDCl_3$) δ 7.68 (2 H, d, J = 8.3 Hz), 7.28 (2 H, d, J = 8.4 Hz), 6.35 (1 H, t, J = 4.3 Hz), 5.26 (1 H, t, J = 7.0 Hz), 3.99 - 3.97 (1 H, m), 2.39 (3 H, s), 1.82 - 1.73 (2 H, m), 1.53 (3 H, s), 1.51 - 1.43 (1 H, m), 1.26 -1.12 (1 H, m), 0.99 (3 H, t, J = 7.4 Hz), 0.21 (3 H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 135.4, 129.4, 127.6, 123.5, 118.3, 84.0, 69.9, 24.4, 23.8, 21.4, 16.3, 9.2, 6.7; EIMS *m/z* (relative intensity) 309 (13), 280 (15), 252 (12), 155 (11), 96 (100), 91 (36), 81 (9); exact mass calcd for $C_{16}H_{23}NO_3S$ 309.1399, found 309.1414.

2,6-Diethyl-3,6-Dihydro-5-methyl-3-phenylsulfonyl-2*H*-1,3-oxazine (2b). The general procedure was followed using *N*-sulfinylbenzenesulfonamide[15] (0.66 g, 3.25 mmol), propionaldehyde (0.23 mL, 3.2 mmol), BF_3•OEt_2 (0.6 mL, 4.86 mmol), and 3-hydroxy-2-methylpentanal[5,16] (0.9 mL, 7.60 mmol). The crude product was purified by silica gel chromatography (10% ethyl acetate / hexane, R_f = 0.33) to yield 0.64 g (67 %) of the oxazine. The product was recrystallized from ethanol to yield colorless needles, mp 71-74 °C; ^1H-NMR (200 MHz, $CDCl_3$) δ 7.82 (2 H, dd, *J* = 1.4, 1.9 Hz), 7.56 - 7.43 (3 H, m), 6.34 (1 H, d, *J* = 1.0 Hz), 5.27 (1 H, t, *J* = 7.0 Hz), 3.95 (1 H, t, *J* = 3.8 Hz), 1.82 - 1.67 (2 H, m), 1.49 (3 H, s), 1.46 - 1.37 (1 H, m), 1.17 - 1.01 (1 H, m), 0.95 (3 H, t, *J* = 7.5 Hz), 0.13 (3 H, t, *J* = 7.4 Hz); ^{13}C-NMR (360 MHz, $CDCl_3$) δ 138.4, 132.6, 128.8, 127.6, 123.8, 118.2, 84.1, 70.0, 24.4, 23.8, 16.2, 9.2, 6.9; EI-MS *m/z* (relative intensity) 295 (11), 266 (14), 238 (11), 141 (6), 125 (6), 96 (100), 77 (25).

3,6-Dihydro-2,5-dimethyl-6-ethyl-3-tosyl-2*H*-1,3-oxazine (7e). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.18 g, 0.83 mmol), acetaldehyde (0.046 mL, 0.83 mmol), BF_3•OEt_2 (0.15 mL, 1.2 mmol) and 3-hydroxy-2-methylpentanal[5,16] (0.20 g, 1.7 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.32) to yield 0.17 g (71%) of oxazine. IR (film) 3060, 2960, 2920, 2840, 1645, 1595, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.67 (2 H, d, J = 8.3 Hz), 7.26 (2 H, d, J = 8.4 Hz), 6.32 (1 H, s), 5.55 (1 H, q, J = 5.5 Hz), 4.01 - 3.99 (1 H, m), 2.38 (3 H, s), 1.54 (3 H, s), 1.53-1.46 (1 H, m), 1.43 (3 H, d, J = 6.1 Hz), 1.21-1.13 (1 H, m), 0.21 (3 H, t, J = 7.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.3, 135.3, 129.3, 127.5, 123.0, 118.0, 79.1, 69.7, 23.7, 21.4, 18.2, 16.3, 6.7; CIMS *m/z* (relative intensity) 296 (M^+ + 1, 32), 278 (2), 266 (7), 252 (100), 96 (24).

EIMS, *m/z* (relative intensity) 295 (5), 266 (7), 251 (3), 155 (11), 143 (5), 115 (5), 96 (100), 91 (42), 41 (25); exact mass calcd for $C_{15}H_{21}NO_3S$ 295.1242, found 295.1257.

3,6-Dihydro-6-methyl-2-propyl-3-tosyl-2*H*-1,3-oxazine (7f). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.18 g, 0.83 mmol), butyraldehyde (0.074 mL, 0.83 mmol), BF_3•OEt_2 (0.15 mL, 1.2 mmol) and 3-hydroxybutanal[5,16] (0.15 g, 1.7 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.35) to yield 0.098 g (40%) of oxazine. IR (film) 3050, 2960, 2920, 2880, 1660, 1590, 1160 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.70 (2 H, d, J = 8.3 Hz), 7.29 (2 H, d, J = 8.2 Hz), 6.54 (1 H, d, J = 8.2 Hz), 5.23 (1 H, t, J = 7.2 Hz), 5.14 (1 H, dd, J = 8.2, 1.6 Hz), 4.23 (1 H, q, J = 6.7 Hz), 2.40 (3 H, s), 1.79 - 1.68 (2 H, m), 1.52 - 1.33 (3 H, m), 1.24 - 1.08 (1 H, m), 0.97 (3 H, t, J = 7.3 Hz), 0.84 (3 H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 135.3, 129.4, 127.5, 122.2, 117.2, 83.5, 62.8, 33.3, 21.5, 19.9, 18.0, 13.9; CIMS *m/z* (relative intensity) 296 (M^+ +1, 24), 252 (11), 224 (100).

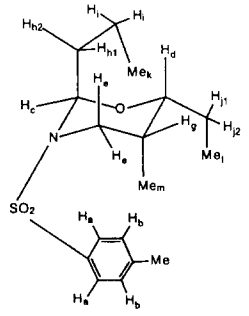
3,6-Dihydro-2-ethyl-6-methyl-3-tosyl-2*H*-1,3-oxazine (7g). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.18 g, 0.83 mmol), propionaldehyde (0.061 mL, 0.83 mmol), BF_3•OEt_2 (0.15 mL, 1.2 mmol) and 3-hydroxybutanal[5,16] (0.15 g, 1.7 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.34) to yield 0.12 g (51%) of oxazine. IR (film) 3060, 2960, 2920, 2840, 1645, 1595, 1450, 1400, 1360, 1345, 1180, 1160, 1145, cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.71 (2 H, d, J = 8.3 Hz), 7.30 (2 H, d, J = 8.1 Hz), 6.53 (1 H, d, J = 8.2 Hz), 5.21 (1 H, t, J = 7.2 Hz), 5.12 (1 H, dd, J = 8.2, 1.5 Hz), 4.23 (1 H, q, J = 6.6 Hz), 2.42 (3 H, s), 1.87 - 1.80 (2 H, m), 0.98 (3 H, t, J = 7.4 Hz), 0.87 (3 H, d, J = 6.6 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.6, 135.3, 129.4, 127.5, 122.2, 117.2, 84.6, 62.8, 24.4, 21.5, 19.9, 9.1; CIMS *m/z* (relative intensity) 282 (M^+ +1, 35), 264 (18), 252 (8), 224 (100).

3,6-Dihydro-6-isopropyl-2-propyl-3-tosyl-2*H*-1,3-oxazine (7h). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.50 g, 2.3 mmol), butyraldehyde (0.21 mL, 2.3 mmol), BF_3•OEt_2 (0.44 mL, 3.5 mmol) and 3-hydroxy-4-methylpentanal[5,16] (0.53 g, 4.6 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.30) to yield 0.35 g (47%) of oxazine. IR (film) 3040, 2940, 2845, 1630, 1585, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (2 H, d, J = 8.3 Hz), 7.28 (2 H, d, J = 8.2 Hz), 6.56 (1 H, d, J = 8.3 Hz), 5.33 (1 H, t, J = 6.9 Hz), 5.09 (1 H, dd, J = 8.3, 1.5 Hz), 3.94 (1 H, bs), 2.38 (3 H, s), 1.83 - 1.75 (2 H, m), 1.58 - 1.51 (1 H, m), 1.49 - 1.38 (2 H, m), 0.96 (3 H, t, J = 7.4 Hz), 0.54 (3 H, d, J = 6.9 Hz), 0.50 (3 H, d, J = 6.9 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 135.4, 129.5, 127.4, 123.2, 113.7, 83.1, 70.7, 33.4, 31.2, 21.4, 17.8, 17.1, 16.7, 13.6; CIMS *m/z* (relative intensity) 324 (M^+ + 1, 9), 280 (33), 252 (100).

3,6-Dihydro-2-propyl-6-tetradecyl-3-tosyl-2*H*-1,3-oxazine (7i). The general procedure was followed using *N*-sulfinyl-*p*-toluenesulfonamide (0.22 g, 1.0 mmol), butyraldehyde (0.090 mL, 1.0 mmol), BF_3•OEt_2 (0.19 mL, 1.5 mmol) and 3-hydroxyheptadecanal (0.54 g, 2.0 mmol). The crude product was purified by flash chromatography (10% EtOAc / hexanes, R_f 0.38) to yield 0.20 g (42%) of oxazine. IR

(film) 3050, 2960, 2880, 1590, 1120 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.67 (2 H, d, J = 8.3 Hz), 7.27 (2 H, d, J = 8.1 Hz), 6.51 (1 H, d, J = 8.2 Hz), 5.32 (1 H, t, J = 7.0 Hz), 5.09 (1 H, dd, J = 8.2, 1.3 Hz), 4.11 (1 H, t, J = 5.4 Hz), 2.39 (3 H, s), 1.81 - 1.75 (2 H, m), 1.47 - 1.39 (2 H, m), 1.25 (26 H, bs), 0.95 (3 H, t, J = 7.4 Hz), 0.87 (3 H, t, J = 6.6 Hz), ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.3, 135.5, 129.3, 127.4, 122.5, 116.0, 83.1, 66.3, 33.8, 33.3, 31.8, 29.6, 29.3, 23.9, 22.6, 21.4, 17.9, 14.0, 13.6; CIMS *m/z* (relative intensity) 478 (M^+ + 1, 3), 434 (8), 406 (100).

Preparation of 6-Ethyl-5-methyl-2-propyl-3-tosyl-tetrahydro-1,3-oxazine (8a). A suspension of oxazine **1d** (0.035 g, 0.11 mmol), and a catalytic amount of 20% $Pd(OH)_2$ on carbon containing 31% H_2O (4 mg, 0.01 mmol) in 2 mL of ethanol was stirred under one atmosphere of hydrogen for 17 h. The black mixture was filtered through a pad of Celite, which was washed several times with ethyl acetate. The filtrate was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by preparative tlc (10% EtOAc / hexanes, R_f 0.40) to yield 0.033 g (95%) of tetrahydrooxazine **8a**. IR (film) 2960, 2920, 2870, 1590, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (2 H, d, J = 8.3 Hz), 7.27 (2 H, d, J = 8.1 Hz), 5.44 (1 H, dd, J = 9.6, 5.0 Hz), 3.67 (1 H, ddd, J = 3.3, 2.5, 2.2 Hz), 3.53 (2 H, dd, J = 13.8, 3.3 Hz), 2.42 (3H, s), 2.18-2.10 (1 H, m), 0.93 (3 H, d, J = 7.4 Hz), 0.87 (3 H, t, J = 7.4 Hz), 0.59 (3 H, d, J = 7.0 Hz); ^1H NMR NOE's (500 MHz, $CDCl_3$) (see atom labelling below) : H_c to H_a (9%), H_{h2} (7%), H_i (7%), H_k (2%); H_d to H_{h1} (12%), H_g (11%), H_{j1} (4%), H_{j2} (4%), H_i (3%), Me_l (7%); $H_e$eq to H_a (4%), H_g (5%), Me_m (2%); $H_e$ax to H_d (3%), H_h (3%), H_g (8%); H_h to H_c (3%), H_d (10%), $H_e$ax (3%), H_{h2} (21%), H_{j1} (5%), Me_k (2%); H_g to H_d (10%), $H_e$ax (10%), Me_m (10%); H_i to H_c (10%), H_d (3%), H_h (4%), Me_k (15%); H_{j2} to H_d (4%), H_{j1} (21%), Me_l (7%), Me_m (3%); Me_k to H_c (4%), H_{h1} (2%), H_{h2} (4%), H_i (15%); Me_l to H_d (7%), H_g (3%), H_{j1} (8%), H_{j2} (7%); Me_m to H_a (7%), H_c (2%), $H_e$eq (5%), H_g (14%), H_{j1} (4%), H_{j2} (4%); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.0, 138.3, 129.5, 127.1, 83.5, 71.6, 46.1, 31.6, 30.9, 25.4, 21.5, 18.1, 13.6, 10.7, 10.0; CIMS *m/z* (relative intensity) 326 (M^+ + 1, 15), 283 (55), 226 (100).



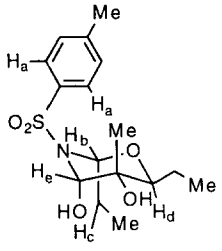
2,6-Diethyl-5-methyl-3-tosyl-tetrahydro-1,3-oxazine (8b). A suspension of oxazine **2** (0.10 g, 0.33 mmol), and a catalytic amount of 20% $Pd(OH)_2$ on carbon containing 31% H_2O (4 mg, 0.01 mmol) in 2 mL of ethanol was stirred under one atmosphere of hydrogen for 17 h. The black mixture was filtered through a pad of Celite, which was washed several times with ethyl acetate. The filtrate was dried over $MgSO_4$ and the

solvent was removed by rotary evaporation. The crude product was purified by preparative tlc (10% EtOAc / hexanes, R_f 0.42) to yield 0.097 g (94%) of tetrahydrooxazine **8b**. IR (film) 2960, 2920, 2860, 1590, 1330 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (2 H, d, J = 7.4 Hz), 7.20 (2 H, d, J = 7.4 Hz), 5.28 - 5.20 (1 H, m), 3.59 - 3.39 (3 H, m), 2.33 (3 H, s), 2.12 - 2.02 (1 H, m), 1.49 - 1.16 (4 H, m), 0.84 - 0.79 (6 H, m), ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 138.1, 129.2, 126.7, 84.6, 71.3, 45.9, 30.6, 25.2, 22.3, 21.2, 10.4, 9.8, 9.0; CIMS *m/z* (relative intensity) 312 (M^+ + 1, 70), 282 (44), 226 (100), 157 (36).

2-Methyl-1-(*N*-tosylamino)-3-pentanol (9). Oxazine **8b** (0.042 g, 0.14 mmol), 1 mL H_2O, 4 mL THF and concentrated HCl (20 drops) were heated at reflux for 1h, cooled to rt, and 10 mL of 3 N NaOH was added. This mixture was diluted with 50 mL of H_2O and extracted with three 50 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified using preparative tlc (50% EtOAc / hexanes, R_f 0.50) to yield 0.034 g (94%) of 1,3-amino alcohol derivative **9**. IR (film) 3540, 3340, 2960, 2880, 1600, 1570, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.73 (2 H, d, J = 8.3 Hz), 7.27 (2 H, d, J = 8.2 Hz), 5.48 (1 H, t, J = 6.3 Hz), 3.64 - 3.54 (1 H, m), 3.02 - 2.74 (2 H, m), 2.38 (3 H, s), 2.21 (1 H, bs), 1.73 - 1.65 (1 H, m), 1.43 - 1.22 (2 H, m), 0.85 (3 H, t, J = 7.3 Hz), 0.78 (3 H, d, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 136.8, 129.6, 73.5, 46.5, 37.1, 26.7, 21.4, 10.7, 10.5; EIMS *m/z* (relative intensity) 271 (1), 253 (2), 242 (2), 184 (40), 91 (100); exact mass calcd for $C_{13}H_{21}NO_3S$ 271.1237, found 271.1217.

5-Acetoxy-2-propyl-6-(2-propyl)-3-tosyl-tetrahydro-1,3-oxazine (11). A solution of oxazine **10** (0.23 g, 0.75 mmol) in 5 mL of dry THF was cooled to 0 °C prior to the addition of a 2.0 M solution of BH_3•Me_2S in THF (0.75 mL, 1.5 mmol). The reaction mixture was allowed to warm to rt, stirred for 4 h, heated at reflux for 2h, and allowed to cool to rt. Aqueous 3 N NaOH (0.25 mL, 0.75 mmol) was added followed by slow addition of aqueous 30% H_2O_2 solution (0.25 mL, 2.2 mmol). The reaction mixture was heated at reflux for 1 h, cooled to rt, diluted with 50 mL of brine, and extracted three 50 mL portions of Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude hydroxyoxazine, Et_3N (0.13 mL, 0.92 mmol) and a catalytic amount of DMAP in 10 mL of dry CH_2Cl_2 was cooled to 0 °C prior to the addition of Ac_2O (0.064 mL, 0.69 mmol). The reaction mixture was allowed to warm to rt, stirred for 18 h and 10 mL of 5% HCl was added. The mixture was diluted with 20 mL of 5% HCl and extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (35% EtOAc / hexanes, R_f 0.32) to yield 0.15 g (55%) of acetate **11**. IR (film) 3050, 2950, 2880, 1730, 1590, 1450, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (2 H, d, J = 8.2 Hz), 7.31 (2 H, d, J = 8.3 Hz), 5.41 (1 H, t, J = 7.3 Hz), 4.10 - 4.00 (1 H, m), 3.45 (1 H, dd, J = 9.5, 2.0 Hz), 3.15 - 3.05 (1 H, m), 2.38 (3 H, s), 2.04 - 1.99 (1 H, m), 1.96 (3 H, s), 1.88 - 1.78 (1 H, m), 1.58 - 1.48 (1 H, m), 0.94 (3 H, t, J = 7.4 Hz), 0.78 (3 H, d, J = 7.0 Hz), 0.29 (3 H, d, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 143.7, 137.4, 129.7, 127.6, 84.4, 73.2, 62.8, 42.0, 27.4, 22.5, 21.4, 20.7, 19.0, 14.1, 9.4; CIMS *m/z* (relative intensity) 368 (M^+ + 1, 100).

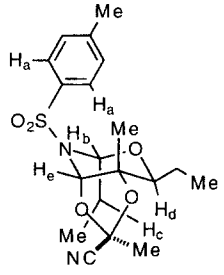
Preparation of Diol 12. To a solution of oxazine **2** (0.51 g, 1.7 mmol) and trimethylamine N-oxide (0.28 g, 2.5 mmol) in 10 mL of a *t*-BuOH / acetone (4:1) mixture was added a catalytic amount of osmium tetraoxide (approximately 20 mg). After the mixture was stirred for 20 h at rt, 5 mL of saturated $NaHSO_3$ solution was added and the mixture was stirred for 1 h. The mixture was diluted with 200 mL of saturated $NaHSO_3$ solution and extracted with three 200 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (25% EtOAc / hexanes, R_f 0.28) to yield 0.47 g (81%) of diol **12**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (2 H, d, J = 8.2 Hz), 7.27 (2 H, d, J = 8.1 Hz), 5.15 (1 H, dd, J = 10.5, 3.9 Hz), 5.03 (1H, s), 4.52 (1H, s), 3.65 (1 H, d, J = 9.9 Hz), 3.01 (1 H, s), 2.55 - 2.42 (1 H, m), 2.38 (3 H, s), 1.79 - 1.62 (2 H, m), 1.24 - 1.14 (1 H, m), 0.96 - 0.90 (6 H, m), 0.69 (6 H, m); ^1H NMR NOE's (300 MHz, $CDCl_3$) (see atom labelling below) : H_a to H_e (2%), H_a to H_b (2%), H_a to (ax) Me (2%), H_c to H_d (4%), H_d to H_c (4%), H_b to H_a (2%), H_e to H_a (2%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 137.4, 129.7, 126.9, 85.2, 82.1, 71.2, 69.1, 27.5, 21.5, 20.6, 17.1, 11.0, 10.0; CIMS *m/z* (relative intensity) 326 (M^+ - OH, 14), 268 (23), 212 (100).



4,5-Diacetoxy-2,6-diethyl-5-methyl-3-tosyl-tetrahydro-1,3-oxazine (13). A solution of diol **12** (0.39 g, 1.1 mmol), Et_3N (0.93 mL, 6.7 mmol) and a catalytic amount of DMAP in 10 mL of dry CH_2Cl_2 was cooled to 0 °C prior to the addition of Ac_2O (0.48 mL, 5.1 mmol). The reaction mixture was allowed to warm to rt, stirred for 18 h and 10 mL of 5% HCl was added. The mixture was diluted with 20 mL of 5% HCl and extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (25% EtOAc / hexanes, R_f 0.29) to yield 0.49 g (69%) of diacetate **13**. IR (film) 3020, 2970, 2920, 2870, 1760, 1740, 1590, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (2 H, d, J = 8.2 Hz), 7.24 (2 H, d, J = 8.1 Hz), 7.09 (1 H, s), 5.22 (1 H, dd, J = 10.2, 4.5 Hz), 3.81 (1 H, dd, J = 10.1, 1.4 Hz), 2.36 (3 H, s), 2.29 - 2.18 (1 H, m), 1.97 (3 H, s), 1.89 (3 H, s), 1.63 - 1.55 (1 H, m), 1.49 - 1.40 (1 H, m), 1.35 (3 H, s), 1.33 - 1.23 (1 H, m), 0.94 (3 H, t, J = 7.3 Hz), 0.77 (3 H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 167.9, 143.9, 136.9, 129.6, 127.5, 84.9, 78.2, 76.8, 69.8, 26.0, 21.5, 21.4, 21.0, 20.9, 15.2, 10.6, 9.8; CIMS *m/z* (relative intensity) 398 (M^+ - C_2H_5, 20), 368 (40), 214 (100).

Preparation of Cyano Acetal 14. A solution of diacetate **13** (0.093 g, 0.22 mmol) in 5 mL of dry CH_2Cl_2 was cooled to -20 °C prior to the addition of a 1.0 M solution of Et_2AlCN in CH_2Cl_2 (0.55 mL, 0.55 mmol). The reaction mixture was stirred for 1 h, allowed to warm to 0 °C, stirred for 4 h and 10 mL of

saturated $NaHCO_3$ solution was added. The mixture was diluted with 40 mL of saturated $NaHCO_3$ solution and extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified using preparative tlc (25% EtOAc / hexanes, R_f 0.38) to yield 0.066 g (77%) of nitrile **14**. IR (film) 3050, 2970, 2930, 2880, 2220, 1590, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2 H, d, J = 8.2 Hz), 7.34 (2 H, d, J = 8.1 Hz), 5.58 (1 H, s), 5.31 (1 H, dd, J = 10.0, 4.5 Hz), 3.39 (1 H, dd, J = 10.0, 2.9 Hz), 2.44 (3 H, s), 2.15 - 2.04 (1 H, m), 1.76 (3 H, s), 1.75 - 1.67 (1 H, m), 1.55 - 1.47 (1 H, m), 1.37 - 1.28 (1 H, m), 1.03 (3 H, s), 0.98 - 0.88 (6 H, m); ^1H NMR NOE's (300 MHz, $CDCl_3$) (see atom labelling below) : H_a to H_e (2%), H_a to H_b (3%), H_c to Hd (4%), H_d to H_c (4%), H_b to H_a (3%), H_e to H_a (2%), H_e to angular Me (1%), acetal Me to H_d (3%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 137.0, 129.9, 127.0, 117.4, 95.5, 89.2, 84.3, 75.2, 73.1, 26.4, 26.2, 21.5, 21.4, 16.2, 10.7, 9.3; CIMS *m/z* (relative intensity) 395 (M^+ + 1, 10), 368 (97), 365 (24) 157 (100).

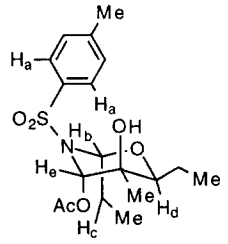


Preparation of Nitriles 15 and 16. A solution of diol **12** produced via the OsO_4 pathway (0.098 g, 0.29 mmol) and trimethylsilyl cyanide (0.076 mL, 0.57 mmol) in 5 mL of dry CH_2Cl_2 was cooled to 0 °C prior to the addition of a BF_3•Et_2O (0.090 mL, 0.71 mmol). The reaction mixture was stirred for 5 h and 10 mL of saturated $NaHCO_3$ solution was added. The mixture was diluted with 40 mL of saturated $NaHCO_3$ solution and extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude products were purified by preparative tlc (25% EtOAc / hexanes, R_f 0.50 and 0.31) to yield 0.035 g (35%) of nitrile **15** and 0.043 g (43%) of nitrile **16**. Nitrile **15**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (2 H, d, J = 8.3 Hz), 7.32 (2 H, d, J = 8.3 Hz), 5.25 (1 H, s), 5.17 (1H, dd, J = 10.7, 4.1 Hz), 3.71 (1 H, dd, J = 9.8, 2.1 Hz), 2.44 (3 H, s), 2.26 - 2.15 (1 H, m), 1.61 - 1.48 (2 H, m), 1.46 - 1.19 (2 H, m), 1.00 - 0.95 (6 H, m), 0.88 (3 H, t, J = 7.4 Hz). Nitrile **16**: H NMR (300 MHz, $CDCl_3$) δ 7.71 (2H, d, J = 8.3 Hz), 7.34 (2 H, d, J = 8.3 Hz), 5.34 (1 H, dd, J = 10.5, 4.6 Hz), 4.83 (1 H, s), 3.68 (1 H, dd, J = 10.0, 1.4 Hz), 2.52 - 2.38 (4 H, m), 2.25 (1 H, s), 1.79 - 1.68 (1 H, m), 1.63 - 1.51 (1 H, m), 1.35 - 1.24 (1 H, m), 1.12 (3 H. s), 1.00 (3 H, t, J = 7.3 Hz), 0.88 (3 H, t, J = 7.4 Hz).

2,6-Diethyl-4,5-dihydroxy-5-methyl-3-tosyl-tetrahydro-1,3-oxazine (17). Oxazine **2** (0.83 g, 2.7 mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C. An 0.08 M solution of dimethyldioxirane[13] in acetone (40 mL, 3.2 mmol) was added and the resulting mixture was stirred for 4 h. The mixture was diluted with 100 mL of CH_2Cl_2, dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (25% EtOAc / hexanes, R_f 0.40) to yield 0.68 g (74%) of diol **17**. IR (film) 3460, 2960, 2920, 1590, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76

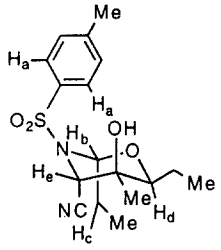
(2 H, d, J = 8.0 Hz), 7.30 (2 H, d, J = 7.9 Hz), 5.18 (1 H, dd, J = 10.4, 4.0 Hz), 4.99 (1 H, s), 3.81 (1 H, d, J = 8.8 Hz), 3.56 (1 H, d, J = 2.4 Hz), 2.57 - 2.47 (1H, m), 2.40 (3 H, s), 2.03 (1 H, s), 1.91 - 1.82 (1 H, m), 1.54 - 1.32 (2 H, m), 1.11 (3 H, s), 0.98 - 0.91 (6 H, m), ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 137.3, 129.9, 126.9, 85.3, 83.6, 70.8, 69.2, 27.4, 21.5, 20.1, 20.0, 10.3, 9.9.

4-Acetoxy-2,6-diethyl-5-hydroxy-5-methyl-3-tosyl-tetrahydro-1,3-oxazine (18). A solution of diol **17** (0.60 g, 1.8 mmol), Et_3N (0.37 mL, 2.7 mmol) and a catalytic amount of DMAP in 10 mL of dry CH_2Cl_2 was cooled to 0 °C prior to the addition of Ac_2O (0.20 mL, 2.2 mmol). The reaction mixture was allowed to warm to rt, stirred for 18 h and 10 mL of 5% HCl was added. The mixture was diluted with 20 mL of 5% HCl and extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (35% EtOAc / hexanes, R_f 0.29) to yield 0.58 g (86%) of acetate **18**. IR (thin film) 3540, 2980, 2920, 2870, 1740, 1590 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (2 H, d, J = 8.3 Hz), 7.31 (2 H, d, J = 8.3 Hz), 6.28 (1 H, s), 5.27 (1 H, dd, J = 10.3, 4.4 Hz), 3.70 (1 H, dd, J = 9.9, 2.9 Hz), 2.40 (3 H, s), 2.34 - 2.21 (2 H, m), 2.04 (3 H, s), 1.75 - 1.61 (1 H, m), 1.55 - 1.34 (2 H, m), 1.01 (3 H, s), 0.96 - 0.87 (6 H, m). ^1H NMR NOE's (300 MHz, $CDCl_3$) (see atom labelling below) : H_a to H_e (2%), H_a to H_b (2%), H_a to OH (1%), H_d to H_c (4%), H_c to H_d (4%), H_b to H_a (2%), H_e to H_a (2%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 144.1, 136.8, 129.8, 127.4, 85.1, 80.8, 71.5, 68.5, 26.1, 21.5, 21.1, 20.9, 18.9, 10.1, 9.7.

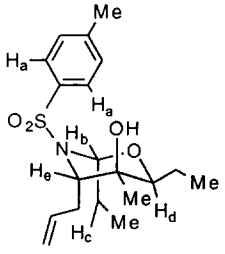


4-Cyano-2,6-diethyl-5-hydroxy-5-methyl-3-tosyl-tetrahydro-1,3-oxazine (19). A solution of acetate **18** (0.10 g, 0.27 mmol) in 5 mL of dry CH_2Cl_2 was cooled to -78 °C prior to the addition of a 1.0 M solution of Et_2AlCN in CH_2Cl_2 (0.68 mL, 0.68 mmol). The reaction mixture was stirred for 1 h, allowed to warm to 0 °C, stirred for 4 h and 10 mL of saturated $NaHCO_3$ solution was added. The mixture was diluted with 40 mL of saturated $NaHCO_3$ solution and extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified using preparative tlc (2.5% EtOAc / CH_2Cl_2, R_f 0.38) to yield 0.071 g (75%) of nitrile **19**. IR (film) 3500, 3040, 2960, 2920, 2860, 2220, 1590, 1350, 1160, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2 H, d, J = 8.3 Hz), 7.37 (2 H, d, J = 8.3 Hz), 5.31 (1 H, dd, J = 9.9, 5.8 Hz), 4.73 (1 H, s), 3.77 (1 H, J = 10.0, 2.5 Hz), 2.63 (1 H, s), 2.45 (3 H, s), 2.43 - 2.30 (1 H, m), 1.81 - 1.72 (1 H, m), 1.69 - 1.52 (1 H, m), 1.50 - 1.37 (1 H, m), 1.33 (3 H, s), 0.98 - 0.88 (6 H, m); ^1H NMR NOE's (300 MHz, $CDCl_3$) (see atom labelling below) : H_a to H_e (2%), H_a to H_b (2%), H_a to OH (1%), H_d to H_c (4%), H_c to H_d (4%), H_b to

H_a (2%), H_e to H_a (2%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 135.9, 130.1, 127.4, 117.3, 85.6, 72.8, 68.7, 52.2, 23.6, 21.6, 20.5, 20.4, 9.9, 9.5; CIMS *m/z* (relative intensity) 353 (M^+ + 1, 100), 326 (81), 323 (50), 268 (99); EIMS *m/z* (relative intensity) 352 (2), 323 (33), 250 (17), 95 (100); exact mass calcd for $C_{17}H_{24}N_2O_4S$ 352.1451, found 352.1479.

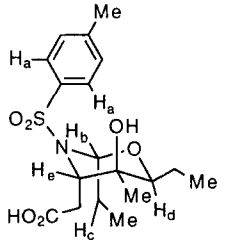


2,6-Diethyl-5-hydroxy-5-methyl-4-(3-propenyl)-3-tosyl-tetrahydro-1,3-oxazine (20). A solution of acetate **18** (0.27 g, 0.70 mmol) and allyltrimethylsilane (0.22 mL, 1.4 mmol) in 6 mL of dry CH_2Cl_2 was cooled to -78 °C prior to the addition of BF_3•Et_2O (0.10 mL, 0.84 mmol). The reaction mixture was stirred for 4 h and 10 mL of a saturated $NaHCO_3$ solution was added. The mixture was diluted with 40 mL of a saturated $NaHCO_3$ solution and extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified using preparative tlc (25% EtOAc / hexanes, R_f 0.41) to yield 0.15 g (57%) of oxazine **20**. IR (film) 3540, 3060, 2960, 1630, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2 H, d, J = 8.3 Hz), 7.32 (2 H, d, J = 8.3 Hz), 6.04 - 5.90 (1 H, m), 5.20 (1 H, dd, J = 10.0, 4.6 Hz), 5.15 - 5.05 (2 H, m), 3.96 (1 H, dd, J = 9.8, 6.2 Hz), 3.54 (1 H, dd, J = 10.0, 2.7 Hz), 2.50 - 2.33 (5 H, m), 2.17 (1 H, s), 2.13 - 2.01 (1 H, m), 1.78 - 1.64 (1 H, m), 1.51 - 1.25 (2 H, m), 1.03 (3 H, s), 0.98 - 0.86 (6 H, m); ^1H NMR NOE's (300 MHz, $CDCl_3$) (see atom labelling below) : H_a to H_e (2%), H_a to H_b (2%), H_d to H_c (4%), H_c to H_d (4%), H_b to H_a (2%), H_e to H_a (2%), H_d to allyl H (3%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 137.3, 135.4, 129.7, 127.4, 117.2, 85.0, 71.5, 69.5, 63.2, 37.2, 26.7, 21.5, 21.1, 20.4, 10.3, 10.2; CIMS *m/z* (relative intensity) 368 (M^+ + 1, 15), 350 (20), 338 (42), 326 (8), 224 (100).

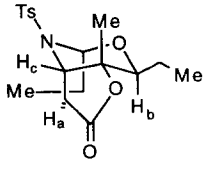


Preparation of Acid 21. To a solution of alkene **20** (0.11 g, 0.29 mmol) dissolved in 5 mL of acetone was added 0.10 mL of a 4 wt % solution of OsO_4 in water and 1.3 mL (3.5 mmol of Cr^{VI}) of Jones reagent. After the mixture was stirred for 20 h at rt, 1 mL of 2-propanol was added followed by 0.35 g of

$NaHSO_3$. The mixture was diluted with 10 mL of water and stirred until a dark green homogeneous solution was produced. The solution was diluted with 20 mL of water and extracted with three 25 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified using preparative tlc (EtOAc, R_f 0.18) to yield 0.091 g (81%) of acid **21**. IR (film) 3540, 2970, 2920, 2870, 1720, 1590, 1460, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (2 H, d, J = 8.3 Hz), 7.34 (2 H, d, J = 8.3 Hz), 5.33 (1 H, dd, J = 9.9, 4.7 Hz), 4.38 (1 H, t, J = 6.8 Hz), 3.51 (1 H, dd, J = 9.8, 2.6 Hz), 2.76 (2 H, d, J = 6.8 Hz), 2.42 (3 H, s), 2.11 - 1.98 (1 H, m), 1.82 - 1.68 (1 H, m), 1.53 - 1.31 (2 H, m), 1.25 (1 H, s), 1.03 (3 H, s), 0.98 - 0.89 (6 H, m); ^1H NMR NOE's (300 MHz, $CDCl_3$) (see atom labelling below) : H_a to H_e (2%), H_a to H_b (2%), H_d to H_c (4%), H_c to H_d (4%), H_b to H_a (2%), H_e to H_a (2%), H_d to proton α to CO_2H (3%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 143.9, 137.0, 129.9, 127.2, 84.9, 71.3, 69.4, 59.0, 39.3, 27.0, 21.5, 20.3, 19.7, 10.2, 10.0; CIMS *m/z* (relative intensity) 386 (M^+ + 1, 100), 368 (33), 356 (50); EIMS *m/z* (relative intensity) 356 (91), 242 (16), 155 (52), 91 (100); exact mass calcd for (M - C_2H_5) $C_{16}H_{22}NO_6S$ 356.1162, found 356.1158.



Preparation of Lactone 22. Acid **21** (0.030 g, 0.078 mmol), 5 mL of toluene and a catalytic amount of *p*-TsOH were heated at reflux for 3 h, cooled to rt, and 10 mL of saturated $NaHCO_3$ solution was added. This mixture was diluted with 20 mL of saturated $NaHCO_3$ solution and extracted with three 25 mL portions of CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude product was purified by preparative tlc (75% EtOAc / hexanes, R_f 0.25) to yield 0.021 g (75%) of lactone **22**. IR (film) 2960, 2920, 1740, 1590, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (2 H, d, J = 8.3 Hz), 7.38 (2 H, d, J = 8.0 Hz), 4.88 (1 H, dd, J = 6.5, 2.3 Hz), 3.88 (1 H, dd, J = 6.3, 1.0 Hz), 3.79 (1 H, dd, J = 10.0, 2.7 Hz), 2.93 (1 H, dd, J = 16.1, 1.2 Hz), 2.63 (1 H, dd, J = 16.1, 6.2 Hz), 2.45 (3 H, s), 1.92 - 1.59 (4 H, m), 1.05 (3 H, t, J = 7.4 Hz), 0.89 (3 H, t, J = 7.4 Hz), 0.83 (3 H, s); ^1H NMR NOE's (300 MHz, $CDCl_3$) (see atom labelling below) : H_a to H_b (2%), H_b to H_a (2%), axial Me to H_c (7%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 144.7, 133.7, 129.9, 127.9, 91.3, 81.8, 80.4, 61.7, 36.1, 28.5, 21.6, 20.6, 10.2, 7.5; CIMS *m/z* (relative intensity) 368 (M^+ + 1, 44), 338 (14), 214 (100).



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