A Convenient Procedure for the Synthesis of 3-Substituted 5,6-Dihydro-4*H*-1,2-oxazines from Nitroethane

Alexey Yu. Sukhorukov, Michael S. Klenov, Pavel E. Ivashkin, Alexey V. Lesiv,* Yulya A. Khomutova, Sema L. Ioffe*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation
Fax +7(095)1355328; E-mail: iof@ioc.ac.ru

Received 16 June 2006; revised 2 September 2006

Abstract: A novel and efficient four-step procedure for the synthesis of C-3-functionalised 5,6-dihydro-4*H*-1,2-oxazines from nitroethane is described. It includes preparation of 3-methyl-substituted six-membered cyclic nitronates, 3-(bromomethyl)-substituted 5,6-dihydro-4*H*-1,2-oxazines as intermediates, and nucleophilic substitution of bromine. Total yields of the target C-3-functionalised oxazines are 15–30% from nitroethane.

Key words: nitro compounds, heterocycles, 1,2-oxazines, silylation, unnatural amino acids

5,6-Dihydro-4*H*-1,2-oxazines are convenient precursors for the synthesis of various useful products such as substituted pyrrolidines,[1] piperidines,[2] unnatural α-amino acids,[3] amino alcohols,[4] and pyrroles.[5] However, application of 5,6-dihydro-4*H*-1,2-oxazines in organic synthesis is significantly limited, because only one common method for their preparation is known: [4+2] cycloaddition of conjugated nitrosoalkenes with electron-rich alkenes.[6] Furthermore, because of the high instability and wide variability of reactivity of nitrosoalkenes, problematic optimisation is necessary in each case.[7] Therefore, new approaches to the synthesis of 5,6-dihydro-4*H*-1,2-oxazines are needed.

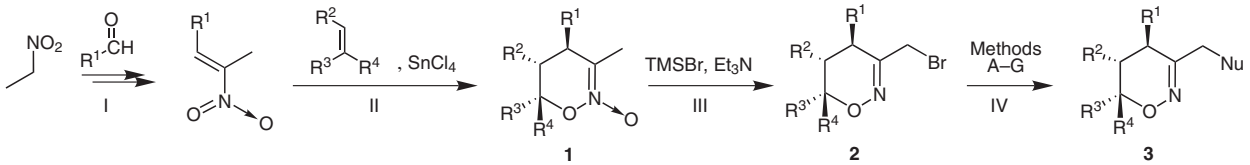
Recently we reported a new convenient procedure for the preparation of previously rare 3-(α-haloalkyl)-substituted 5,6-dihydro-4*H*-1,2-oxazines from six-membered cyclic nitronates containing an alkyl group at the C-3-position.[8] The synthesis of these products includes a simultaneous reduction of the nitronate function and a halogenation at the α-position of the alkyl substituent at C-3. The obtained (α-haloalkyl)-substituted cyclic oxime ethers can be considered as convenient precursors of different C-3-functionalised 5,6-dihydro-4*H*-1,2-oxazines. As a development of this strategy, a general and simple method for the synthesis of C-3-functionalised 5,6-dihydro-4*H*-1,2-oxazines **3** from nitroethane via six-membered cyclic nitronates **1** and 3-(bromomethyl)-substituted oxazines **2** is reported here (Scheme 1, Table 1).

This methodology includes four steps (Scheme 1). Overall yields of the target products **3** are 15–31% from nitroethane. Readily available aromatic and aliphatic aldehydes and olefins were used as additional reagents. The first two steps were accomplished by previously described procedures,[9] giving cyclic nitronates **1**.

The third step (Scheme 1, step III) was carried out according to our recent publication.[8] However, a previously suggested procedure[8] has been modified and expanded to develop a general and simple method for the synthesis of the target (bromomethyl)oxazines **2** as key intermediates on a molar scale (see experimental part for details). This modification was accompanied by a decrease in the yields of products **2a**–**l** by 10–20% in comparison to the yields obtained in the previous work.[8] It is more appropriate to use bromides **2** for the synthesis of oxazines **3**, because the chloride analogues of **2** were too inert towards nucleophilic substitution, while the iodides were unstable and unselective in the fourth step of the general procedure.

We focused on the optimisation of the fourth step of the synthesis shown in Scheme 1.

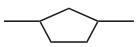
Apart from our previous publication,[8] nucleophilic substitution of halogen in α-halo-substituted oxime ethers has not been studied before (the interaction of α-halo oximes with nucleophiles leads to nitrosoalkenes[6]). The reaction which could compete with nucleophilic substitution in (halomethyl)oxazines **2** is elimination of a proton from the C-4 atom, followed by fragmentation with loss of the C-6



Scheme 1

SYNTHESIS 2007, No. 1, pp 0097–0107
Advanced online publication: 12.12.2006
DOI: 10.1055/s-2006-958930; Art ID: P07406SS

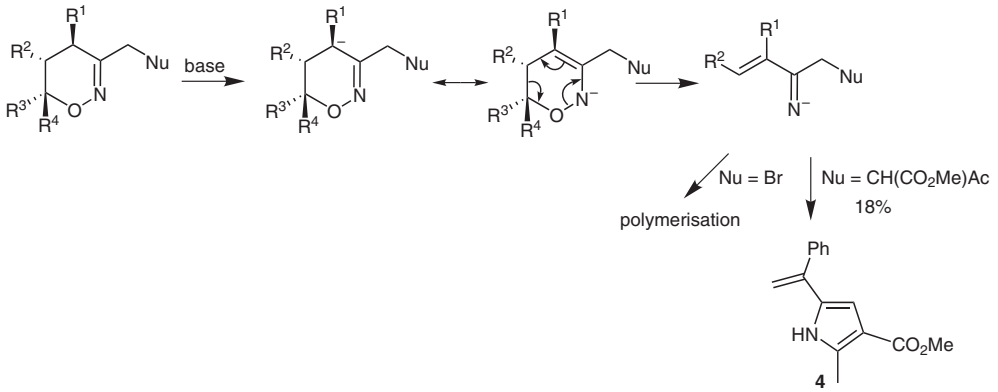
Table 1 Synthesis of 5,6-Dihydro-4*H*-1,2-oxazines **3a–v**

Entry	**1** and **2**	**3**	R^1	R^2	R^3	R^4	Nu	Yield[a] of **3** (%)	Overall yield[b] of **3** (%)	Method[c]
1	**a**	**a**[d]	Ph	H	Me	Me	CN	99	28	A
2	**a**	**b**[d]	Ph	H	Me	Me	$CH(CO_2Me)_2$	98	29	B
3	**a**	**c**	Ph	H	Me	Me	$CH(CO_2Me)CN$	98	29	B
4	**a**	**d**	Ph	H	Me	Me	$CH(CO_2Me)Ac$	78	22	B
5	**a**	**e**[e]	Ph	H	Me	Me	PPh_3	94	27	C
6	**a**	**f**	Ph	H	Me	Me	N_3	78	22	D
7	**a**	**g**	Ph	H	Me	Me	NPhth	99	30	A
8	**a**	**h**	Ph	H	Me	Me	OEt	65	19	E
9	**a**	**i**[f]	Ph	H	Me	Me	NH_2	69	20	F
10	**a**	**j**[e]	Ph	H	Me	Me	MeIm[g]	99	30	G
11	**b**	**k**	Ph	$-(CH)_3-$		H	$CH(CO_2Me)_2$	90	29	B
12	**c**	**l**	Ph	$-(CH)_4-$		H	$CH(CO_2Me)_2$	96	27	B
13	**d**	**m**	Ph			H	$CH(CO_2Me)_2$	60	24	B
14	**e**	**n**	Ph	H	H	Ph	$CH(CO_2Me)_2$	55	19	B
15	**f**	**o**	4-$MeOC_6H_4$	H	Me	Me	$CH(CO_2Me)_2$	81	31	B
16	**g**	**p**	4-$MeOC_6H_4$	$-(CH)_4-$		H	$CH(CO_2Me)_2$	95	28	B
17	**h**	**r**	4-$MeOC_6H_4$	H	H	OEt	$CH(CO_2Me)_2$	93	30	B
18	**i**	**s**	4-$MeOC_6H_4$	H	Me	OMe	$CH(CO_2Me)_2$	87	31	B
19	**j**	**t**	4-ClC_6H_4	H	Me	Me	$CH(CO_2Me)_2$	86	30	B
20	**k**	**u**	Me	H	Me	Me	$CH(CO_2Me)_2$	70	24	B
21	**l**	**v**	OBz	H	Me	Me	$CH(CO_2Me)_2$	69	15	B

[a] Yield of **3** over one step (Scheme 1, step IV) from **2**.
[b] Overall yield of **3** from nitroethane.
[c] Method A: NuK, DMF, 2 h, 50–60 °C; Method B: NuH, *t*-BuOK, DMF, 2 h, 60 °C; Method C: Nu, toluene, 2 h, 110 °C; Method D: NuNa, DMF, 2 h, 50–60 °C; Method E: NuH, Na, EtOH, 2 h, 60 °C; Method F: NaN_3, DMF, 1 h, 100 °C, then PPh_3, H_2O, HCl, 24 h, 20 °C; Method G: Nu, toluene, 5 h, 110 °C.
[d] This compound **3** was previously obtained by a similar procedure.[8]
[e] This compound **3** was isolated as a bromide salt.
[f] This compound **3** was isolated as a chloride salt.
[g] MeIm = 3-methylimidazol-1-yl.

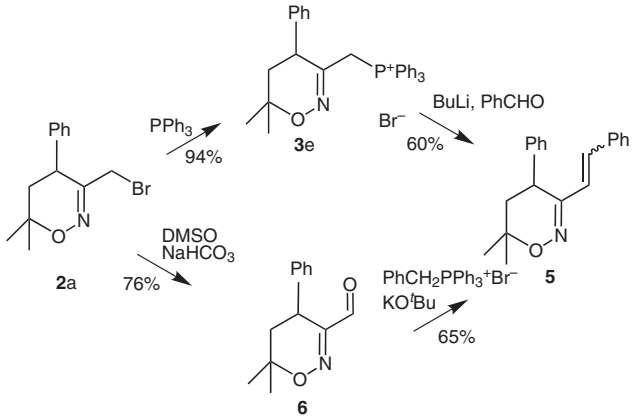
atom. This process was observed in the synthesis of oxazine **3d** from (bromomethyl)oxazine **2a** (Table 1, entry 4). Interaction of (bromomethyl)oxazine **2a** (R^1 = Ph; R^2 = H; R^3 = R^4 = Me) with an acetylacetic ester by use of an excess of base leads to polymerisation of the active vinyl imine intermediate, but pyrrole **4**, its cyclisation product, can also be isolated in 18% yield (Scheme 2).[10]

Variation of the nucleophile (Scheme 1, step IV) was investigated on the model 3-(bromomethyl)oxazine **2a** (Table 1, entries 1–10). We found optimal reaction conditions for each nucleophile to achieve the maximum yields of target oxazines **3a–j**. 1,3-Dicarbonyl compounds (malonic and acetylacetic esters), a cyanoacetic ester, as well as heteronucleophiles (azide, ethoxide, and phthalimide anions) react easily with 3-(bromomethyl)oxazine **2a** under moderate heating. More inert nucleophiles (nitroethane, phenylacetylene anions) in alcohols underwent no reaction with **2a**. The interaction of oxazine **2a** with more active nucleophiles (e.g., metalloorganic compounds) gives complex mixtures of unidentified products. Reaction of oxazine **2a** with diastereotopic nucleophiles (cyanoacetic or acetylacetic esters; Table 1, entries 3 and 4) leads to the formation of both of the corresponding diastereomers in nearly equimolar quantities.



Scheme 2

Interaction of oxazine **2a** with triphenylphosphine or *N*-methylimidazole (Table 1, entries 5 and 10) gives salts **3e** and **3j**, respectively. The Wittig reaction of **3e** with benzaldehyde leads to previously unknown 3-styryloxazine **5** (*Z*/*E*, 8:5) in high yield (Scheme 3). 3-Styryloxazine **5** was prepared by an alternative route via aldehyde **6** (oxidation of **2a** with DMSO in the presence of base), which underwent a Wittig reaction with a benzyl(triphenyl)phosphonium salt (Scheme 3).



Scheme 3

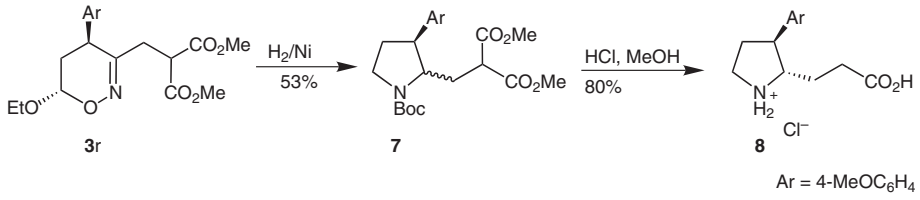
We have also investigated the reaction of dimethyl malonate with a representative series of (bromomethyl)oxazines **2a–l** (Table 1, entries 2, 11–21). Nucleophilic substitution of bromine by the dimethyl malonate anion goes smoothly, and gives target oxazines **3b**,**k–v** in 55–96% yield.

Oxazines **3b**,**k–v** (Table 1, entries 11–21) incorporating the fragment $-CH(CO_2Me)_2$ can be considered as convenient precursors of various useful products, especially unnatural amino acids. This was demonstrated by the synthesis of amino acid **8** during selective catalytic hydrogenation of the oxyimino fragment in oxazine **3r** (Scheme 4).

The structure and purity of compounds **2–8** were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic data as well as elemental analysis. The relative configurations of the stereocentres in initial nitronates **1** remained unchanged during their further transformations.

In conclusion, a novel strategy for the synthesis of C-3-functionalised 5,6-dihydro-4*H*-1,2-oxazines from nitroethane via diastereomerically pure six-membered cyclic nitronates **1** and 3-(bromomethyl)-5,6-dihydro-4*H*-1,2-ozaxines **2** has been elaborated. By this means, (bromomethyl)oxazines **2** can be considered as a kind of 'bridge' connecting easily accessible six-membered cyclic nitronates **1** and practically unavailable six-membered cyclic ethers of oximes **3**. Undoubtedly, this new approach will allow the application of cyclic oxime ethers to be expanded in organic synthesis.

All silylation reactions were performed in oven-dried (150 °C) glassware under an atmosphere of dry argon. NMR spectra were recorded on a Bruker AM-300 instrument (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz) and referenced to the residual solvent peaks. Atom numbering for peak assignment is shown in Figures 1 and 2. Melting points were determined on a Koffler melting point apparatus and are uncorrected. Analytical TLC was performed on Merck silica gel plates with QF-254 as indicator. All solvents for chromatography and extractions were technical grade. Hexane and EtOAc were distilled from P_2O_5. Column chromatography was performed on silica gel (Merck, 230–400-mesh).



Scheme 4

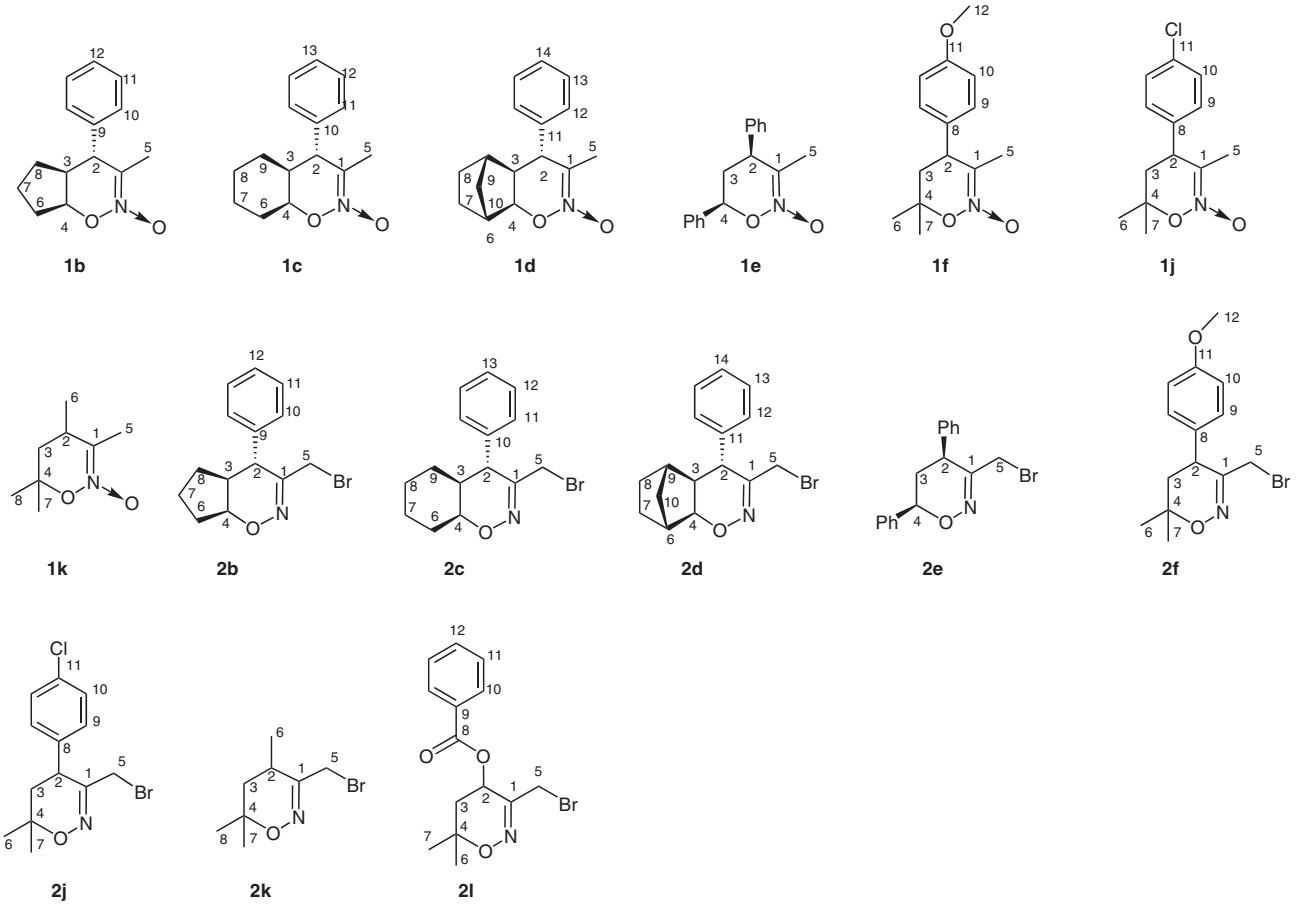


Figure 1

5,6-Dihydro-4*H*-1,2-oxazine 2-Oxides 1a–l

1,2-Oxazine 2-oxides **1a**,**g**,**h**,**i**[9] and **1l**[8] were prepared by known procedures. The 2-oxides **1b**–**d** were obtained by a procedure used for the synthesis of *rel*-(4*R*,5*S*,6*S*)-4-(4-methoxyphenyl)-3-methyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine 2-oxide,[9] with small modifications: for compounds **1c**,**d**, the reaction mixture was kept at –30 °C for 30 min. The 2-oxides **1e**,**f**,**j**,**k** were obtained by a procedure used for the synthesis of 5,6-dihydro-3,6,6-trimethyl-4-phenyl-1,2-oxazine 2-oxide.[9]

***rel*-(4*S*,4a*S*,7a*S*)-3-Methyl-4-phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*e*][1,2]oxazine 2-Oxide (1b)**

Yield: 75%; mp 91–95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.93 [m, 6 H, $H_2C(6)$, $H_2C(7)$, $H_2C(8)$], 1.76 [s, 3 H, $H_3C(5)$], 2.32 [dd, *J* = 4.6, 5.3 Hz, 1 H, HC(3)], 3.47 [d, *J* = 4.6 Hz, 1 H, HC(2)], 4.81 [dt, *J* = 3.3, 5.3 Hz, 1 H, HC(4)], 7.08–7.31 [m, 5 H, HC(10), HC(11), HC(12)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (C-5), 22.4, 30.4, 31.9 (C-6, C-7, C-8), 46.8 (C-3), 48.0 (C-2), 84.7 (C-4), 124.2 (C-1), 127.6, 128.2, 129.1 (C-10, C-11, C-12), 140.1 (C-9).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.63; H, 7.41; N, 6.00.

***rel*-(4*S*,4a*S*,8a*S*)-3-Methyl-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine 2-Oxide (1c)**

Yield: 80%; mp 87–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45–2.15 [m, 9 H, HC(3), $H_2C(6)$, $H_2C(7)$, $H_2C(8)$, $H_2C(9)$], 1.87 [s, 3 H, $H_3C(5)$], 3.33 [s, 1 H, HC(2)], 4.56 [s, 1 H, HC(4)], 7.15–7.36 [m, 5 H, HC(11), HC(12), HC(13)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (C-5), 19.9, 24.6, 27.4, 28.7 (C-6, C-7, C-8, C-9), 42.3 (C-2), 55.4 (C-3), 78.9 (C-4), 121.0 (C-1), 126.5, 128.6, 128.8 (C-11, C-12, C-13), 136.9 (C-10).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.40; H, 7.80; N, 5.81.

***rel*-(4*R*,4a*S*,5*S*,8a*S*)-3-Methyl-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-5,8-methano-1,2-benzoxazine 2-Oxide (1d)**

Yield: 72%; mp 110–111 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19–1.72 [m, 6 H, $H_2C(7)$, $H_2C(8)$, $H_2C(10)$], 2.06 [s, 3 H, $H_3C(5)$], 2.27, 2.31–2.45 [2 m, 3 H, HC(3), HC(6), HC(9)], 3.57 [br s, 1 H, HC(2)], 4.06 [br s, 1 H, HC(4)], 7.18–7.36 [m, 5 H, HC(12), HC(13), HC(14)].

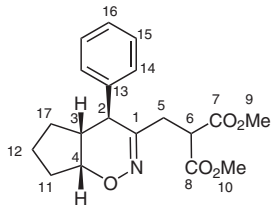
^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (C-5), 21.0, 26.1, 34.3 (C-7, C-8, C-10), 37.4, 42.6 (C-6, C-9), 44.0, 44.2 (C-2, C-3), 75.5 (C-4), 122.0 (C-1), 126.7, 128.9, 128.7 (C-12, C-13, C-14), 136.9 (C-11).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.65; H, 7.40; N, 5.13.

***rel*-(4*S*,6*R*)-3-Methyl-4,6-diphenyl-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide (1e)**

Yield: 75%; mp 60–68 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 [s, 3 H, $H_3C(5)$], 2.21 [ddd, *J* = 11.0, 13.2, 8.8 Hz, 1 H, $H_2C(3)$], 2.45 [dd, *J* = 8.5, 13.2 Hz, 1 H,



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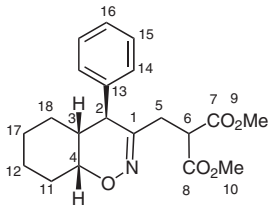

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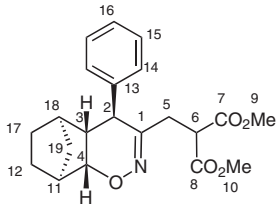

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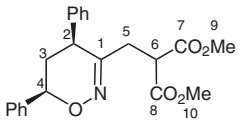

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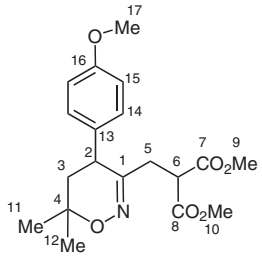

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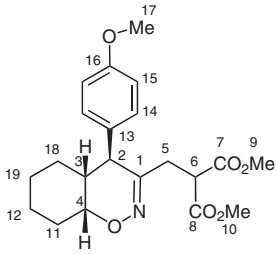

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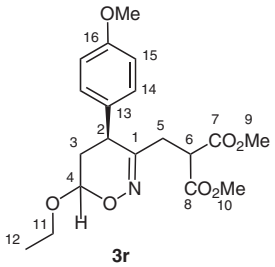

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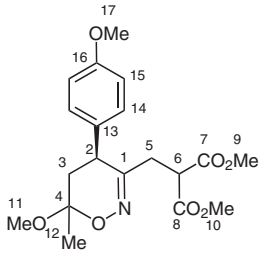

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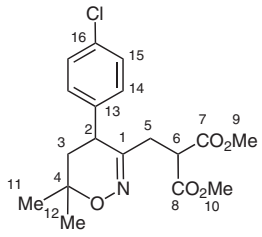

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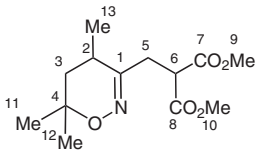

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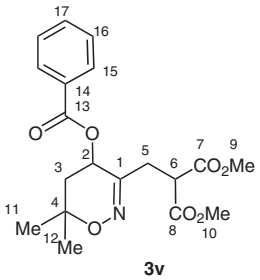

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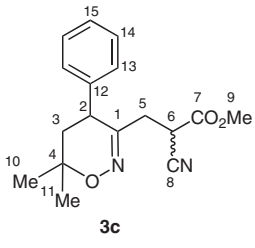

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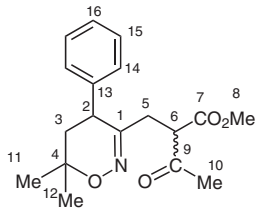

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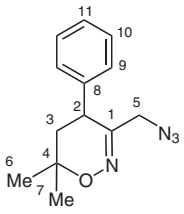

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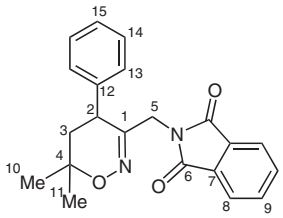

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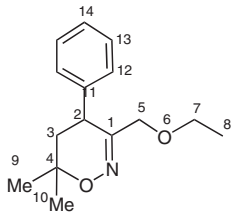

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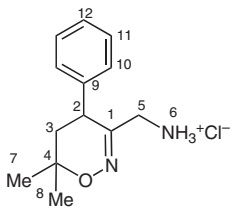
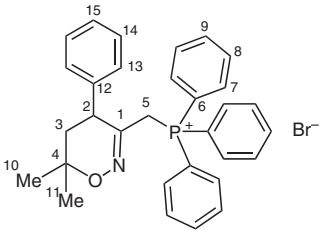
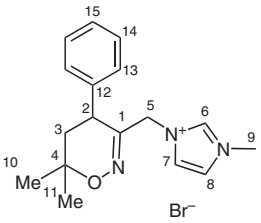


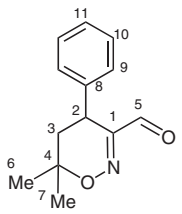
3i



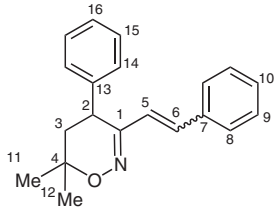
3e



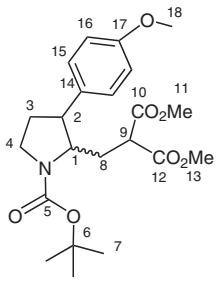
3j



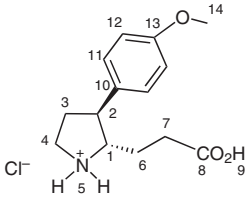
6



5



7



8

Figure 2

$H_2C(3)$], 3.57 [dd, J = 8.5, 8.8 Hz, 1 H, HC(2)], 5.65 [d, J = 11.0 Hz, 1 H, HC(4)], 7.30–7.36 [m, 10 H, Ph].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5 (C-5), 37.1 (C-3), 40.2 (C-2), 82.3 (C-4), 122.7 (C-1), 126.8, 126.9, 128.4, 128.6, 128.8, 136.7, 137.3 (Ph).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.90; H, 6.04; N, 5.59.

4-(4-Methoxyphenyl)-3,6,6-trimethyl-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide (1f)
Yield: 71%; mp 114–115 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37, 1.43 [2 s, 6 H, $H_3C(6)$, $H_3C(7)$], 1.82 [s, 3 H, $H_3C(5)$], 1.91 [dd, J = 10.4, 13.8 Hz, 1 H, $H_2C(3)$], 2.06 [dd, J = 8.2, 13.8 Hz, 1 H, $H_2C(3)$], 3.42 [dd, J = 8.2, 10.4 Hz, 1 H, HC(2)], 3.77 [s, 3 H, $H_3C(12)$], 6.85 [d, J = 7.9 Hz, 2 H, HC(10)], 7.08 [d, J = 7.9 Hz, 2 H, HC(9)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2 (C-5, C-6), 27.8 (C-7), 41.8 (C-3), 42.5 (C-2), 55.3 (C-12), 81.2 (C-4), 114.6 (C-10), 122.1 (C-1), 128.9 (C-9), 132.3 (C-8), 159.1 (C-11).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.44; H, 7.63; N, 5.60.

4-(4-Chlorophenyl)-3,6,6-trimethyl-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide (1j)
Yield: 83%; mp 67–69 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34, 1.43 [2 s, 6 H, $H_3C(6)$, $H_3C(7)$], 1.92 [s, 3 H, $H_3C(5)$], 1.90 [dd, J = 10.7, 13.5 Hz, 1 H, $H_2C(3)$], 2.12 [dd, J = 8.5, 13.5 Hz, 1 H, $H_2C(3)$], 3.40 [dd, J = 8.5, 10.7 Hz, 1 H, HC(2)], 7.13 [d, J = 8.8 Hz, 2 H, HC(10)], 7.33 [d, J = 8.8 Hz, 2 H, HC(9)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (C-5), 22.7 (C-6), 27.8 (C-7), 40.1 (C-3), 43.6 (C-2), 80.7 (C-4), 122.1 (C-1), 129.3, 129.7 (C-9, C-10), 133.3 (C-8), 138.6 (C-11).

Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.88; H, 6.53; N, 5.21.

3,4,6,6-Tetramethyl-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide (1k)
Yield: 61%; oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 [d, J = 5.0 Hz, 3 H, $H_3C(6)$], 1.29, 1.31 [2 s, 6 H, $H_3C(7)$, $H_3C(8)$], 1.52 [dd, J = 10.3, 13.5, 1 H, HC(3)], 1.86 [dd, J = 7.4, 13.5 Hz, 1 H, HC(3)], 2.00 [s, 3 H, $H_3C(5)$], 2.54 [m, 1 H, HC(2)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9 (C-6), 18.3 (C-5), 22.6, 27.7 (C-7, C-8), 30.2 (C-2), 40.0 (C-3), 80.6 (C-4), 124.1 (C-1).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.40; H, 9.90; N, 8.96.

3-(Bromomethyl)-5,6-dihydro-4*H*-1,2-oxazines 2a–l; General Procedure
The appropriate 1,2-oxazine 2-oxide **1** (0.1 mol) was slowly added to a stirred soln of TMSBr (39.6 mL, 0.3 mol) and Et_3N (16.7 mL, 0.12 mol) in CH_2Cl_2 (0.5 L) at –80 °C. The resulting mixture was stirred for 1 h at –80 °C, then MeCN (50 mL) was added and the temperature was increased to –30 °C within 1 h. The mixture was kept for 3 h at –30 °C and then diluted with EtOAc (0.5 L) and poured into a mixture of EtOAc (1.0 L) and a sat. aq soln of $NaHCO_3$ (0.5 L). The aqueous phase was back-extracted with EtOAc (2 × 100 mL), and the combined organic layers were washed with H_2O (2 × 100 mL) and brine (200 mL) and dried (Na_2SO_4). The solvents were evaporated in vacuo and the residue was filtered through a thin layer of silica gel. Bromide **2e** was further recrystallised from hexane–EtOAc (5:1). (The characteristics of oxazines **2a**,**g–i** have been published elsewhere.[8])

***rel*-(4*S*,4a*S*,7a*S*)-3-(Bromomethyl)-4-phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*e*][1,2]oxazine (2b)**
Yield: 50%; mp 45–49 °C; (hexane–AcOEt, 1:1); R_f = 0.81 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–2.18 [m, 7 H, HC(3), $H_2C(6)$, $H_2C(7)$, $H_2C(8)$], 3.72 [s, 1 H, HC(2)], 3.77 [d, J = 9.9 Hz, 1 H, $H_2C(5)$], 4.09 [d, J = 9.9 Hz, 1 H, $H_2C(5)$], 4.22 [t, J = 3.3 Hz, 1 H, HC(4)], 7.14–7.41 [m, 5 H, HC(10), HC(11), HC(12)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 28.9, 31.5 (C-6, C-7, C-8), 31.9 (C-5), 38.7 (C-3), 43.6 (C-2), 75.7 (C-4), 127.4, 127.9, 129.2 (C-10, C-11, C-12), 141.0 (C-9), 153.5 (C-1).

Anal. Calcd for $C_{14}H_{16}BrNO$: C, 57.16; H, 5.48; N, 4.76. Found: C, 57.57; H, 5.43; N, 4.50.

***rel*-(4*S*,4a*S*,8a*S*)-3-(Bromomethyl)-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine (2c)**
Yield: 40%; mp 70–74 °C; (hexane–EtOAc, 1:1); R_f = 0.80 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79–2.14 [m, 9 H, HC(3), $H_2C(6)$, $H_2C(7)$, $H_2C(8)$, $H_2C(9)$], 3.61 [s, 1 H, HC(2)], 3.81 [d, J = 10.3 Hz, 1 H, $H_2C(5)$], 4.04 [s, 1 H, HC(4)], 4.16 [d, J = 10.3 Hz, 1 H, $H_2C(5)$], 7.13–7.39 [m, 5 H, HC(11), HC(12), HC(13)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 24.9, 27.4, 29.1 (C-6, C-7, C-8, C-9), 32.0 (C-5), 38.3 (C-3), 43.2 (C-2), 69.4 (C-4), 127.4, 128.2, 129.0 (C-11, C-12, C-13), 140.6 (C-10), 152.2 (C-1).

Anal. Calcd for $C_{15}H_{18}BrNO$: C, 58.45; H, 5.89; N, 4.54. Found: C, 58.30; H, 5.90; N, 4.60.

***rel*-(4*R*,4a*S*,5*S*,8a*S*)-3-(Bromomethyl)-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-5,8-methano-1,2-benzoxazine (2d)**
Yield: 64%; mp 51–57 °C; (hexane–EtOAc, 1:1); R_f = 0.73 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.70, 1.98–2.30 [2 m, 8 H, HC(3), $H_2C(7)$, $H_2C(8)$, $H_2C(10)$, HC(9)], 2.47 [d, J = 4.6 Hz, 1 H, HC(6)], 3.39 [d, J = 7.5 Hz, 1 H, HC(2)], 3.90 [d, J = 5.5 Hz, 1 H, HC(4)], 4.04 [s, 2 H, $H_2C(5)$], 7.20–7.44 [m, 5 H, HC(12), HC(13), HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 28.5, 29.0, 33.5 (C-7, C-8, C-10, C-5), 39.9 (C-2), 42.0, 42.5 (C-3, C-9), 53.4 (C-6), 83.0 (C-4), 127.6, 129.0, 129.5 (C-12, C-13, C-14), 137.6 (C-11), 172.6 (C-1).

Anal. Calcd for $C_{16}H_{18}BrNO$: C, 60.01; H, 5.67; N, 4.37. Found: C, 60.42; H, 5.90; N, 4.56.

***rel*-(4*S*,6*R*)-3-(Bromomethyl)-4,6-diphenyl-5,6-dihydro-4*H*-1,2-oxazine (2e)**
Yield: 53%; mp 83–87 °C; R_f = 0.79 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 [ddd, J = 12.0, 11.8, 13.3 Hz, 1 H, $H_2C(3)$], 2.49 [ddd, J = 2.0, 8.6, 13.3 Hz, 1 H, $H_2C(3)$], 3.88 [d, J = 12.0 Hz, 1 H, $H_2C(5)$], 4.10 [dd, J = 8.6, 12.0 Hz, 1 H, HC(2)], 4.22 [d, J = 12.0 Hz, 1 H, $H_2C(5)$], 4.88 [dd, J = 2.0, 11.8 Hz, 1 H, HC(4)], 7.36–7.41 [m, 10 H, Ph].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.5 (C-5), 34.0 (C-3), 36.6 (C-2), 73.8 (C-4), 126.7, 126,8, 128.6, 128.7, 129.0, 129.3, 139.0, 140.6 (Ph), 153.9 (C-3).

Anal. Calcd for $C_{17}H_{16}BrNO$: C, 61.83; H, 4.88; N, 4.24. Found: C, 61.95; H, 5.00; N, 4.50.

3-(Bromomethyl)-4-(4-methoxyphenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazine (2f)
Yield: 57%; oil; R_f = 0.88 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32, 1.37 [2 s, 6 H, $H_3C(6)$, $H_3C(7)$], 1.94 [dd, *J* = 12.5, 13.3 Hz, 1 H, $H_2C(3)$], 2.11 [dd, *J* = 7.8, 13.3 Hz, 1 H, $H_2C(3)$], 3.63 [d, *J* = 9.8 Hz, 1 H, $H_2C(5)$], 3.80 [dd, *J* = 7.8, 12.5 Hz, 1 H, HC(2)], 3.81 [s, 3 H, $H_3C(12)$], 3.98 [d, *J* = 9.8 Hz, 1 H, $H_2C(5)$], 6.89 [d, *J* = 6.8, 2 H, HC(10)], 7.14 [d, *J* = 6.8, 2 H, HC(9)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4 (C-6, C-7), 31.9 (C-5), 36.1 (C-3), 40.2 (C-2), 55.3 (C-12), 75.8 (C-4), 114.7 (C-10), 129.4 (C-9), 130.9 (C-8), 155.8 (C-1), 159.1 (C-11).

Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.86; H, 5.81; N, 4.49. Found: C, 53.80; H, 6.00; N, 4.40.

3-(Bromomethyl)-4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazine (2j)

Yield: 47%; mp 87–88 °C; (hexane–EtOAc, 1:1); R_f = 0.76 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32, 1.38 [2 s, 6 H, $H_3C(6)$, $H_3C(7)$], 1.91 [dd, *J* = 12.3, 13.5 Hz, 1 H, HC(3)], 2.11 [dd, *J* = 13.5, 7.6 Hz, 1 H, HC(3)], 3.62 [d, *J* = 10.1 Hz, 1 H, $H_2C(5)$], 3.85 [dd, *J* = 12.3, 7.6 Hz, 1 H, HC(2)], 4.01 [d, *J* = 10.1 Hz, 1 H, $H_2C(5)$], 7.19 [d, *J* = 7.6 Hz, 2 H, HC(10)], 7.35 [d, *J* = 7.6 Hz, 2 H, HC(9)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 28.3 (C-6, C-7), 31.3 (C-5), 38.2 (C-2), 40.0 (C-3), 77.1 (C-4), 129.5, 129.7 (C-9, C-10), 132.1 (C-8), 137.6 (C-11), 154.9 (C-1).

Anal. Calcd for $C_{13}H_{15}ClBrNO$: C, 49.31; H, 4.78; N, 4.42. Found: C, 49.50; H, 4.70; N, 4.40.

3-(Bromomethyl)-4,6,6-trimethyl-5,6-dihydro-4*H*-1,2-oxazine (2k)

Yield: 62%; oil; R_f = 0.55 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 [d, *J* = 7.4 Hz, 3 H, $H_3C(6)$], 1.20, 1.31 [2 s, 6 H, $H_3C(7)$, $H_3C(8)$], 1.50 [dd, *J* = 12.5, 13.0 Hz, 1 H, $H_2C(3)$], 1.87 [dd, *J* = 7.4, 13.0 Hz, 1 H, $H_2C(3)$], 2.70 [ddq, *J* = 7.4, 11.0, 12.5 Hz, 1 H, HC(2)], 4.07 [d, *J* = 10.3 Hz, 1 H, $H_2C(5)$], 4.16 [d, *J* = 10.3 Hz, 1 H, $H_2C(5)$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (C-6), 23.5, 24.0 (C-7, C-8), 28.3 (C-5), 31.2 (C-2), 38.8 (C-3), 75.4 (C-4), 156.7 (C-1).

Anal. Calcd for $C_8H_{14}BrNO$: C, 43.65; H, 6.41; N, 6.36. Found: C, 44.01; H, 6.53; N, 6.20.

3-(Bromomethyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazin-4-yl Benzoate (2l)

Yield: 68%; oil; R_f = 0.76 (silica gel, hexane–EtOAc, 1:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40, 1.45 [2 s, 6 H, $H_3C(6)$, $H_3C(7)$], 2.01 [dd, *J* = 6.0, 13.8 Hz, 1 H, $H_2C(3)$], 2.40 [dd, *J* = 6.6, 13.8 Hz, 1 H, $H_2C(3)$], 4.15 [d, *J* = 11.8 Hz, 1 H, $H_2C(5)$], 4.47 [d, *J* = 11.8 Hz, 1 H, $H_2C(5)$], 5.80 [dd, *J* = 6.6, 6.0 Hz, 1 H, HC(2)], 7.48 [t, *J* = 7.2 Hz, 2 H, HC(11)], 7.63 [t, *J* = 7.2 Hz, 1 H, HC(12)], 8.10 [d, *J* = 7.2 Hz, 2 H, HC(10)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (C-6, C-7), 30.3 (C-5), 36.1 (C-3), 59.5 (C-2), 75.7 (C-4), 128.6 (C-11), 129.2 (C-9), 129.7 (C-10), 133.6 (C-12), 151.3 (C-1), 165.2 (C-8).

Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; N, 4.29. Found: C, 51.50; H, 4.90; N, 4.24.

Malonates 3b,k–v; General Procedure

t-BuOK (0.13 g, 1.2 mmol) was added to a stirred soln of dimethyl malonate (0.16 g, 1.2 mmol) in DMF (1 mL) at 0 °C. After 5 min, a soln of the appropriate oxazine **2** (1 mmol) in DMF (1.5 mL) was carefully added. The resulting mixture was stirred for 2 h at 60 °C and poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel to give corresponding derivatives (see Table 1 for yields).

Dimethyl 2-{[*rel*-(4*S*,4a*R*,7a*R*)-4-Phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*e*][1,2]oxazin-3-yl]methyl}malonate (3k)

Mp 120–131 °C; R_f = 0.65 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36–2.03, 2.06–2.22 [2 m, 7 H, HC(3), $H_2C(11)$, $H_2C(12)$, $H_2C(17)$], 2.58 [dd, *J* = 8.1, 16.9 Hz, 1 H, HC(5)], 2.77 [dd, *J* = 7.4, 16.9 Hz, 1 H, HC(5)], 3.22 [d, *J* = 2.2 Hz, 1 H, HC(2)], 3.70, 3.71 [2 s, 6 H, $H_3C(9)$, $H_3C(10)$], 3.98 [dd, *J* = 7.4, 8.1 Hz, 1 H, HC(6)], 4.11 [m, 1 H, HC(4)], 7.16–7.41 [m, 5 H, HC(14), HC(15), HC(16)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 29.6, 31.6 (C-11, C-12, C-17), 33.4 (C-5), 43.3, 44.8 (C-2, C-3), 48.0 (C-6), 52.5 (C-9, C-10), 75.7 (C-4), 127.2, 128.1, 129.0 (C-14, C-15, C-16), 141.0 (C-13), 156.3 (C-1), 169.3, 169.4 (C-7, C-8).

Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.15; H, 6.80; N, 4.10.

Dimethyl 2-{[*rel*-(4*S*,4a*R*,8a*R*)-4-Phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazin-3-yl]methyl}malonate (3l)

Mp 70–77 °C; R_f = 0.59 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15–1.47, 1.50–1.78 [2 m, 9 H, $H_{eq}C(3)$, $H_2C(11)$, $H_2C(12)$, $H_2C(17)$, $H_2C(18)$], 2.60 [dd, *J* = 7.4, 16.9 Hz, 1 H, HC(5)], 2.83 [dd, *J* = 7.4, 16.9 Hz, 1 H, HC(5)], 3.06 [s, 1 H, HC(2)], 3.71 [s, 6 H, $H_3C(9)$, $H_3C(10)$], 3.95 [s, 1 H, HC(4)], 4.02 [t, *J* = 7.4 Hz, 1 H, HC(6)], 7.12–7.39 [m, 5 H, HC(14), HC(15), HC(16)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 25.0, 27.7, 29.2 (C-11, C-12, C-17, C-18), 33.8 (C-5), 39.3 (C-2), 47.5 (C-3), 48.0 (C-6), 52.6 (C-9, C-10), 68.4 (C-4), 127.1, 128.2, 128.9 (C-14, C-15, C-16), 141.2 (C-13), 151.9 (C-1), 169.3, 169.5 (C-7, C-8).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.99; H, 7.13; N, 4.04.

Dimethyl 2-{[*rel*-(4*R*,4a*S*,5*R*,8*S*,8a*S*)-4-Phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-5,8-methano-1,2-benzoxazin-3-yl]methyl}malonate (3m)

Oil; R_f = 0.61 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.70, 1.88–2.19 [2 m, 8 H, HC(3), $H_2C(12)$, $H_2C(17)$, $H_2C(19)$, HC(18)], 2.37 [dd, *J* = 7.2, 17.7 Hz, 1 H, HC(5)], 2.47 [d, *J* = 4.6 Hz, 1 H, HC(11)], 2.72 [dd, *J* = 7.2, 17.2 Hz, 1 H, HC(5)], 3.19 [d, *J* = 10.5 Hz, 1 H, HC(2)], 3.66, 3.69 [s, 6 H, $H_3C(9)$, $H_3C(10)$], 3.90 [s, 1 H, HC(4)], 3.90 [dd, *J* = 7.2, 7.2 Hz, 1 H, HC(6)], 7.20–7.44 [m, 5 H, HC(14), HC(15), HC(16)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 29.0, 27.7, 32.2 (C-12, C-17, C-19), 33.4 (C-5), 39.9 (C-2), 42.0, 43.5 (C-3, C-18), 47.4 (C-6), 52.7, 53.0 (C-9,C-10, C-11), 82.8 (C-4), 127.6, 129.0, 129.5 (C-14, C-15, C-16), 137.6 (C-13), 169.0, 169.5 (C-7, C-8), 172.6 (C-1).

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.82; H, 6.79; N, 3.90.

Dimethyl 2-{[*rel*-(4*S*,6*R*)-4,6-Diphenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl}malonate (3n)

Mp 83–89 °C; R_f = 0.61 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 [ddd, *J* = 6.8, 13.0, 2.0 Hz, 1 H, HC(3)], 2.43 [ddd, *J* = 7.3, 13.0, 10.1 Hz, 1 H, HC(3)], 2.70 [dd, *J* = 8.0, 17.0 Hz, 1 H, HC(5)], 2.92 [dd, *J* = 8.0, 17.0 Hz, 1 H, HC(5)], 3.60 [m, 7 H, HC(2), $H_3C(9)$, $H_3C(10)$], 4.10 [t, *J* = 8.0 Hz,

1 H, HC(6)], 4.99 [dd, 1 H, *J* = 2.0, 10.1 Hz, HC(4)], 7.20–7.44 [m, 10 H, Ph].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.9 (C-5), 34.5 (C-3), 40.0 (C-2), 47.5 (C-6), 52.7, 53.0 (C-9, C-10), 73.0 (C-4), 127.6, 127.9, 128.5, 129.0, 129.5, 138.0, 139.9 (Ph), 153.7 (C-1), 169.0, 169.5 (C-7, C-8).

Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.29; H, 6.12; N, 3.45.

Dimethyl 2-{[4-(4-Methoxyphenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl}malonate (3o)
Oil; R_f = 0.59 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22, 1.32 [2 s, 6 H, H_3C(11), H_3C(12)], 1.88 [dd, *J* = 11.8, 13.2 Hz, 1 H, H_2C(3)], 2.03 [dd, *J* = 8.1, 13.2 Hz, 1 H, H_2C(3)], 2.55 [m, 2 H, H_2C(5)], 3.40 [dd, *J* = 8.1, 11.8 Hz, 1 H, HC(2)], 3.68, 3.69 [2 s, 6 H, H_3C(9), H_3C(10)], 3.81 [s, 3 H, H_3C(17)], 3.96 [t, *J* = 7.9 Hz, 1 H, HC(6)], 6.89 [d, *J* = 8.5 Hz, 2 H, HC(15)], 7.12 [d, *J* = 8.5 Hz, 2 H, HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 28.5 (C-11, C-12), 32.5 (C-5), 39.7 (C-2), 41.3 (C-3), 48.2 (C-6), 52.7 (C-9, C-10), 55.3 (C-17), 74.4 (C-4), 114.6 (C-15), 129.4 (C-14), 131.9 (C-13), 155.6 (C-1), 158.9 (C-16), 169.7 (C-7, C-8).

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.51; H, 6.80; N, 3.80.

Dimethyl 2-{[*rel*-(4*S*,4a*R*,8a*R*)-4-(4-Methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazin-3-yl]methyl}malonate (3p)
Mp 101–107 °C; (hexane–EtOAc, 1:1); R_f = 0.63 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.49, 1.51–1.81 [2 m, 9 H, HC(3), H_2C(11), H_2C(12), H_2C(18), H_2C(19)], 2.59 [dd, *J* = 7.4, 16.9 Hz, 1 H, HC(5)], 2.83 [dd, *J* = 8.1, 16.9 Hz, 1 H, HC(5)], 3.00 [s, 1 H, HC(2)], 3.72, 3.74 [2 s, 6 H, H_3C(9), H_3C(10)], 3.78 [s, 3 H, H_3C(17)], 3.94 [s, 1 H, HC(4)], 4.01 [dd, *J* = 7.4, 8.1 Hz, 1 H, HC(6)], 6.87 [d, *J* = 8.5 Hz, 2 H, HC(15)], 7.07 [d, *J* = 8.5 Hz, 2 H, HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 25.0, 27.6, 29.2 (C-11, C-12, C-18, C-19), 33.7 (C-5), 39.4 (C-2), 46.6 (C-3), 48.0 (C-6), 52.6 (C-9, C-10), 55.2 (C-17), 68.4 (C-4), 114.6 (C-15), 129.4 (C-14), 131.9 (C-13), 152.2 (C-1), 158.7 (C-16), 169.4, 169.5 (C-7, C-8).

Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.90; H, 7.05; N, 3.66.

Dimethyl 2-{[*rel*-(4*S*,6*R*)-6-Ethoxy-4-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl}malonate (3r)
Mp 56–59 °C; (hexane–EtOAc, 1:1); R_f = 0.63 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 [m, 3 H, H_3C(12)], 1.80 [dd, *J* = 11.8, 13.7 Hz, 1 H, H_2C(3)], 2.20 [m, 1 H, H_2C(3)], 2.45 [m, 2 H, H_2C(5)], 3.50 [m, 2 H, HC(2), H_2C(11)], 3.66 [s, 6 H, H_3C(9), H_3C(10)], 3.76 [m, 4 H, H_3C(17), HC(11)], 3.96 [t, *J* = 8.1 Hz, 1 H, HC(6)], 5.64 [br s, 1 H, HC(4)], 6.84 [d, *J* = 8.5 Hz, 2 H, HC(15)], 7.07 [d, *J* = 8.5 Hz, 2 H, HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3 (C-12), 32.8 (C-5), 37.4 (C-2), 40.0 (C-3), 48.0 (C-6), 52.7 (C-9, C-10), 55.2 (C-17), 62.3 (C-11), 101.0 (C-4), 114.5 (C-15), 129.4 (C-14), 131.5 (C-13), 158.1 (C-1), 158.8 (C-16), 169.3, 169.4 (C-7, C-8).

Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.35; H, 6.69; N, 3.81.

Dimethyl 2-{[*rel*-(4*S*,6*S*)-6-Methoxy-4-(4-Methoxyphenyl)-6-methyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl}malonate (3s)
Oil; R_f = 0.61 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 [s, 3 H, H_3C(12)], 1.85 [dd, *J* = 11.8, 13.2 Hz, 1 H, H_2C(3)], 2.19 [dd, *J* = 8.1, 13.2 Hz, 1 H, H_2C(3)], 2.51 [m, 2 H, H_2C(5)], 3.20 [s, 3 H, H_3C(11)], 3.50 [dd, *J* = 8.1, 11.8 Hz, 1 H, HC(2)], 3.66 [s, 6 H, H_3C(9), H_3C(10)], 3.76 [s, 3 H, H_3C(17)], 3.96 [t, *J* = 8.1 Hz, 1 H, HC(6)], 6.84 [d, *J* = 8.5 Hz, 2 H, HC(15)], 7.07 [d, *J* = 8.5 Hz, 2 H, HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (C-12), 32.4 (C-5), 38.5, 39.6 (C-2, C-3), 48.0 (C-6), 49.3 (C-11), 52.6 (C-9, C-10), 55.2 (C-17), 97.4 (C-4), 114.5 (C-15), 129.4 (C-14), 131.5 (C-13), 157.7 (C-1), 158.8 (C-16), 169.3, 169.4 (C-7, C-8).

Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 59.88; H, 6.35; N, 3.90.

Dimethyl 2-{[4-(4-Chlorophenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl}malonate (3t)
Oil; R_f = 0.69 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22, 1.32 [2 s, 6 H, H_3C(11), H_3C(12)], 1.83 [dd, *J* = 11.8, 13.2 Hz, 1 H, H_2C(3)], 2.03 [dd, *J* = 8.1, 13.2 Hz, 1 H, H_2C(3)], 2.52 [m, 2 H, H_2C(5)], 3.38 [dd, *J* = 8.1, 11.8 Hz, 1 H, HC(2)], 3.70 [s, 6 H, H_3C(9), H_3C(10)], 3.97 [t, *J* = 7.7 Hz, 1 H, HC(6)], 7.13 [d, *J* = 8.8 Hz, 2 H, HC(15)], 7.33 [d, *J* = 8.8 Hz, 2 H, HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 28.3 (C-11, C-12), 32.4 (C-5), 40.0 (C-2), 41.3 (C-3), 48.2 (C-6), 52.6 (C-9, C-10), 74.2 (C-4), 129.3, 129.7 (C-14, C-15), 133.3 (C-13), 138.6 (C-16), 154.6 (C-1), 169.4, 169.5 (C-7, C-8).

Anal. Calcd for $C_{18}H_{22}ClNO_5$: C, 58.78; H, 6.03; N, 3.81. Found: C, 58.27; H, 5.87; N, 3.49.

Dimethyl 2-[(4,6,6-Trimethyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl]malonate (3u)
Mp 71–79 °C; (hexane–EtOAc, 1:1); R_f = 0.57 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07, 1.22 [2 s, 6 H, H_3C(11), H_3C(12)], 1.13 [d, *J* = 6.6 Hz, 3 H, H_3C(13)], 1.43 [dd, *J* = 11.8, 13.2 Hz, 1 H, H_2C(3)], 1.77 [dd, *J* = 7.4, 13.2 Hz, 1 H, H_2C(3)], 2.24 [m, 1 H, HC(2)], 2.72 [dd, *J* = 8.1, 16.7 Hz, 1 H, HC(5)], 2.87 [dd, *J* = 7.4, 16.7 Hz, 1 H, HC(5)], 3.69, 3.70 [2 s, 6 H, H_3C(9), H_3C(10)], 3.95 [dd, *J* = 7.4, 8.1 Hz, 1 H, HC(6)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1 (C-13), 23.0, 27.1 (C-11, C-12), 28.2 (C-2), 31.5 (C-5), 39.6 (C-3), 48.0 (C-6), 52.5 (C-9, C-10), 73.9 (C-4), 156.9 (C-1), 169.5, 169.6 (C-7, C-8).

Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.29; H, 7.89; N, 5.00.

Dimethyl 2-{[4-(Benzoyloxy)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl}malonate (3v)
Oil; R_f = 0.61 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30, 1.40 [2 s, 6 H, H_3C(11), H_3C(12)], 1.93 [dd, *J* = 6.2, 12.5 Hz, 1 H, H_2C(3)], 2.17 [dd, *J* = 7.0, 12.5 Hz, 1 H, H_2C(3)], 2.69 [m, 2 H, H_2C(5)], 3.68 [s, 6 H, H_3C(9), H_3C(8)], 3.72 [t, *J* = 7.8 Hz, 1 H, HC(6)], 5.60 [dd, *J* = 6.2, 7.0 Hz, 1 H, HC(2)], 7.45 [t, *J* = 7.2 Hz, 2 H, HC(16)], 7.65 [t, *J* = 7.2 Hz, 1 H, HC(17)], 8.10 [d, *J* = 7.2 Hz, 2 H, HC(15)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 27.0 (C-11, C-12), 31.5 (C-5), 40.2 (C-3), 48.0 (C-6), 52.5 (C-9, C-10), 60.0 (C-2), 73.9 (C-4), 128.7 (C-16), 129.0 (C-14), 129.9 (C-15), 133.4 (C-17), 151.9 (C-1), 165.2 (C-13), 169.5, 169.6 (C-7, C-8).

Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.78; H, 6.01; N, 4.02.

Methyl 2-Cyano-3-(6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)propanoate (3c)

Methyl cyanoacetate (0.1 mL, 1.2 mmol) was added dropwise to a stirred soln of *t*-BuOK (0.13 g, 1.2 mmol) in DMF (1 mL) at 0 °C. After 20 min, a soln of oxazine **2a** (0.28 g, 1 mmol) in DMF (1.5 mL) was added, and the resulting mixture was stirred for 2 h at 60 °C. Then the mixture was poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL); and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel; this gave **3c** as a mixture of isomers (1.1:1).

Yield: 0.29 g (98%); oil; R_f = 0.62 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25, 1.28, 1.34 [3 s, 3 H, 3 H, 6 H, H_3C(10), H_3C(11)], 1.90 [dd, *J* = 11.8, 13.8 Hz, 1 H, H_2C(3)], 2.08 [dd, *J* = 7.9, 13.8 Hz, 1 H, H_2C(3)], 2.47, 2.57, 2.71 [dd, *J* = 7.2, 16.7 Hz, d, *J* = 7.2 Hz, dd, *J* = 6.6, 16.7 Hz, 2 H, H_2C(5)], 3.40 [dd, *J* = 7.9, 11.8 Hz, 1 H, HC(2)], 3.76, 3.78 [s, 3 H, H_3C(9)], 3.96, 4.02 [dd, *J* = 7.2, 6.6 Hz, dd, *J* = 7.2, 7.2 Hz, 1 H, HC(6)], 7.12–7.42 [m, 5 H, HC(13), HC(14), HC(15)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 22.7, 28.4 (C-10, C-11), 32.8, 33.1, 33.2, 33.8 (C-5, C-6), 40.4 (C-2), 40.9 (C-3), 53.6 (C-9), 74.9 (C-4), 116.5 (C-8), 127.7, 128.3, 129.4 (C-13, C-14, C-15), 139.4 (C-12), 152.9, 153.1 (C-1), 166.1 (C-7).

Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.15; H, 6.63; N, 9.04.

Methyl 2-[(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl]-3-oxobutanoate (3d)

Methyl acetoacetate (0.15 mL, 1.2 mmol) was added dropwise to a stirred soln of *t*-BuOK (0.13 g, 1.2 mmol) in DMF (1 mL), and then a soln of oxazine **2a** (0.28 g, 1 mmol) in DMF (1.5 mL) was added dropwise. The resulting mixture was stirred for 3 h at 60 °C and poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel; this gave **3d** as a mixture of isomers (1.1:1).

Yield: 0.26 g (78%); oil; R_f = 0.58 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17, 1.22, 1.30 [3 s, 3 H, 3 H, 6 H, H_3C(11), H_3C(12)], 1.83 [dd, *J* = 7.2, 13.1 Hz, 1 H, H_2C(3)], 2.02 [dd, *J* = 8.2, 13.1 Hz, 1 H, H_2C(3)], 2.29 [s, 3 H, H_3C(10)], 2.37 [dd, *J* = 11.6, 17.1 Hz, 1 H, H_2C(5)], 2.59 [dd, *J* = 9.2, 17.1 Hz, 1 H, H_2C(5)], 3.35 [dd, *J* = 8.2, 11.2 Hz, 1 H, HC(2)], 3.66 [s, 3 H, H_3C(8)], 4.13 [m, 1 H, HC(6)], 7.08–7.39 [m, 5 H, HC(14), HC(15), HC(16)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 28.5 (C-11, C-12), 31.8 (C-5), 40.5, 40.8 (C-2, C-10), 41.4 (C-3), 52.6 (C-8), 54.8 (C-6), 74.3 (C-4), 127.5, 128.4, 129.2 (C-14, C-15, C-16), 140.2 (C-13), 155.6, 155.9 (C-1), 169.8 (C-7), 202.9 (C-9).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.25; H, 7.33; N, 4.01.

1,2-Oxazines 3a,f,g; General Procedure

To a soln of oxazine **2a** (0.28 g, 1 mmol) in DMF (2.5 mL) was added the corresponding nucleophile (2 mmol). The resulting mixture was stirred for 2 h at 50–60 °C and poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (see Table 1 for yields).

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl Azide (3f)

Oil; R_f = 0.66 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33, 1.38 [2 s, 6 H, H_3C(6), H_3C(7)], 1.94 [dd, *J* = 11.8, 13.1 Hz, 1 H, H_2C(3)], 2.12 [dd, *J* = 7.9, 13.1 Hz, 1 H, H_2C(3)], 3.59 [dd, *J* = 7.9, 11.8 Hz, 1 H, HC(2)], 3.49, 3.87 [2 d, *J* = 13.1 Hz, 2 H, H_2C(5)], 7.16–7.42 [m, 5 H, HC(9), HC(10), HC(11)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 28.4 (C-6, C-7), 37.8 (C-2), 40.1 (C-3), 52.7 (C-5), 75.1 (C-4), 127.7, 128.3, 129.3 (C-9, C-10, C-11), 139.3 (C-8), 154.4 (C-1).

Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93. Found: C, 63.82; H, 6.30; N, 22.92.

2-[(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (3g)

Mp 148–150 °C; R_f = 0.59 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29, 1.32 [2 s, 6 H, H_3C(10), H_3C(11)], 1.91 [dd, *J* = 11.8, 13.5 Hz, 1 H, H_2C(3)], 2.09 [dd, *J* = 7.9, 13.5 Hz, 1 H, H_2C(3)], 3.51 [dd, *J* = 7.9, 11.8 Hz, 1 H, HC(2)], 4.12, 4.27 [2 d, *J* = 16.7 Hz, 2 H, H_2C(5)], 7.16–7.42 [m, 5 H, HC(13), HC(14), HC(15)], 7.63–7.73, 7.75–7.84 [2 m, 4 H, HC(8), HC(9)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8, 28.3 (C-10, C-11), 39.2 (C-2), 40.0 (C-3), 41.1 (C-5), 74.9 (C-4), 123.4 (C-8), 127.7, 128.3, 129.3 (C-13, C-14, C-15), 132.3 (C-7), 133.9 (C-9), 139.1 (C-12), 152.0 (C-1), 166.0 (C-6).

Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.29; H, 5.70; N, 8.13.

3-(Ethoxymethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine (3h)

A soln of oxazine **2a** (0.28 g, 1 mmol) in EtOH (3 mL) was added to a soln of NaOEt [freshly obtained from Na (0.025 g, 1.1 mmol) and EtOH (2 mL)]. The resulting mixture was stirred for 4 h at 50–60 °C and poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL); the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel.

Yield: 0.16 g (65%); colourless oil; R_f = 0.66 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 [dd, *J* = 6.6, 7.2 Hz, 3 H, H_3C(8)], 1.31, 1.36 [2 s, 6 H, H_3C(9), H_3C(10)], 1.91 [dd, *J* = 11.8, 13.8 Hz, 1 H, H_2C(3)], 2.08 [dd, *J* = 7.9, 13.8 Hz, 1 H, H_2C(3)], 3.19, 3.40 [2 m, 2 H, H_2C(7)], 3.59 [dd, *J* = 7.9, 11.8 Hz, 1 H, HC(2)], 3.80 [s, 2 H, H_2C(5)], 7.16–7.38 [m, 5 H, HC(12), HC(13), HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (C-8), 22.8, 28.6 (C-9, C-10), 37.3 (C-2), 40.1 (C-3), 65.8, 70.2 (C-5, C-7), 74.6 (C-4), 127.2, 128.5, 128.9 (C-9, C-10, C-11), 140.3 (C-11), 156.5 (C-1).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.59; H, 8.43; N, 5.19.

(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methanaminium Chloride (3i)

To a soln of oxazine **2a** (0.28 g, 1 mmol) in DMF (2.5 mL) was added NaN_3 (0.13 g, 2 mmol). The resulting mixture was stirred for 1 h at 100 °C and poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL); the combined organic layer was collected, concentrated in vacuo, and dissolved in Et_2O (1.2 mL). PPh_3 (0.33 g, 1.26 mmol) was added to the mixture at r.t., and after 3 h, H_2O (0.066 mL, 3.6

mmol) was added. The mixture was stirred for 24 h at r.t., the solvent was evaporated in vacuo, and the residue was subjected to column chromatography on silica gel. This gave the free amine as a colourless oil; to this 4 M HCl in dioxane (0.6 mL) was added, and the resulting solid was dried in vacuo.

Yield: 0.20 g (69%); mp 32–39 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30, 1.32 [2 s, 6 H, H_3C(7), H_3C(8)], 1.84 [dd, *J* = 12.5, 12.9 Hz, 1 H, H_2C(3)], 2.06 [dd, *J* = 7.4, 12.9 Hz, 1 H, H_2C(3)], 3.48, 3.60 [2 m, 3 H, HC(2), HC(5)], 7.17–7.38 [m, 5 H, HC(10), HC(11), HC(12)], 8.6 [br, 3 H, HN(6)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 28.3 (C-7, C-8), 38.8 (C-2), 40.3, 40.6 (C-5, C-3), 75.8 (C-4), 127.8, 128.4, 129.4 (C-10, C-11, C-12), 138.4 (C-9), 151.3 (C-1).

Anal. Calcd for $C_{13}H_{19}ClN_2O$: C, 61.29; H, 7.52; N, 11.00. Found: C, 61.34; H, 7.60; N, 11.04.

[(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl]triphenylphosphonium Bromide (3e)

A soln of oxazine **2a** (0.28 g, 1 mmol) and PPh_3 (0.26 g, 1 mmol) in toluene (3 mL) was boiled for 2 h. After the mixture had cooled to r.t., the resulting white precipitate was collected by filtration.

Yield: 0.51 g (94%); white crystals; mp 112–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22, 1.36 [2 s, 6 H, H_3C(10), H_3C(11)], 1.83 [dd, *J* = 12.5, 13.1 Hz, 1 H, H_2C(3)], 2.11 [dd, *J* = 7.9, 13.1 Hz, 1 H, H_2C(3)], 4.57 [m, 1 H, HC(2)], 3.33, 6.63 [2 dd, *J* = 11.2, 18.4, 13.8, 18.4 Hz, 2 H, H_2C(5)], 7.17–7.41 [m, 5 H, HC(12), HC(13), HC(14)], 7.49–7.94 [m, 15 H, HC(7), HC(8), HC(9)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 28.0 (C-10, C-11), 29.6 (d, *J* = 57.5 Hz, C-5), 39.7 (d, *J* = 7.2 Hz, C-2), 40.7 (C-3), 76.0 (C-4), 119.9 (d, *J* = 89.8 Hz, C-6), 127.5, 128.9, 129.4 (C-13, C-14, C-15), 129.9 (d, *J* = 14.4 Hz, C-8), 133.8 (d, *J* = 10.8 Hz, C-7), 134.3 (d, *J* = 3.6 Hz, C-9), 139.6 (C-12), 153.3 (d, *J* = 7.2 Hz, C-1).

Anal. Calcd for $C_{31}H_{31}BrNOP$: C, 68.39; H, 5.74; N, 2.57. Found: C, 68.18; H, 5.72; N, 2.50.

1-[(6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazin-3-yl)methyl]-3-methyl-1*H*-imidazol-3-ium Bromide (3j)

A soln of oxazine **2a** (0.28 g, 1 mmol) and *N*-methylimidazole (0.16 g, 1 mmol) in toluene (3 mL) was boiled for 5 h. After the mixture had cooled to r.t., the solvent was evaporated in vacuo.

Yield: 0.44 g (99%); colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22, 1.35 [2 s, 6 H, H_3C(10), H_3C(11)], 1.80 [dd, *J* = 12.5, 13.7 Hz, 1 H, H_2C(3)], 2.20 [dd, *J* = 7.0, 13.7 Hz, 1 H, H_2C(3)], 3.77 [dd, *J* = 12.5, 7.0 Hz, 1 H, HC(2)], 3.90 [s, 3 H, H_3C(9)], 5.04 [s, 2 H, H_2C(5)], 7.17–7.41 [m, 5 H, HC(12), HC(13), HC(14)], 7.77, 7.84 [2 s, 2 H, HC(7), HC(8)], 9.45 [s, 1 H, HC(6)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 28.1 (C-10, C-11), 35.8 (C-9), 40.0 (C-2), 40.5 (C-3), 54.3 (C-5), 78.2 (C-4), 123.0, 123.6 (C-7, C-8), 127.9, 129.1, 129.5 (C-13, C-14, C-15), 137.3, 140.0 (C-12, C-6), 157.1 (C-1).

Anal. Calcd for $C_{17}H_{22}BrN_3O$: C, 56.05; H, 6.09; N, 11.54. Found: C, 56.43; H, 6.46; N, 12.00.

6,6-Dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine-3-carbaldehyde (6)

To a soln of oxazine **2a** (0.28 g, 1 mmol) in DMSO (5.0 mL) was added $NaHCO_3$; the resulting mixture was stirred for 1.5 h at 110–120 °C and then poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL); the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel.

Yield: 0.16 g (76%); colourless oil; R_f = 0.76 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30, 1.45 [2 s, 6 H, H_3C(6), H_3C(7)], 1.89 [dd, *J* = 11.4, 14.0 Hz, 1 H, H_2C(3)], 2.19 [dd, *J* = 8.1, 14.0 Hz, 1 H, H_2C(3)], 3.71 [dd, *J* = 8.1, 11.4 Hz, 1 H, HC(2)], 7.10–7.37 [m, 5 H, HC(9), HC(10), HC(11)], 9.48 [s, 1 H, HC(5)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 28.0 (C-6, C-7), 34.8 (C-2), 40.5 (C-3), 78.4 (C-4), 127.1, 127.4, 129.0 (C-9, C-10, C-11), 134.7 (C-8), 157.9 (C-1), 189.9 (C-5).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.89; H, 7.26; N, 6.80.

6,6-Dimethyl-4-phenyl-3-styryl-5,6-dihydro-4*H*-1,2-oxazine (5)

To a stirred soln of phosphonium bromide **3e** (0.15 g, 0.28 mmol) in toluene–CH_2Cl_2 (2:1, 1.5 mL) at –78 °C was added a 2.5 M soln of *n*-BuLi in hexane (0.11 mL). The mixture was stirred for 0.5 h, and a soln of PhCHO (0.031 mL, 0.3 mmol) in toluene (1.5 mL) was added. The temperature was raised to 0 °C, and the mixture was stirred for 1 h at the same temperature and then poured into a mixture of EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL); the combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel.

Yield: 0.048 g (60%); colourless oil; R_f = 0.72 (silica gel, hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (*cis*-**5**) = 1.32 [s, 6 H, H_3C(11), H_3C(12)], 1.79 [dd, *J* = 12.1, 13.1 Hz, 1 H, H_2C(3)], 1.95 [dd, *J* = 7.9, 13.1 Hz, 1 H, H_2C(3)], 3.33 [dd, *J* = 7.9, 12.1 Hz, 1 H, HC(2)], 5.97, 6.47 [2 d, *J* = 12.5 Hz, 2 H, HC(5), HC(6)], 6.77, 7.16–7.42 [2 m, 2 H, 8 H, HC(8), HC(9), HC(10), HC(14), HC(15), HC(16)].

^{1}H NMR (300 MHz, $CDCl_3$): δ (*trans*-**5**) = 1.36 [s, 6 H, H_3C(11), H_3C(12)], 1.92 [dd, *J* = 11.5, 13.1 Hz, 1 H, H_2C(3)], 2.29 [dd, *J* = 8.2, 13.1 Hz, 1 H, H_2C(3)], 3.77 [dd, *J* = 8.2, 11.5 Hz, 1 H, HC(2)], 6.55, 6.68 [2 d, *J* = 16.9 Hz, 2 H, HC(5), HC(6)], 6.77, 7.16–7.42 [2 m, 2 H, 8 H, HC(8), HC(9), HC(10), HC(14), HC(15), HC(16)].

^{13}C NMR (75 MHz, $CDCl_3$): δ (mixture of *cis*- and *trans*-**5**) = 22.9, 23.4, 28.3, 28.5 (C-11, C-12), 37.6, 39.1 (C-2), 41.1, 42.5 (C-3), 74.3, 74.9 (C-4), 124.4, 125.7 (C-5), 126.7, 126.7, 126.9, 127.8, 127.9, 128.0, 128.2, 128.2, 128.5, 128.6, 129.0, 129.1 (C-8, C-9, C-10, C-14, C-15, C-16), 133.8, 134.2 (C-6), 140.8, 143.4 (C-7, C-13), 155.4, 156.7 (C-1).

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.90; H, 7.41; N, 4.48.

Dimethyl 2-{[1-(*tert*-Butoxycarbonyl)-3-(4-methoxyphenyl)pyrrolidin-2-yl]methyl}malonate (7)

A suspension of Raney Ni (ca. 10 g) in MeOH (8 mL) was blown out with H_2 from a Kipp apparatus for 1 h, then a soln of oxazine **3r** (0.3 g, 0.8 mmol), Boc_2O (0.26 g, 1.2 mmol), and Et_3N (0.07 mL, 0.5 mmol) in MeOH (16 mL) was added, and H_2 was bubbled through the resulting mixture for 3 h. The mixture was filtered, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel.

Yield: 0.179 g (53%); colourless oil; R_f = 0.75 (silica gel, hexane–EtOAc, 1:1), *cis*/*trans* = 15:85.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, H_3C(7)], 1.87 [m, *J* = 5.9 Hz, 1 H, HC(3)], 2.27 [dd, m, *J* = 6.6, 6.6 Hz, 3 H, H_2C(8), HC(3)], 2.50 [dd, *J* = 7.4, 7.4 Hz, 2 H, H_2C(8), minor isomer], 3.29

[ddd, *J* = 5.9, 6.6, 11.0 Hz, 1 H, HC(2)], 3.69, 3.74, 3.78 [3 s, 9 H, $H_3C(11)$, $H_3C(13)$, $H_3C(18)$], 3.04, 3.62, 4.0 [3 m, 4 H, HC(8), HC(1), $H_2C(4)$], 6.83 [d, *J* = 8.8 Hz, 2 H, HC(16)], 6.87 [d, *J* = 8.8 Hz, 2 H, HC(16), minor isomer], 7.06 [d, *J* = 8.8 Hz, 2 H, HC(15)], 7.16 [d, *J* = 8.8 Hz, 2 H, HC(15)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4 (C-7), 32.3, 33.7 (C-8, C-3), 45.6 (C-4), 48.6, 48.7, 48.9 (C-2, C-9), 52.3, 52.5 (C-11, C-13), 55.2 (C-18), 62.3 (C-1), 79.7 (C-6), 114.1, 114.2, 127.8, 129.0 (C-15, C-16), 135.2 (C-14), 154.7 (C-17), 158.5 (C-5), 168.7, 169.5, 169.7 (C-10, C-12).

***rel*-(2*R*,3*S*)-2-(2-Carboxyethyl)-3-(4-methoxyphenyl)pyrrolidinium Chloride (8)**

A soln of pyrrolidine (0.11 g, 0.26 mmol) in a mixture of MeOH (1.5 mL) and 4 M aq HCl (5.8 mL) was refluxed for 24 h; then the solvent was evaporated and the crude product was recrystallised from $CHCl_3$.

Yield: 0.06 g (80%); white solid; mp 71–74 °C ($CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 [ddd, *J* = 7.5, 7.5, 7.5 Hz, 2 H, $H_2C(3)$], 2.14 [dddd, *J* = 9.7, 9.7, 9.7, 12.3 Hz, 1 H, HC(6)], 2.37 [ddd, *J* = 2.2, 7.0, 7.0 Hz, 2 H, $H_2C(7)$], 2.42 [m, 1 H, HC(6)], 3.09 [ddd, *J* = 7.5, 11.0 Hz, 1 H, HC(2)], 3.41 [ddd, *J* = 7.5, 7.5, 9.2 Hz, 1 H, HC(4)], 3.54 [ddd, *J* = 7.5, 9.7, 9.7 Hz, 1 H, HC(1)], 3.56 [ddd, *J* = 7.5, 7.5, 9.2 Hz, 1 H, HC(4)], 3.78 [s, 3 H, $H_3C(14)$], 4.77 [br, 3 H, $H_2N(5)$, HO(9)], 6.93 [d, *J* = 8.8 Hz, 2 H, HC(15)], 7.25 [d, *J* = 8.8 Hz, 2 H, HC(14)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (C-3), 29.7 (C-7), 32.3 (C-6), 43.5 (C-4), 48.8 (C-2), 53.9 (C-14), 64.6 (C-1), 113.6 (C-12), 127.8 (C-11), 130.8 (C-10), 158.9 (C-13), 175.4 (C-8).

Anal. Calcd for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.05; N, 4.90. Found: C, 58.80; H, 7.11; N, 4.95.

Acknowledgment

This work was supported by the RFBR (grants 05-03-32733, 05-03-08175).

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