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Enantiopure 4-oxazolin-2-ones and 4-methylene-2-oxazolidinones as chiral building blocks in a divergent asymmetric synthesis of heterocycles

Blanca M. Santoyo[1] | Carlos González-Romero[1,2] | Daniel Zárate-Zárate[1] | R. Israel Hernández-Benitez[1] | Vanessa Pelayo[1] | Edson Barrera[1] | Carlos H. Escalante[1] | Aydeé Fuentes-Benites[1,2] | Guadalupe Martínez-Morales[1] | Julio López[3] | Miguel A. Vázquez[3] | Francisco Delgado[1] | Hugo A. Jiménez-Vázquez[1] | Joaquín Tamariz[1]

[1]Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City, Mexico

[2]Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Toluca, State of Mexico, Mexico

[3]Departamento de Química, Universidad de Guanajuato, Guanajuato, Guanajuato, Mexico

Correspondence
Joaquín Tamariz, Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol Carpio y Plan de Ayala S/N, Mexico City 11340, Mexico.
Email: jtamarizm@gmail.com; jtamariz@woodward.encb.ipn.mx

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Abstract

Enantiopure 3-((*R*)- and 3-((*S*)-1-phenylethyl)-4-oxazoline-2-ones were evaluated as chiral building blocks for the divergent construction of heterocycles with stereogenic quaternary centers. The *N*-(*R*)- or *N*-(*S*)-1-phenylethyl group of these compounds proved to be an efficient chiral auxiliary for the asymmetric induction of the 4- and 5-positions of the 4-oxazolin-2-one ring through thermal and MW-promoted nucleophilic conjugated addition to Michael acceptors and alkyl halides. The resulting adducts were transformed via a cascade process into fused six-membered carbo- and heterocycles. The structure of the reaction products depended on the electrophiles and reaction conditions used. Alternative isomeric 4-methylene-2-oxazolidinones served as chiral precursors for a versatile and divergent approach to highly substituted cyclic carbamates. DFT quantum calculations showed that the formation of bicyclic pyranyl compounds was generated by a diastereoselective concerted hetero-Diels-Alder cycloaddition.

KEYWORDS

(*R*)- and (*S*)-1-phenylethylamine, 4-methylene-2-oxazolidinones, 4-oxazolin-2-ones, hetero-Diels-Alder reaction, microwave irradiation

1 | INTRODUCTION

Chiral 1,3-oxazolidin-2-ones have been widely used as efficient auxiliaries for the asymmetric synthesis of a large variety of enantiopure and highly functionalized carbonylic compounds.[1-9] Likewise, the preparation of α-amino alcohols and α-amino acids has been designed based on the approach of the transformation of chiral 1,3-oxazolidin-2-ones,[10-13] which in turn can be obtained from optically pure α-amino alcohols[10] and α-amino acids, among other substrates.[1-9] The synthetic applicability of these heterocycles has increased with the development of new methods for their construction.[14-21] Functionalized 4-methylene-1,3-oxazolidin-2-ones have

also proven to be versatile synthons in the formation of diverse molecular systems.[22,23]

Preformed or in situ-generated chiral enamines and enamides proved to be highly diastereoselective species in diversity-oriented asymmetric synthesis.[24-30] It is possible to carry out this synthetic approach via aldol, Mannich, Michael condensations, addition to metal π-double and π-triple activated C–C bonds, and Heck arylation,[31-33] as well as in cascade vicinal difunctionalization or pericyclic reactions, leading to the formation of complex molecules with the generation of a number of stereogenic centers, including the total synthesis of natural products.[34,35] Among the chiral auxiliaries used in asymmetric synthesis, those based on the 1-phenylethylamino group-containing scaffolds proved to be very efficient in many diastereoselective processes.[36-43]

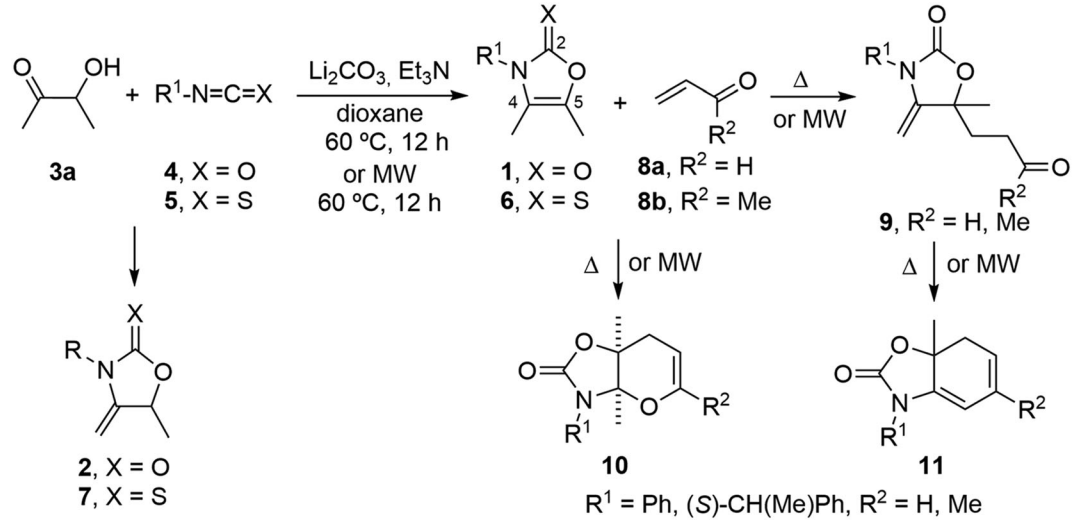
On the basis of the previously developed regioselective synthesis of *N*-substituted 4-oxazolin-2-ones **1** and 4-methylene-2-oxazolidinones **2**, resulting from the condensation of α-ketol **3a** and isocyanates **4** (Scheme 1),[44,45] in a preliminary report, we presented the one-pot synthesis of the optically pure version of heterocycles **1-2** by introducing the *N*-(*S*)-methylbenzyl moiety as the chiral auxiliary.[46] Although this methodology was also efficient for the preparation of the corresponding 3-substituted 4-oxazolin-2-thiones **6** and 4-methylene-1,3-oxazolidin-2-thiones **7**,[47] these heterocycles were not able to undergo further reactions when utilizing the thioenamide functionality as a nucleophile.[44-46] In contrast, compounds **1** behave as an enolate equivalent in the presence of a Michael acceptor, in which the regioselectivity was totally controlled by the enamide moiety, leading to the addition product at C-5 of compound **9** (R^2 = Me). The use of acrolein (**8a**) as the electrophile did not afford the expected conjugated addition product **9** (R^2 = H), but instead, the bicyclic pyranyl compound **10** or to the cyclohexadiene product **11**, depending on the reaction conditions.[45,46] More severe thermal conditions for the reaction between substrates **1** and **8b**, or thermal treatment of the 1,4-addition product **9** yielded the fused bicyclic compounds **10** or **11** (R^2 = Me), respectively.

These favorable properties make 4-oxazolin-2-ones very adaptable tools for asymmetric synthesis. Because of the importance of chiral oxazolidinones in the development of optically pure β-amino alcohols or β-hydroxy amides, we herein describe an extensive evaluation of the chiral heterocycles **1** and **2** as useful and versatile chiral building blocks in the construction of a variety of substituted bicyclic structures bearing quaternary stereocenters. A computational study was conducted to rationalize the diastereoselectivity and reaction mechanisms present in such processes.

2 | MATERIALS AND METHODS

2.1 | General

Melting points were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a FT-IR Perkin Elmer 2000 spectrophotometer. ^{1}H (300 or 500 MHz) and ^{13}C (75.4 or 125 MHz) NMR spectra were recorded on Varian Mercury-300 or Varian VNMR System instruments, with TMS as



SCHEME 1 Synthesis of 4-oxazolin- and oxazolidin-2-ones as well as 4-oxazolin- and oxazolidin-2-thiones, and evaluation of their reactivity with Michael acceptors

internal standard. Mass spectra (MS) were taken in the electron impact (EI) mode on Hewlett-Packard 5971A and Thermo-Finnigan Polaris Q spectrometers. High-resolution mass spectra (HRMS) were obtained in electron impact and FAB^+ modes on Jeol JSM-GCMateII and Jeol JMS-SX 102 spectrometers, respectively. Optical rotations were determined on a Jasco P-200 polarimeter. X-ray crystallographic structures were accomplished on Siemens P4 (Cu Kα radiation) and Oxford XcaliburS (Mo Kα radiation) diffractometers. Microwave (MW) irradiation was carried out on a CEM MW reactor and SEV/MIC-1 (Mexico) MW reactor.[48] All air moisture sensitive reactions were carried out under nitrogen atmosphere with oven-dried glassware. Prior to use, THF, toluene, and xylene were freshly distilled from sodium, and ethyl acetate, methylene chloride, and MeCN from calcium hydride. DMF was distilled from 4 Å molecular sieves, and Et_3N from NaOH. Li_2CO_3 was dried overnight at 120°C before use. All other reagents and solvents were employed without further purification.

2.2 | Synthesis

2.2.1 | General procedures for the preparation of 4,5-dimethyl-3-((*R*)-1-phenylethyl) oxazol-2(3*H*)-ones (1a) and 5-methyl-4-methylene-3-((*R*)-1-phenylethyl)oxazolidin-2-one (2a)

Method A. A mixture of 3-hydroxy-2-butanone (**3a**) (0.030 g, 0.34 mmol), **4a** (0.050 g, 0.34 mmol), and Et_3N (0.069 g, 0.68 mmol) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and heated at 120°C for 24 hours. The reaction crude was filtered over celite and purified by column chromatography over silica gel (30 g/1 g of crude, hexane/EtOAc, 9:1) to give **1a** (0.055 g, 75%) as an amber oil.

Method B. A mixture of **3a** (0.100 g, 1.14 mmol) and **4a** (0.200 g, 1.36 mmol) was put into a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and irradiated with MW (200 W) at 170°C for 8.0 minutes. The mixture was diluted with CH_2Cl_2 (10 mL), stirred for 30 minutes and filtered. The solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to afford a mixture of **1a** (0.135 g, 55%) as an amber oil and **2a** (65:35) (0.072 g, 29%) as a white solid. Data for **1a**: *R*f 0.35 (hexane/EtOAc, 8:2). $[\alpha]_D^{26}$ = +27.0 (*c* 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1750, 1701, 1451, 1355, 1246, 1025, 758, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67 (q, *J* = 0.9 Hz, 3H, C*H*$_3$C-4), 1.81 (*d*, *J* = 7.2 Hz, 3H, C*H*$_3$C-1′), 1.98 (q, *J* = 0.9 Hz, 3H, C*H*$_3$C-5), 5.33 (q, *J* = 7.2 Hz, 1H, H-1′), 7.24-7.39 (m, 5H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 8.8 (*C*H$_3$C-4), 9.7 (*C*H$_3$C-5), 18.3 (*C*H$_3$C-1′), 51.7 (C-1′), 117.1 (C-4), 126.4 (2 C, arom. *C*H), 127.6 (arom. *C*H), 128.6 (2 C, arom. *C*H), 131.7 (C-5), 140.1 (arom. C), 155.6 (C-2) ppm. EM (70 eV): *m/z* (%) = 218 (17) $[M + 1]^+$, 114 (60), 106 (100), 104 (34), 80 (38), 77 (21). HRMS (EI): *m/z* = 217.1103 $[M]^+$, calcd for $C_{13}H_{15}NO_2$ 217.1103. Data for **2a** (65:35): R_f 0.60 (hexane/EtOAc, 7:3); m.p. 72-75°C; $[\alpha]_D^{23}$ = +56.5 (c 0.20, $CHCl_3$). IR (film): $\bar{\nu}$ = 2922, 1745, 1698, 1449, 1351, 1243, 1021, 756, and 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (*d*, *J* = 6.3 Hz, 3H, C*H*$_3$C-5), 1.79 (br d, *J* = 7.2 Hz, 3H, C*H*$_3$C-1′), 3.89-3.95 (m, 2H, C), 4.94-5.05 (m, 1H, H-5), 5.32 (q, *J* = 7.2 Hz, 1H, H-1′), 7.25-7.40 (m, 5H, Ph-H). Signals attributed to the minor isomer: 1.47 (*d*, *J* = 6.3 Hz, C*H*$_3$C-5), 1.77 (*d*, *J* = 7.5 Hz, C*H*$_3$C-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.6 (*C*H$_3$C-5), 21.3 (CH$_3$C-1′), 51.3 (C-1′), 74.3 (C-5), 82.7 (*C*), 126.5 (2 C, arom. *C*H), 127.5 (arom. *C*H), 128.5 (2 C, arom. *C*H), 138.7 (arom. C), 144.5 (C-4), 156.5 (C-2). Signals attributed to the minor isomer: 21.2 (*C*H$_3$C-1′), 51.4 (C-1′), 144.6 (C-4) ppm. EM (70 eV): *m/z* (%) = 218 (16) $[M + 1]^+$, 114 (22), 106 (100), 105 (38), 80 (32), 78 (18). HRMS (EI): *m/z* = 217.1105 $[M]^+$, calcd for $C_{13}H_{15}NO_2$ 217.1103.

2.2.2 | 4,5-Dimethyl-3-((*S*)-1-phenylethyl) oxazol-2(3*H*)-one (1b) and 5-methyl-4-methylene-3-((*S*)-1-phenylethyl) oxazolidin-2-one (2b)

Method A. Following method A for the preparation of **1a**/**2a**, the mixture of **3a** (0.144 g,

1.64 mmol), **4b** (0.200 g, 1.36 mmol), and Et_3N (0.275 g, 2.72 mmol) provided **1b** (0.221 g, 75%) as an amber oil.

Method B. According to method B for the preparation of **1a**/**2a**, the mixture of **3a** (0.072 g, 0.818 mmol), **4b** (0.100 g, 0.68 mmol), and Et_3N (0.069 g, 0.68 mmol) was irradiated with MW (200 W) at 140°C for 8 minutes to furnished a mixture of **1b** (0.023 g, 16%) as an amber oil and **2b** (54:46) (0.058 g, 39%) as a pale yellow powder. Data for **1b**:[46,49] R_f 0.35 (hexane/EtOAc, 8:2). $[\alpha]_D^{26} = -33.8$ (*c* 0.500, $CHCl_3$). IR (film): $\bar{\nu}$ = 1743, 1700, 1495, 1448, 1351, 1244, 1122, 1024, 979, 757, and 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67 (q, J = 0.9 Hz, 3H, C*H*$_3$C-4), 1.81 (*d*, J = 7.2 Hz, 3H, C*H*$_3$C-1′), 1.98 (q, J = 0.9 Hz, 3H, C*H*$_3$C-5), 5.33 (q, J = 7.2 Hz, 1H, H-1′), 7.22-7.40 (m, 5H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 8.7 (*C*H$_3$C-4), 9.6 (*C*H$_3$C-5), 18.2 (*C*H$_3$C-1′), 51.7 (C-1′), 117.1 (C-4), 126.3 (2 C, arom. *C*H), 127.5 (arom. *C*H), 128.5 (2 C, arom. *C*H), 131.6 (C-5), 140.1 (arom. C), 155.5 (C-2) ppm. EM (70 eV): *m/z* (%) = 217 (5) $[M]^+$, 146 (15), 120 (35), 113 (30), 105 (100), 103 (34), 91 (15), 79 (36), 77 (44). HRMS (EI): *m/z* = 217.1101 $[M]^+$, calcd for $C_{13}H_{15}NO_2$ 217.1103. Data for **2b** (54:46): R_f 0.66 (hexane/EtOAc, 7:3); m.p. 71-73°C. $[\alpha]_D^{23} = -55.5$ (c 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1757, 1672, 1449, 1377, 1320, 1221, 1201, 1072, 1024, 756, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (*d*, J = 6.3 Hz, 3H, C*H*$_3$C-5), 1.78 (*d*, J = 7.4 Hz, 3H, C*H*$_3$C-1′), 3.88-3.95 (m, 2H, C), 4.94-5.04 (m, 1H, H-5), 5.32 (q, J = 7.4 Hz, 1H, H-1′), 7.16-7.45 (m, 5H, Ph-H). Signals attributed to the minor isomer: 1.47 (*d*, J = 6.3 Hz, C*H*$_3$C-5), 1.79 (*d*, J = 6.9 Hz, C*H*$_3$C-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.6 (*C*H$_3$C-5), 21.2 (*C*H$_3$C-1′), 51.5 (C-1′), 74.3 (C-5), 82.7 (*C*H$_2$=), 126.5 (2 C, arom. *C*H), 127.5 (arom. *C*H), 128.5 (2 C, arom. *C*H), 138.7 (arom. C), 144.5 (C-4), 156.4 (C-2). Signals attributed to the minor isomer: 21.3 (*C*H$_3$C-1′), 51.3 (C-1′), 126.6 (arom. *C*H), 144.7 (C-4) ppm. EM (70 eV): *m/z* (%) = 218 (39) $[M + 1]^+$, 174 (14), 159 (11), 114 (22), 106 (100), 80 (30), 77 (18). HRMS (EI): *m/z* = 217.1106 $[M]^+$, calcd for $C_{13}H_{15}NO_2$ 217.1103.

2.2.3 | (4*R*,5*R*)-4-Hydroxy-4,5-dimethyl-3-((*S*)-1-phenylethyl)oxazolidin-2-one (12) and (4*R*,5*S*)-4-hydroxy-4,5-dimethyl-3-((*S*)-1-phenylethyl)oxazolidinone (13)

A mixture of **3a** (0.880 g, 0.01 mol) and **4b** (1.470 g, 0.01 mol) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and irradiated with MW (200 W) at 120°C for 90 minutes. The mixture was diluted in CH_2Cl_2 (40 mL), poured into H_2O (100 mL), and stirred for 30 minutes. The precipitate was filtered, and the aqueous layer was washed with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **1b** (1.10 g, 51%) and a mixture of **12/13** (61:39) (0.82 g, 35%), which after recrystallization (hexane/CH_2Cl_2, 6:1) resulted in **12** as a white solid. Data for **12**: R_f 0.15 (hexane/EtOAc, 7:3); m.p. 87°C to 88°C. $[\alpha]_D^{26} = -51.0$ (*c* 0.100, $CHCl_3$). IR (film): $\bar{\nu}$ = 3325, 2982, 1720, 1655, 1551, 1418, 1379, 1311, 1213, 1176, 1081, 913, 766, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (*d*, J = 6.6 Hz, 3 H, C*H*$_3$C-1′), 1.40 (s, 3 H, C*H*$_3$C-4), 1.83 (*d*, J = 7.1 Hz, 3 H, C*H*$_3$C-1′), 3.96 (br s, 1 H, OH), 4.27 (q, J = 6.6 Hz, 1 H, H-5), 4.66 (q, J = 7.1 Hz, 1 H, H-1′), 7.20-7.37 (m, 3 H, Ph-H), 7.40-7.51 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.0 (*C*H$_3$C-5), 20.1 (*C*H$_3$C-4), 23.9 (*C*H$_3$C-1′), 51.6 (C-1′), 79.4 (C-5), 89.0 (C-4), 127.2 (2 C, arom. *C*H), 127.4 (arom. *C*H), 128.5 (2 C, arom. *C*H), 142.3 (arom. C), 156.6 (C-2) ppm. $C_{13}H_{17}NO_3$ (235.28): calcd. C, 66.36; H, 7.28; N, 5.95; found C, 66.50; H, 7.35; N, 6.17. Signals attributed to the minor isomer **13**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, C*H*$_3$C-4), 1.31 (*d*, J = 6.6 Hz, C*H*$_3$C-5), 3.72 (br s, OH), 4.19 (q, J = 6.6 Hz, H-5), 5.00 (q, J = 7.1 Hz, H-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 12.8 (*C*H$_3$C-5), 17.8 (*C*H$_3$C-4), 23.4 (*C*H$_3$C-1′), 51.0 (C-1′), 79.8 (C-5), 88.8 (C-4), 127.4 (arom. *C*H), 128.6 (arom. *C*H), 141.6 (arom. C), 157.0 (C-2) ppm.

2.2.4 | 5,5-Dimethyl-4-methylene-3-((*R*)-1-phenylethyl)oxazolidin-2-one (14a)

A mixture of **3b** (0.200 g, 1.96 mol) and **4a** (0.346 g, 2.35 mmol) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and irradiated with MW (60 W) at 200°C for 20 minutes. The mixture was diluted with CH_2Cl_2 (10 mL) and stirred for 30 minutes and filtered.

The solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **14a** (0.30 g, 66%) as a pale yellow oil. R_f = 0.69 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = +53.0 (*c* 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1760, 1678, 1455, 1393, 1296, 1200, 1098, 1076, 1039, 817, 760, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, CH_3C-5), 1.48 (s, 3 H, CH_3C-5), 1.78 (*d*, *J* = 7.1 Hz, 3H, CH_3C-1′), 3.85-3.90 (m, 2 H, C), 5.33 (q, *J* = 7.1 Hz, 1H, H-1′), 7.22-7.40 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.5 (*C*H_3C-1′), 27.8 (*C*H_3C-5), 27.9 (*C*H_3C-5), 51.2 (C-1′), 81.5 (C-5), 81.9 (*C*), 126.4 (2 C, arom. *C*H), 127.4 (arom. *C*H), 128.5 (2 C, arom. *C*H), 138.8 (arom. C), 148.7 (C-4), 155.6 (C-2) ppm. MS (70 eV): *m/z* (%) = 233 (54) $[M + 2]^+$, 188 (20), 173 (11), 128 (22), 106 (100), 105 (24), 80 (29). HRMS (EI): *m/z* = 231.1260 $[M]^+$, calcd for $C_{14}H_{17}NO_2$ 231.1259.

2.2.5 | General procedures for the preparation of 5,5-dimethyl-4-methylene-3-((*S*)-1-phenylethyl)oxazolidin-2-one (14b)[46]

Method A. A mixture of **3b** (0.200 g, 1.96 mol) and **4b** (0.346 g, 2.35 mmol) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. The mixture was stirred and heated at 130°C for 24 hours. The mixture was diluted with CH_2Cl_2 (15 mL), stirred for 30 minutes, and then filtered. The solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **14b** (0.354 g, 78%) as a pale yellow oil.

Method B. A mixture of **3b** (0.200 g, 1.96 mmol) and **4b** (0.346 g, 2.35 mmol) was put into in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and irradiated with MW (300 W) at 140°C for 3 hours. The mixture was diluted with CH_2Cl_2 (10 mL), stirred for 30 minutes, and filtered. The solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **14b** (0.38 g, 84%) as a pale yellow oil. R_f = 0.67 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = −54.3 (*c* 0.233, $CHCl_3$). IR (film): $\bar{\nu}$ = 1763, 1678, 1452, 1393, 1373, 1296, 1201, 1098, 1039, 966, 816, 760, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, CH_3C-5), 1.48 (s, 3 H, CH_3C-5), 1.78 (*d*, *J* = 7.4 Hz, 3H, CH_3C-1′), 3.85-3.89 (m, 2 H, C), 5.33 (q, *J* = 7.4 Hz, 1H, H-1′), 7.20-7.41 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.5 (*C*H_3C-1′), 27.8 (*C*H_3C-5), 27.9 (*C*H_3C-5), 51.2 (C-1′), 81.4 (C-5), 81.9 (*C*), 126.4 (2 C, arom. *C*H), 127.4 (arom. *C*H), 128.4 (2 C, arom. *C*H), 138.8 (arom. C), 148.6 (C-4), 155.6 (C-2) ppm. MS (70 eV): *m/z* (%) = 232 (100) $[M + 1]^+$, 231 (25) $[M]^+$, 187 (10), 132 (10), 120 (94), 105 (96), 91 (14), 79 (25), 77 (16). HRMS (EI): *m/z* = 231.1258 $[M]^+$, calcd for $C_{14}H_{17}NO_2$ 231.1259.

2.2.6 | (4*S*,5*R*)-4,5-Dimethyl-4-methylene-3-((*S*)-1-phenylethyl)oxazolidin-2-one (15) and (4*R*,5*S*)-4,5-dimethyl-4-methylene-3-((*S*)-1-phenylethyl)oxazolidin-2-one (16)[46]

A mixture of **1b** (0.326 g, 1.50 mmol), Pd/C (10%) (0.06 g, 0.3 mmol), and AcOH (0.2 mL) in EtOAc (40 mL) was placed in a high pressure hydrogenation Parr vessel (750 psi) under H_2 atmosphere. It was stirred and heated at 60°C for 24 hours. The mixture was filtered over celite, and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give a mixture of **15/16** (84:16) (0.24 g, 73%) as a colorless oil. R_f = 0.45 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = −40.1 (*c* 0.177, $CHCl_3$). IR (film): $\bar{\nu}$ = 2981, 2937, 1740, 1678, 1451, 1410, 1382, 1236, 1190, 1078, 1024, 765, and 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (*d*, *J* = 6.5 Hz, 3 H, CH_3C-4), 1.26 (*d*, *J* = 6.5 Hz, 3 H, CH_3C-5), 1.70 (*d*, *J* = 7.3 Hz, 3H, CH_3C-1′), 3.86 (*d*q, *J* = 7.5, 6.5 Hz, 1 H, H-4), 4.58 (*d*q, *J* = 7.5, 6.5 Hz, 1 H, H-5), 5.03 (q, *J* = 7.3 Hz, 1H, H-1′), 7.22-7.42 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **16**: 1.09 (*d*, *J* = 6.5 Hz, CH_3C-4), 1.66 (*d*, *J* = 7.3 Hz, CH_3C-1′), 3.45 (*d*q, *J* = 7.5, 6.5 Hz, H-4), 4.48 (*d*q, *J* = 7.5, 6.5 Hz, H-5), 5.16 (q, *J* = 7.3 Hz, 1 H, H-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.1 (*C*H_3C-4), 14.8 (*C*H_3C-5), 17.0 (*C*H_3C-1′), 51.4 (C-1′), 53.0 (C-4), 73.7 (C-5), 126.9 (2 C, arom. *C*H), 127.5 (arom. *C*H), 128.4 (2 C, arom. *C*H), 141.6 (arom. C), 157.8 (C-2) ppm. Signals attributed to the minor isomer **16**: 14.6 (*C*H_3C-4), 15.4 (*C*H_3C-5), 18.5 (*C*H_3C-1′), 52.2 (C-1′), 73.9 (C-5), 127.2 (arom. *C*H), 127.7 (arom. *C*H), 128.6 (arom. *C*H), 139.4 (arom. C) ppm. HRMS (EI): *m/z* = 219.1260 $[M]^+$, calcd for $C_{13}H_{17}NO_2$ 219.1259.

2.2.7 | (4*S*)-4,5,5-Trimethyl-3-((*S*)-1-phenylethyl)oxazolidin-2-one (17) and (4*R*)-4,5,5-trimethyl-3-((*S*)-1-phenylethyl) oxazolidin-2-one (18)[46]

A mixture of **14b** (0.231 g, 1.00 mmol) and Pd $(OH)_2$ (20%) (0.028 g, 0.2 mmol) in MeOH (10 mL) was placed in a round-bottomed flask with a septum provided with an H_2 balloon. It was stirred at room temperature for 24 hours and then filtered over celite. The solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 97:3) to give a mixture of **17/18** (96:4) (0.23 g, 99%) as a pale yellow oil. R_f = 0.40 (hexane/EtOAc, 7:3). $[\alpha]_D^{22} = -129.6$ (*c* 0.100, MeOH). IR (film): $\bar{\nu}$ = 2979, 2936, 1740, 1452, 1408, 1374, 1302, 1282, 1234, 1192, 1083, 1024, 962, 897, 767, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.76 (*d*, *J* = 6.5 Hz, 3 H, CH_3C-4), 1.26 (s, 3 H, CH_3C-5), 1.37 (s, 3 H, CH_3C-5), 1.70 (*d*, *J* = 7.3 Hz, 3H, CH_3C-1′), 3.51 (q, *J* = 6.5 Hz, 1 H, H-4), 5.05 (q, *J* = 7.3 Hz, 1 H, H-1′), 7.23-7.44 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **18**: 1.09 (*d*, *J* = 6.5 Hz, CH_3C-4), 1.23 (s, CH_3C-5), 1.66 (*d*, *J* = 7.3 Hz, CH_3C-1′), 3.09 (q, *J* = 6.5 Hz, H-4) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8 (*C*H_3C-4), 16.4 (*C*H_3C-1′), 21.5 (*C*H_3C-5), 26.9 (*C*H_3C-5), 51.1 (C-1′), 58.9 (C-4), 80.2 (C-5), 126.9 (2 C, arom. *C*H), 127.4 (arom. *C*H), 128.3 (2 C, arom. *C*H), 141.6 (arom. C), 157.4 (C-2) ppm. Signals attributed to the minor isomer **18**: 16.2 (*C*H_3C-4), 127.3 (arom. *C*H), 127.7 (arom. *C*H), 128.6 (arom. C) ppm. HRMS (EI): *m/z* = 233.1411 $[M]^+$, calcd for $C_{14}H_{19}NO_2$ 233.1416.

2.2.8 | (5*R*)-5-Methyl-4-methylene-5-(3-oxobutyl)-3-((*R*)-1-phenylethyl)oxazolidin-2-one (19a) and (5*S*)-5-methyl-4-methylene-5-(3-oxobutyl)-3-((*R*)-1-phenylethyl) oxazolidin-2-one (20a)

A mixture of **1a** (0.210 g, 0.968 mmol) and **8b** (0.203 g, 2.90 mmol) in anhydrous xylene (3 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and heated at 160°C for 96 hours. The solvent was removed under vacuum, and the crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give a mixture of **19a/20a** (72:28) (0.161 g, 58%) as a pale yellow oil. R_f = 0.36 (hexane/EtOAc, 7:3). $[\alpha]_D^{23} = +15.3$ (*c* 0.700, $CHCl_3$). IR (film): $\bar{\nu}$ = 2928, 1760, 1716, 1676, 1373, 1199, 1025, 759, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, CH_3C-5), 1.70-1.96 (m, 1H, CH_2C-5), 1.78 (*d*, *J* = 7.4 Hz, CH_3C-1′), 2.00-2.12 (m, 1H, CH_2C-5), 2.12 (s, 3 H, CH_3CO), 2.24-2.38 (m, 1H, CH_2CO), 2.43-2.59 (m, 1H, CH_2CO), 3.86 (*d*, *J* = 3.3 Hz, 1 H, C), 3.98 (*d*, *J* = 3.3 Hz, 1 H, C), 5.38 (q, *J* = 7.4 Hz, 1 H, H-1′), 7.26-7.39 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **20a**: 2.09 (s, CH_3CO), 5.28 (q, *J* = 6.9 Hz, H-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.2 (*C*H_3C-1′), 27.0 (*C*H_3C-5), 29.9 (*C*H_2C-5), 33.9 (*C*H_3CO), 37.3 (*C*H_2CO), 51.3 (C-1′), 82.6 (*C*), 82.8 (C-5), 126.6 (2 C, arom. *C*H), 127.6 (arom. *C*H), 128.4 (2 C, arom. *C*H), 138.5 (arom. C), 146.5 (C-4), 155.6 (C-2), 207.1 (*C*O) ppm. Signals attributed to the minor isomer **20a**: 15.8 (*C*H_3C-1′), 27.0 (*C*H_3C-5), 34.0 (*C*H_3CO), 37.2 (*C*H_2CO), 51.6 (C-1′), 82.7 (C-5), 126.4 (2 C, arom. *C*H), 127.5 (arom. *C*H), 128.5 (2 C, arom. *C*H), 146.7 (C-4) ppm. MS (70 eV): *m/z* (%) = 230 (26) $[M - 57]^+$, 187 (13), 114 (51), 106 (100), 80 (20), 78 (17). HRMS (EI): *m/z* = 287.1516 $[M]^+$, calcd for $C_{17}H_{21}NO_3$ 287.1521.

2.2.9 | (5*S*)-5-Methyl-4-methylene-5-(3-oxobutyl)-3-((*S*)-1-phenylethyl)oxazolidin-2-one (19b) and (5*R*)-5-methyl-4-methylene-5-(3-oxobutyl)-3-((*S*)-1-phenylethyl) oxazolidin-2-one (20b)[46,49]

A mixture of **1b** (0.200 g, 0.922 mmol) and **8b** (0.258 g, 3.69 mmol) in anhydrous xylene (2 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and heated at 100°C for 72 hours. The solvent was removed under vacuum, and the crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 91:9) to give a mixture of **19b**/**20b** (91:9) (0.11 g, 42%) as a colorless oil. R_f = 0.42 (hexane/EtOAc, 8:2). $[\alpha]_D^{23} = -74.1$ (*c* 0.338, MeOH). IR (film): $\bar{\nu}$ = 2924, 1751, 1702, 1448, 1355, 1243, 1024, 758, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, CH_3C-5), 1.78 (*d*, *J* = 7.5 Hz, 3 H, CH_3C-1′), 1.80-1.93 (m, 1 H, CH_2C-5), 2.00-2.12 (m, 1 H, CH_2C-5), 2.11 (s, 3 H, CH_3CO), 2.23-2.38 (m, 1 H, CH_2CO), 2.45-2.58 (m, 1 H, CH_2CO), 3.85 (*d*, *J* = 3.0 Hz, 1 H, C), 3.98 (*d*, *J* = 3.0 Hz, 1 H, C), 5.38 (q, *J* = 7.5 Hz, 1 H, H-1′), 7.25-7.41 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **20b**: 1.51 (s, CH_3C-5), 3.88 (*d*, *J* = 3.3 Hz, C), 5.28 (q, *J* = 6.9 Hz, H-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.2 (*C*H_3C-1′), 27.1 (*C*H_3C-5), 30.0 (*C*H_2C-5), 34.0 (*C*H_3CO), 37.4 (*C*H_2CO), 51.4 (C-1′), 82.6 (*C*), 82.9 (C-5), 126.7 (2 C, arom. *C*H), 127.7 (arom. *C*H), 128.5 (2 C, arom. *C*H), 138.6 (arom. C), 146.6 (C-4), 155.6 (C-2), 207.1 (*C*O) ppm. Signals attributed to the minor isomer **20b**: 15.9 (*C*H_3C-1′), 27.0 (*C*H_3C-5), 34.1 (*C*H_3CO), 37.2 (*C*H_2CO), 51.7 (C-1′), 82.8 (C-5), 126.5 (2 C, arom. *C*H), 127.6 (arom.

*C*H), 128.6 (2 C, arom. *C*H), 138.9 (arom. C), 147.0 (C-4), 155.5 (C-2) ppm. HRMS (EI): m/z = 287.1529 $[M]^+$, calcd for $C_{17}H_{21}NO_3$ 287.1521.

2.2.10 | (*E*)-5,5-Dimethyl-4-(4-oxopentylidene)-3-((*R*)-1-phenylethyl) oxazolidin-2-one (21a) and (*Z*)-5,5-dimethyl-4-(4-oxopentylidene)-3-((*R*)-1-phenylethyl) oxazolidin-2-one (22a)

To a solution of **8b** (0.109 g, 1.56 mmol) in anhydrous CH_2Cl_2 (2.0 mL) at 0°C and under N_2 atmosphere, iodine (0.0066 g, 0.026 mmol) was added and the mixture stirred at the same temperature for 30 minutes (the solution turned dark red). Subsequently, **14a** (0.120 g, 0.519 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was added, and the mixture stirred at 0°C for 4 hours. The mixture was then diluted with CH_2Cl_2 (20 mL) and poured into a 10% aqueous solution of sodium thiosulfate (10 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL), the organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **21a** (0.08 g, 51%) as a pale yellow oil. R_f = 0.32 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = +17.3 (*c* 0.400, $CHCl_3$). IR (film): $\bar{\nu}$ = 2921, 1753, 1714, 1681, 1449, 1405, 1370, 1318, 1197, 1026, 757, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 6 H, 2CH_3C-5), 1.74 (*d*, *J* = 7.3 Hz, 3 H, CH_3C-1′), 2.00 (s, 3 H, CH_3CO), 2.10-2.23 (m, 2 H, CH_2CH=), 2.24-2.33 (m, 2 H, CH_2CO), 4.16 (t, *J* = 7.8 Hz, 1 H, C*H*=), 5.32 (q, *J* = 7.3 Hz, 1 H, H-1′), 7.20-7.39 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.7 (*C*H_3C-1′), 20.5 (*C*H_2CH=), 26.5 (*C*H_3C-5), 26.6 (*C*H_3C-5), 30.1 (*C*H_3CO), 43.9 (*C*H_2CO), 50.9 (C-1′), 80.9 (C-5), 98.8 (*C*H=), 126.2 (2 C, arom. *C*H), 127.2 (arom. *C*H), 128.4 (2 C, arom. *C*H), 139.0 (arom. C), 140.3 (C-4), 155.4 (C-2), 207.4 (*C*O) ppm. MS(70 eV): m/z (%) = 259 (3) $[M - 42]^+$, 198 (17), 180 (25), 136 (55), 111 (42), 106 (100), 80 (55), 78 (28). HRMS (EI): m/z = 301.1672 $[M]^+$, calcd for $C_{18}H_{23}NO_3$ 301.1678.

2.2.11 | (*E*)-5,5-Dimethyl-4-(4-oxopentylidene)-3-((*S*)-1-phenylethyl) oxazolidin-2-one (21b) and (*Z*)-5,5-dimethyl-4-(4-oxopentylidene)-3-((*S*)-1-phenylethyl) oxazolidin-2-one (22b)

Following the method for the preparation of **21a**/**22a**, a mixture of **14b** (0.300 g, 1.30 mmol), **8b** (0.182 g, 2.60 mmol), and iodine (0.017 g, 0.067 mmol) was stirred at 0°C for 6 hours, to give a mixture of **21b**/**22b** (81:19) (0.215 g, 55%) as a pale yellow oil. R_f = 0.25 (hexane/EtOAc, 8:2). $[\alpha]_D^{23}$ = −45.1 (*c* 0.218, MeOH). IR (film): $\bar{\nu}$ = 2979, 2936, 1753, 1714, 1684, 1449, 1406, 1372, 1324, 1199, 1166, 1045, 1027, 759, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 3 H, CH_3C-5), 1.57 (s, 3 H, CH_3C-5), 1.74 (*d*, *J* = 7.3 Hz, 3 H, CH_3C-1′), 2.00 (s, 3 H, CH_3CO), 2.12-2.23 (m, 2 H, CH_2CH=), 2.25-2.32 (m, 2 H, CH_2CO), 4.15 (*dd*, *J* = 8.0, 7.5 Hz, 1 H, C*H*=), 5.32 (q, *J* = 7.3 Hz, 1 H, H-1′), 7.20-7.40 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **22b**: 1.50 (s, CH_3C-5), 1.51 (s, CH_3C-5), 1.88 (*d*, *J* = 7.3 Hz, CH_3C-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.7 (*C*H_3C-1′), 20.6 (*C*H_2CH=), 26.5 (*C*H_3C-5), 26.6 (*C*H_3C-5), 30.1 (*C*H_3CO), 43.9 (*C*H_2CO), 50.9 (C-1′), 80.9 (C-5), 98.8 (*C*H=), 126.2 (2 C, arom. *C*H), 127.2 (arom. *C*H), 128.4 (2 C, arom. *C*H), 139.0 (arom. C), 140.3 (C-4), 155.4 (C-2), 207.5 (*C*O) ppm. Signals attributed to the minor isomer **22b**: 43.5, 84.9, 126.8 ppm. HRMS (EI): m/z = 301.1672 $[M]^+$, calcd for $C_{18}H_{23}NO_3$ 301.1678.

2.2.12 | (4*S*)-5,5-Dimethyl-4-(4-oxopentyl)-3-((*S*)-1-phenylethyl)oxazolidin-2-one (23a) and (4*R*)-5,5-dimethyl-4-(4-oxopentyl)-3-((*S*)-1-phenylethyl)oxazolidin-2-one (24a)

A mixture of **21b**/**22b** (81:19) (0.075 g, 0.25 mmol) and Pd $(OH)_2$ (20%) (0.035 g, 0.05 mmol) in MeOH (3.0 mL) was placed in a round-bottom flask (25 mL) provided with an H_2 balloon and stirred at room temperature for 24 hours. The reaction mixture was filtered over celite and washed with CH_2Cl_2 (10 mL). The solvent was removed under vacuum, and the crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 95:5) to give a mixture of **23a**/**24a** (98:2) (0.031 g, 41%) as a colorless oil. R_f = 0.30 (hexane/EtOAc, 7:3). $[\alpha]_D^{22}$ = −23.4 (*c* 0.261, MeOH). IR (film): $\bar{\nu}$ = 2976, 1738, 1452, 1412, 1374, 1302, 1221, 1192, 1171, 1025, 765, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.02-1.13 (m, 1 H, CH_2C-4), 1.15-1.29 (m, 2 H, CH_2C-4, CH_2CH$_2$C-4), 1.30-1.39 (m, 1 H, CH_2CH$_2$C-4), 1.35 (s, 3 H, CH_3C-5), 1.39 (s, 3 H, CH_3C-5), 1.70 (*d*, *J* = 7.2 Hz, 3 H, CH_3C-1′), 2.04 (s, 3 H, CH_3CO), 2.18 (td, *J* = 6.6, 2.4 Hz, 2 H, CH_2CO), 3.38 (*dd*, *J* = 9.0, 3.0 Hz, 1 H, H-4), 5.06 (q, *J* = 7.2 Hz, 1 H, H-1′), 7.24-7.37 (m, 3 H, Ph-H), 7.37-7.44 (m, 2 H, Ph-H) ppm. Signals attributed to the minor isomer **24a**: 2.09 (s, CH_3CO), 5.14 (q, *J* = 7.2 Hz, CH_3C-1′) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.6 (*C*H_3C-1′), 19.5 (*C*H_2CH$_2$C-4), 21.4 (*C*H_3C-5), 28.4 (*C*H_3C-5), 28.5 (*C*H_2C-4), 30.0 (*C*H_3CO), 43.0 (*C*H_2CO), 51.5 (C-1′), 63.2 (C-4), 80.4 (C-5), 126.9 (2 C, arom. *C*H), 127.5

(arom. *C*H), 128.4 (2 C, arom. *C*H), 141.5 (arom. C), 157.4 (C-2), 207.9 (*C*O) ppm. Signals attributed to the minor isomer **24a**: 43.3 ppm. HRMS (EI): m/z = 303.1864 $[M]^+$, calcd for $C_{18}H_{25}NO_3$ 303.1834.

2.2.13 | (*E*)-2-(5,5-Dimethyl-2-oxo-3-((*R*)-1-phenylethyl)oxazolidin-4-ylidene)acetaldehyde (25a)

A mixture of $POCl_3$ (0.058 g, 0.378 mmol) and anhydrous DMF (0.028 g, 0.384 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was stirred at 0°C for 30 minutes. Subsequently, a solution of **14a** (0.080 g, 0.346 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred to the same temperature for 3 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with a 10% aqueous solution of NaOH (2 × 20 mL) and with water until neutral. The organic layer was dried (Na_2SO_4), the solvent removed under vacuum, and the crude purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 95:5) to give **25a** (0.069 g, 77%) as a pale yellow solid. R_f = 0.58 (hexane/EtOAc, 7:3); m.p. 102-104°C. $[\alpha]_D^{23}$ = +40.0 (*c* 0.100, $CHCl_3$). IR (film): $\bar{\nu}$ = 1779, 1657, 1619, 1578, 1454, 1404, 1374, 1296, 1262, 1168, 1136, 1029, 758, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.78 (s, 3 H, CH_3C-5), 1.79 (s, 3 H, CH_3C-5), 1.83 (*d*, *J* = 7.3 Hz, 3 H, CH_3C-1′), 5.21 (*d*, *J* = 7.5 Hz, 1 H, C*H*=), 5.47 (q, *J* = 7.3 Hz, 1 H, H-1′), 7.26-7.34 (m, 3 H, Ph-H), 7.36-7.40 (m, 2 H, Ph-H), 9.62 (*d*, *J* = 7.5 Hz, 1 H, C*H*O) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6 (*C*H_3C-1′), 27.9 (*C*H_3C-5), 28.0 (*C*H_3C-5), 52.4 (C-1′), 83.1 (C-5), 101.9 (*C*H=), 126.3 (2 C, arom. *C*H), 128.2 (arom. *C*H), 129.0 (2 C, arom. *C*H), 137.2 (arom. C), 154.2 (C-2), 161.5 (C-4), 186.4 (*C*HO) ppm. MS (70 eV): m/z (%) = 215 (75) $[M - 44]^+$, 200 (100), 186 (21), 172 (27), 157 (13), 110 (78), 105 (84), 77 (56), 70 (23). HRMS (FAB) (*m*NBA): m/z = 260.1278 $[M + 1]^+$, calcd for $C_{15}H_{18}NO_3$ 260.1287.

2.2.14 | (*E*)-2-(5,5-Dimethyl-2-oxo-3-((*S*)-1-phenylethyl)oxazolidin-4-ylidene)acetaldehyde (25b)

According to the method of preparation of **25a**, $POCl_3$ (0.124 g, 0.808 mmol), DMF (0.059 g, 0.808 mmol) and **14b** (0.170 g, 0.736 mmol) were mixed in anhydrous CH_2Cl_2 (1.5 mL) and stirred at 0°C for 6 hours to give **25b** (0.165 g, 87%) as a pale yellow solid. R_f = 0.54 (hexane/EtOAc, 7:3); m.p. 102-103°C. $[\alpha]_D^{23}$ = −47.5 (*c* 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1778, 1656, 1618, 1404, 1375, 1296, 1168, 1137, 969, 759, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.78 (s, 3 H, CH_3C-5), 1.79 (s, 3 H, CH_3C-5), 1.83 (*d*, *J* = 7.3 Hz, 3 H, CH_3C-1′), 5.21 (*d*, *J* = 7.5 Hz, 1 H, C*H*=), 5.47 (q, *J* = 7.3 Hz, 1 H, H-1′), 7.26-7.34 (m, 3 H, Ph-H), 7.35-7.40 (m, 2 H, Ph-H), 9.62 (*d*, *J* = 7.5 Hz, 1 H, C*H*O) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6 (*C*H_3C-1′), 27.9 (*C*H_3C-5), 28.0 (*C*H_3C-5), 52.4 (C-1′), 83.1 (C-5), 101.8 (*C*H=), 126.2 (2 C, arom. *C*H), 128.1 (arom. *C*H), 129.0 (2 C, arom. *C*H), 137.2 (arom. C), 154.2 (C-2), 161.5 (C-4), 186.4 (*C*HO) ppm. MS (70 eV): m/z (%) = 215 (66) $[M - 44]^+$, 200 (100), 186 (20), 172 (24), 110 (80), 105 (88), 91 (25), 79 (39), 77 (50). HRMS (FAB) (*m*NBA): m/z = 260.1290 $[M + 1]^+$, calcd for $C_{15}H_{18}NO_3$ 260.1287.

2.2.15 | (*E*)-4-(Bromomethylene)-5,5-dimethyl-3-((*S*)-1-phenylethyl)oxazolidin-2-one (26)

A mixture of **14b** (0.100 g, 0.433 mmol), NBS (0.077 g, 0.433 mmol), and *p*-TsOH (0.124 g, 0.653 mmol) in MeCN (5.0 mL) was stirred at 60°C for 1 hour. The solvent was removed under vacuum, and the crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 95:5) to give 26 (0.076 g, 57%) as a pale yellow solid. R_f = 0.75 (hexane/EtOAc, 7:3); m.p. 54-55°C. $[\alpha]_D^{23}$ = −18.0 (*c* 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1764, 1644, 1450, 1389, 1369, 1298, 1230, 1199, 1079, 1030, 759, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 3 H, CH_3C-5), 1.72 (s, 3 H, CH_3C-5), 1.75 (*d*, *J* = 7.2 Hz, 3 H, CH_3C-1′), 4.90 (s, 1 H, C*H*=), 5.40 (q, *J* = 7.2 Hz, 1 H, H-1′), 7.23-7.44 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.4 (*C*H_3C-1′), 24.4 (*C*H_3C-5), 24.5 (*C*H_3C-5), 51.4 (C-1′), 76.1 (*C*H=), 82.8 (C-5), 126.2 (2 C, arom. *C*H), 127.8 (arom. *C*H), 128.8 (2 C, arom. *C*H), 137.9 (arom. C), 143.0 (C-4), 154.7 (C-2) ppm. MS (70 eV): m/z (%) = 312 (16) $[M + 2]^+$, 310 (15) $[M]^+$, 230 (17), 207 (30), 205 (31), 126 (21), 105 (100), 77 (28). HRMS (FAB) (*m*NBA): m/z = 310.0439 $[M + 1]^+$, calcd for $C_{14}H_{17}NO_2Br$ 310.0443.

2.2.16 | 5-Methyl-3-((*R*)-1-phenylethyl)oxazolidine-2,4-dione (27)

To a mixture of **2a** (52:48) (0.100 g, 0.461 mmol) in anhydrous CH_2Cl_2 (2 mL), MCPBA (77%) (0.310 g, 1.38 mmol) was added at room temperature and under N_2 atmosphere. The mixture was stirred for 72 hours, diluted with CH_2Cl_2 (30 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL) and with cold water until neutral. The organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The crude was purified by column

chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 95:5) to give a mixture of **27** (56:44) (0.078 g, 77%) as a pale yellow oil. R_f = 0.55 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = +60.0 (*c* 0.400, $CHCl_3$). IR (film): $\bar{\nu}$ = 1810, 1734, 1447, 1404, 1369, 1312, 1218, 1182, 1074, 764, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.54 (*d*, *J* = 7.0 Hz, 3 H, C*H*$_3$C-5), 1.86 (*d*, *J* = 7.5 Hz, 3 H, C*H*$_3$C-1′), 4.74 (q, *J* = 7.0 Hz, 1 H, H-5), 5.31 (q, *J* = 7.5 Hz, 1 H, H-1′), 7.28-7.37 (m, 3 H, Ph-H), 7.44-7.48 (m, 2 H, Ph-H) ppm. Signals attributed to the minor isomer: 1.55 (*d*, *J* = 7.0 Hz, C*H*$_3$C-5), 1.87 (*d*, *J* = 7.5 Hz, C*H*$_3$C-1′), 4.75 (q, *J* = 7.0 Hz, H-5), 5.30 (q, *J* = 7.5 Hz, H-1′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.59 (*C*H$_3$C-5), 16.63 (*C*H$_3$C-1′), 51.78 (C-1′), 75.2 (C-5), 127.4 (2 C, arom. *C*H), 128.3 (arom. *C*H), 128.6 (2 C, arom. *C*H), 138.7 (arom. C), 154.6 (C-2), 173.4 (C-4) ppm. Signals attributed to the minor isomer: 16.57, 16.8, 51.81 (C-1′), 127.3, 138.8 (arom. C), 173.3 (C-4) ppm. MS (70 eV): *m/z* (%) = 220 (58) $[M + 1]^+$, 219 (15) $[M]^+$, 192 (9), 174 (12), 160 (24),146 (92), 132 (39), 120 (19), 105 (92), 104 (100), 77 (23). HRMS (EI): *m/z* = 219.0900 $[M]^+$, calcd for $C_{12}H_{13}NO_3$ 219.0895.

2.2.17 | 5-Methyl-3-((*S*)-1-phenylethyl)oxazolidine-2,4-dione (28)

Following the method of preparation of **27**, a mixture of **2b** (54:46) (0.060 g, 0.276 mmol) and MCPBA (77%) (0.123 g, 0.553 mmol) in anhydrous CH_2Cl_2 (2 mL) was stirred at 0°C for 8 hours to give a mixture of **28** (56:46) (0.057 g, 94%) as a pale yellow oil. R_f = 0.52 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = −68.0 (*c* 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1811, 1735, 1451, 1406, 1376, 1314, 1219, 1183, 1075, 764, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.54 (*d*, *J* = 7.0 Hz, 3 H, C*H*$_3$C-5), 1.87 (*d*, *J* = 7.0 Hz, 3 H, C*H*$_3$C-1′), 4.74 (q, *J* = 7.0 Hz, 1 H, H-5), 5.31 (q, *J* = 7.0 Hz, 1 H, H-1′), 7.29-7.38 (m, 3 H, Ph-H), 7.44-7.49 (m, 2 H, Ph-H) ppm. Signals attributed to the minor isomer: 1.53 (*d*, *J* = 7.0 Hz, C*H*$_3$C-5), 1.86 (*d*, *J* = 7.0 Hz, C*H*$_3$C-1′), 4.76 (q, *J* = 7.0 Hz, H-5), 5.30 (q, *J* = 7.0 Hz, H-1′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7 (*C*H$_3$C-5), 16.8 (*C*H$_3$C-1′), 51.8 (C-1′), 75.2 (C-5), 127.4 (2 C, arom. *C*H), 128.3 (arom. *C*H), 128.7 (2 C, arom. *C*H), 138.8 (arom. C), 154.6 (C-2), 173.4 (C-4) ppm. Signals attributed to the minor isomer: 16.6 (*C*H$_3$C-5), 16.7 (*C*H$_3$C-1′), 51.9 (C-1′), 127.3 (2 C, arom. *C*H), 138.7 (arom. C), 173.3 (C-4) ppm. MS(70 eV): *m/z* (%) = 219 (16) $[M]^+$, 176 (9), 160 (22), 146 (100), 132 (42), 120 (19), 105 (77), 104 (91), 77 (46). HRMS (EI): *m/z* = 219.0894 $[M]^+$, calcd for $C_{12}H_{13}NO_3$ 219.0895.

2.2.18 | (3a*R*,7a*S*)-3a,7a-Dimethyl-3-((*R*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (29a) and (3a*S*,7a*R*)-3a,7a-dimethyl-3-((*R*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (30a)

A mixture of **1a** (0.150 g, 0.691 mmol) and **8a** (0.155 g, 2.77 mmol) in anhydrous xylene (3 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2atmosphere. It was kept in the dark, stirred, and heated at 60°C for 5 days. The content of the tube was extracted with EtOAc (3 × 15 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic layers were filtered, the solvent was removed under vacuum, and the crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **29a**/**30a** (<1:99) (0.173 g, 92%) as colorless crystals. R_f = 0.54 (hexane/EtOAc, 7:3); m.p. 153-154°C. $[\alpha]_D^{23}$ = +111.5 (*c* 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1739, 1413, 1353, 1227, 1051, 1025, 975, 733, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, C*H*$_3$C-3a), 1.51 (s, 3 H, C*H*$_3$C-7a), 1.82 (*d*, *J* = 7.2 Hz, 3 H, C*H*$_3$C-1′), 2.19 (*dt*, *J* = 16.5, 2.7 Hz, 1 H, H-7), 2.42 (*dd*, *J* = 16.5, 6.9 Hz, 1 H, H-7), 4.58 (q, *J* = 7.2 Hz, 1 H, H-1′), 5.14-5.26 (m, 1 H, H-6), 6.40 (*dd*, *J* = 5.7, 2.7 Hz, 1 H, H-5), 7.20-7.52 (m, 5 H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.4 (*C*H$_3$C-1′), 21.2 (*C*H$_3$C-7a), 24.3 (*C*H$_3$C-3a), 29.6 (C-7), 51.5 (C-1′), 83.6 (C-7a), 94.8 (C-3a), 105.5 (C-6), 126.2 (2 C, arom. *C*H), 127.1 (arom. *C*H), 128.5 (2 C, arom. *C*H), 142.2 (arom. C), 143.3 (C-5), 155.4 (C-2) ppm. HRMS (EI): *m/z* = 273.1372 $[M]^+$, calcd for $C_{16}H_{19}NO_3$ 273.1365.

2.2.19 | (3a*R*,7a*S*)-3a,7a-Dimethyl-3-((*S*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (29b) and (3a*S*,7a*R*)-3a,7a-dimethyl-3-((*S*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (30b)[46]

Method A. According to the method of preparation of **29a**/**30a**, the reaction of **1b** (0.217 g, 1.00 mmol) and **8a** (0.56 g, 1.0 mmol) resulted in a mixture of **29b**/**30b** (93:7) (0.202 g, 74%) as a white solid.

Method B. A mixture of **1b** (0.100 g, 0.46 mmol) and **8a** (0.103 g, 1.84 mmol) was stirred under MW irradiation (100 W) at 110°C for 5 hours. The reaction crude was purified by column chromatography over silica gel

(30 g/g of crude, hexane/EtOAc, 95:5) to give a mixture of **29b**/**30b** (92:8) (0.06 g, 48%) as white crystals. R_f = 0.40 (hexane/EtOAc, 8:2); m.p. 156-157°C (hexane/EtOAc, 9:1). $[\alpha]_D^{23}$ = −114.9 (*c* 0.123, MeOH); $[\alpha]_D^{23}$ = −101.0 (*c* 2.20, $CHCl_3$). IR (film): $\bar{\nu}$ = 1733, 1650, 1412, 1352, 1228, 1075, 1052, 1027, 976, 735, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, CH_3C-3a), 1.51 (s, 3 H, CH_3C-7a), 1.82 (*d*, *J* = 7.3 Hz, 3 H, CH_3C-1′), 2.20 (*dt*, *J* = 16.1, 2.8 Hz, 1 H, H-7), 2.43 (*dd*, *J* = 16.1, 6.8 Hz, 1 H, H-7), 4.58 (q, *J* = 7.3 Hz, 1 H, H-1′), 5.19 (ddd, *J* = 6.8, 5.2, 2.8 Hz, 1 H, H-6), 6.40 (dd, *J* = 5.2, 2.9 Hz, 1 H, H-5), 7.22-7.36 (m, 3 H, Ph-H), 7.40-7.45 (m, 2 H, Ph-H) ppm. Signals attributed to the minor isomer **30b**: 2.37 (dd, *J* = 16.3, 6.5 Hz, H-7), 4.91 (q, *J* = 7.2 Hz, H-1′), 5.01 (ddd, *J* = 6.5, 5.4, 2.6 Hz, H-6) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.4 (*C*H_3C-1′), 21.2 (*C*H_3C-7a), 24.3 (*C*H_3C-3a), 29.6 (C-7), 51.5 (C-1′), 83.6 (C-7a), 94.8 (C-3a), 105.5 (C-6), 126.6 (2 C, arom. *C*H), 127.2 (arom. *C*H), 128.5 (2 C, arom. *C*H), 142.3 (arom. C), 143.3 (C-5), 155.4 (C-2) ppm. MS(70 eV): *m/z* (%) = 274 (45) $[M + 1]^+$, 255 (15), 218 (32), 212 (45), 211 (40), 170 (24), 152 (15), 113 (50), 105 (100), 79 (83), 77 (68), 51 (24). HRMS (EI): *m/z* = 273.1344 $[M]^+$, calcd for $C_{16}H_{19}NO_3$ 273.1365.

2.2.20 | (3a*R*,7a*S*)-3a,5,7a-Trimethyl-3-((*R*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (29c) and (3a*S*,7a*R*)-3a,5,7a-trimethyl-3-((*R*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (30c)

Following the method of preparation of **29a**/**30a**, a mixture of **1a** (0.060 g, 0.28 mmol) and **8b** (0.097 g, 1.39 mmol) in anhydrous xylene (5 mL) was stirred at 60°C for 5 days to give **29c**/**30c** (<1:99) (0.036 g, 45%) as a pale yellow solid. R_f = 0.57 (hexane/EtOAc, 7:3); m.p. 141-143°C. $[\alpha]_D^{23}$ = +43.0 (*c* 0.100, $CHCl_3$). IR (film): $\bar{\nu}$ = 2924, 1758, 1714, 1675, 1371, 759, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.427 (s, 3 H, CH_3C-3a), 1.431 (s, 3 H, CH_3C-7a), 1.81 (br s, 3H, CH_3C-5), 1.84 (d, *J* = 7.5 Hz, 3 H, CH_3C-1′), 2.17 (dm, *J* = 16.0 Hz, 1 H, H-7), 2.35 (dd, *J* = 16.0, 7.0 Hz, 1 H, H-7), 4.57 (q, *J* = 7.5 Hz, 1 H, H-1′), 4.87 (dq, *J* = 7.0, 1.0 Hz, 1 H, H-6), 7.22-7.27 (m, 1 H, Ph-H), 7.30-7.35 (m, 2 H, Ph-H), 7.41-7.45 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7 (*C*H_3C-5), 20.6 (*C*H_3C-1′), 21.4 (*C*H_3C-7a), 24.2 (*C*H_3C-3a), 30.5 (C-7), 51.7 (C-1′), 83.3 (C-7a), 94.8 (C-3a), 99.1 (C-6), 126.5 (2 C, arom. *C*H), 127.1 (arom. *C*H), 128.6 (2 C, arom. *C*H), 143.0 (arom. C), 150.9 (C-5), 155.7 (C-2) ppm. MS (70 eV): *m/z* (%) = 243 (1) $[M - 44]^+$, 228 (32), 200 (5), 186 (12), 113 (51), 105 (100), 103 (26), 79 (31), 77 (30). HRMS (EI): *m/z* = 287.1519 $[M]^+$, calcd for $C_{17}H_{21}NO_3$ 287.1521.

2.2.21 | (3a*R*,7a*S*)-3a,5,7a-Trimethyl-3-((*S*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (29d) and (3a*S*,7a*R*)-3a,5,7a-trimethyl-3-((*S*)-1-phenylethyl)-3,3a,7,7a-tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (30d)

Method A. According to method A for the preparation of **29b**/**30b**, a mixture of **1b** (0.200 g, 0.922 mmol) and **8b** (0.258 g, 3.69 mmol) in anhydrous xylene (3 mL) was stirred at 60°C for 7 days to give **29d**/**30d** (>99:1) (0.037 g, 14%) as a pale yellow solid.

Method B. According to method B for the preparation of **29b**/**30b**, a mixture of **1b** (0.100 g, 0.46 mmol) and **8b** (0.129 g, 1.84 mmol) provided **29d**/**30d** (98:2) (0.055 g, 42%) as white crystals.

Data for the mixture of **29d**/**30d** (>99:1): R_f = 0.55 (hexane/EtOAc, 7:3); m.p. 152-154°C. $[\alpha]_D^{23}$ = −50.5 (*c* 0.200, $CHCl_3$). IR (film): $\bar{\nu}$ = 1734, 1686, 1417, 1357, 1227, 1135, 1090, 1049, 745, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3C-3a), 1.43 (s, 3 H, CH_3C-7a), 1.81 (br s, 3H, CH_3C-5), 1.84 (d, *J* = 7.2 Hz, 3 H, CH_3C-1′), 2.16 (dm, *J* = 16.2 Hz, 1 H, H-7), 2.35 (dd, *J* = 16.2, 6.8 Hz, 1 H, H-7), 4.57 (q, *J* = 7.2 Hz, 1 H, H-1′), 4.86 (dm, *J* = 6.8 Hz, 1 H, H-6), 7.20-7.36 (m, 3 H, Ph-H), 7.39-7.46 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.6 (*C*H_3C-5), 20.5 (*C*H_3C-1′), 21.4 (*C*H_3C-7a), 24.1 (*C*H_3C-3a), 30.4 (C-7), 51.6 (C-1′), 83.3 (C-7a), 94.7 (C-3a), 99.1 (C-6), 126.4 (2 C, arom. *C*H), 127.1 (arom. *C*H), 128.5 (2 C, arom. *C*H), 143.0 (arom. C), 150.8 (C-5), 155.6 (C-2) ppm. MS (70 eV): *m/z* (%) = 288 (1) $[M + 1]^+$, 228 (32), 186 (11), 113 (47), 105 (100), 103 (23), 77 (27). HRMS (EI): *m/z* = 287.1521 $[M]^+$, calcd for $C_{17}H_{21}NO_3$ 287.1521.

2.2.22 | (3a*R*,7a*S*)-3a,7a-Dimethyl-3-((*S*)-1-phenylethyl)hexahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (31a) and (3a*S*,7a*R*)-3a,7a-dimethyl-3-((*S*)-1-phenylethyl)hexahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (32a)

A mixture of **29b**/**30b** (93:7) (0.100 g, 0.36 mmol) and Pd $(OH)_2$ (20%) (0.0024 g, 0.017 mmol) in MeOH (5 mL) was stirred under H_2 (1 atm) atmosphere at room temperature for 12 hours. The content of the flask was filtered, the solvent was removed under vacuum, and the crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give a mixture of **31a**/**32a** (92:8) (0.10 g, 99%) as colorless crystals. R_f = 0.29 (hexane/EtOAc, 7:3); m.p. 101-102°C. $[\alpha]_D^{25}$ = −1.87 (*c* 0.400, $CHCl_3$). IR (film): $\bar{\nu}$ = 2951, 2890, 1746, 1406, 1344, 1284, 1233, 1140, 1108, 1028, 970, 773, 750, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, CH_3C-7a), 1.31 (s, 3 H, CH_3C-3a), 1.66-1.74 (m, 1 H, H-7), 1.76-1.81 (m, 2 H, H-6), 1.83 (d, *J* = 7.5 Hz, 3 H, CH_3C-1′), 1.96 (dt, *J* = 13.7, 4.0 Hz, 1 H, H-7), 3.61-3.71 (m, 2 H, H-5), 4.45 (q, *J* = 7.5 Hz, 1 H, H-1′), 7.21-7.25 (m, 1 H, Ph-H), 7.29-7.34 (m, 2 H, Ph-H), 7.41-7.45 (m, 2 H, Ph-H) ppm. Signals attributed to the minor isomer **32a**: 1.26 (s, CH_3C-3a), 1.28 (s, CH_3C-7a), 7.79-7.51 (m, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (C-6), 19.5 (*C*H_3C-1′), 20.0 (*C*H_3C-3a), 24.0 (*C*H_3C-7a), 27.3 (C-7), 51.3 (C-1′), 57.9 (C-5), 80.3 (C-7a), 92.3 (C-3a), 126.4 (2 C, arom. *C*H), 127.0 (arom. *C*H), 128.4 (2 C, arom. *C*H), 142.8 (arom. C), 156.3 (C-2) ppm. Signals attributed to the minor isomer **32a**: 17.8, 18.3, 19.9, 23.5, 27.5, 50.9, 57.9, 127.2, 127.6, 128.0 ppm. HRMS (EI): *m/z* = 275.1529 $[M]^+$, calcd for $C_{16}H_{21}NO_3$ 275.1521.

2.2.23 | (3a*R*,5*R*,7a*S*)-3a,5,7a-Trimethyl-3-((*S*)-1-phenylethyl)hexahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (31b) and (3a*S*,5*S*,7a*R*)-3a,5,7a-trimethyl-3-((*S*)-1-phenylethyl)hexahydro-2*H*-pyrano[2,3-*d*]oxazol-2-one (32b)

Following the method of preparation of **31a**/**32a**, the reaction of **29d**/**30d** (>99:1) (0.100 g, 0.35 mmol) and Pd $(OH)_2$ (20%) (0.0024 g, 0.017 mmol) resulted in a mixture of **31b**/**32b** (>99:1) (0.10 g, 99%) as white crystals. R_f = 0.26 (hexane/EtOAc, 7:3); m.p. 145-147°C. $[\alpha]_D^{25}$ = +10.3 (*c* 0.160, MeOH). IR (film): $\bar{\nu}$ = 2988, 2928, 1751, 1497, 1447, 1401, 1387, 1344, 1227, 1100, 1065, 1027, 977, 779, 746, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.5 Hz, 3 H, CH_3C-5), 1.24 (s, 3 H, CH_3C-7a), 1.43-1.48 (m, 1 H, H-5), 1.45 (s, 3 H, CH_3C-3a), 1.50-1.60 (m, 1 H, H-6), 1.60-1.69 (m, 1 H, H-7), 1.84 (d, *J* = 7.0 Hz, 3 H, CH_3C-1′), 2.13 (dt, *J* = 15.0, 3.1 Hz, 1 H, H-7), 3.43-3.50 (m, 1 H, H-5), 4.55 (q, *J* = 7.0 Hz, 1 H, H-1′), 7.21-7.25 (m, 1 H, Ph-H), 7.30-7.34 (m, 2 H, Ph-H), 7.40-7.44 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.9 (*C*H_3C-3a), 19.4 (*C*H_3C-1′), 21.8 (*C*H_3C-5), 24.6 (*C*H_3C-7a), 27.9 (C-6), 30.6 (C-7), 51.5 (C-1′), 67.8 (C-5), 78.8 (C-7a), 92.6 (C-3a), 126.7 (2 C, arom. *C*H), 126.9 (arom. *C*H), 128.4 (2 C, arom. *C*H), 142.8 (arom. C), 157.0 (C-2) ppm. HRMS (EI): *m/z* = 289.1678 $[M]^+$, calcd for $C_{17}H_{23}NO_3$ 289.1678.

2.2.24 | (7a*S*)-7a-Methyl-3-((*R*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (33a) and (7a*R*)-7a-Methyl-3-((*R*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (34a)

A mixture of **1a** (0.100 g, 0.46 mmol), **8a** (0.155 g, 2.77 mmol), and MeI (0.131 g, 0.923 mmol) in anhydrous xylene (1 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was kept in the dark, stirred, and heated at 140°C for 24 hours. During this period, **8a** (0.155 g, 2.77 mmol) was added every 6 hours (four times). The content of the tube was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were filtered. The solvent was removed under vacuum, and the crude purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **33a**/**34a** (20:80) (0.071 g, 60%) as an amber liquid. R_f = 0.71 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = +45.2 (*c* 0.730, $CHCl_3$). IR (film): $\bar{\nu}$ = 2926, 1761, 1668, 1584, 1450, 1403, 1371, 1311, 1224, 1197, 1025, 755, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 0.6 Hz, 3 H, CH_3C-7a), 1.75 (d, *J* = 7.2 Hz, 3 H, CH_3C-1′), 2.39 (ddd, *J* = 16.5, 6.0, 0.6 Hz, 1 H, H-7), 2.54 (dm, *J* = 16.5 Hz, 1 H, H-7), 4.76 (d, *J* = 5.7 Hz, 1 H, H-4), 5.38 (q, *J* = 7.2 Hz, 1 H, H-1′), 5.51-5.58 (m, 1 H, H-6), 5.79-5.86 (m, 1 H, H-5), 7.24-7.38 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **33a**: 1.32 (d, *J* = 0.6 Hz, CH_3C-7a), 1.77 (d, *J* = 7.5 Hz, CH_3C-1′), 2.38 (br dd, *J* = 16.2, 5.4 Hz, H-7), 4.69 (d, *J* = 5.1 Hz, H-4) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.9 (*C*H_3C-1′), 21.7 (*C*H_3C-7a), 33.7 (C-7), 51.3 (C-1′), 80.4 (C-7a), 94.1 (C-4), 118.4 (C-6), 124.4 (C-5), 126.6 (2 C, arom. *C*H), 127.6 (arom. *C*H), 128.5 (2 C, arom. *C*H), 138.9 (arom. C), 139.7 (C-3a), 156.5 (C-2) ppm. Signals attributed to the minor isomer **33a**: 15.8 (*C*H_3C-1′), 33.8 (C-7), 51.8 (C-1′), 80.1 (C-7a), 118.1 (C-6) ppm. HRMS (EI): *m/z* = 255.1265 $[M]^+$, calcd for $C_{16}H_{17}NO_2$ 255.1259.

2.2.25 | (7a*S*)-7a-Methyl-3-((*S*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (33b), (7a*R*)-7a-methyl-3-((*S*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (34b), 3-((7a*S*)-7a-methyl-2-oxo-3-((*S*)-1-phenylethyl)-2,3,7,7a-tetrahydrobenzo[*d*]oxazol-6-yl)propanal (33e), and 3-((7a*R*)-7a-methyl-2-oxo-3-((*S*)-1-phenylethyl)-2,3,7,7a-tetrahydrobenzo[*d*]oxazol-6-yl)propanal (34e)[46]

Method A. Following the method of preparation of **33a**/**34a**, the reaction of **1b** (0.291 g, 1.34 mmol), **8a** (0.375 g, 6.70 mmol), and MeI (0.381 g, 2.68 mmol) provided a mixture of **33b**/**34b** (83:17) (0.207 g, 61%) as a colorless oil, as well as a mixture of **33e**/**34e** (86:14) (0.098 g, 32%) as a colorless oil.

Method B. A mixture of **33b**/**34b** (83:17) (0.100 g, 0.39 mmol), **8a** (0.056 g, 1.17 mmol), and MeI (0.111 g, 0.78 mmol) in anhydrous xylene (1 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was kept in the dark, stirred, and heated at 160°C for 24 hours. During this period, **8a** (0.056 g, 1.17 mmol) was added twice. The content of the tube was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were filtered, and the solvent was removed under vacuum. The reaction crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1) to give **33e**/**33e** (85:15) (0.05 g, 41%) as an amber liquid. Data for **33b**/**34b** (83:17): R_f = 0.75 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = −68.9 (*c* 0.195, MeOH). IR (film): $\bar{\nu}$ = 1762, 1670, 1583, 1496, 1451, 1403, 1376, 1314, 1221, 1197, 1069, 1026, 757, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 0.6 Hz, 3 H, C*H*$_3$C-7a), 1.76 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$C-1′), 2.40 (ddd, *J* = 16.4, 6.2, 0.6 Hz, 1 H, H-7), 2.50-2.60 (m, 1 H, H-7), 4.76 (dt, *J* = 5.5, 0.6 Hz, 1 H, H-4), 5.39 (q, *J* = 7.3 Hz, 1 H, H-1′), 5.52-5.60 (m, 1 H, H-6), 5.80-5.87 (m, 1 H, H-5), 7.30-7.40 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **34b**: 1.32 (d, *J* = 0.5 Hz, C*H*$_3$C-7a), 1.77 (d, *J* = 7.3 Hz, C*H*$_3$C-1′), 2.39 (ddd, *J* = 16.6, 6.2, 0.6 Hz, H-7), 4.69 (dt, *J* = 5.5, 0.6 Hz, H-4) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.9 (*C*H$_3$C-1′), 21.7 (*C*H$_3$C-7a), 33.7 (C-7), 51.3 (C-1′), 80.4 (C-7a), 94.1 (C-4), 118.5 (C-6), 124.4 (C-5), 126.6 (2 C, arom. *C*H), 127.6 (arom. *C*H), 128.5 (2 C, arom. *C*H), 138.8 (arom. C), 139.7 (C-3a), 156.6 (C-2) ppm. Signals attributed to the minor isomer **34b**: 15.8 (*C*H$_3$C-1′), 33.9 (C-7), 51.9 (C-1′), 80.2 (C-7a), 118.2 (C-6), 127.7 (arom. *C*H), 138.6 (arom. C), 140.1 (C-3a), 158.5 (C-2) ppm. HRMS (EI): *m/z* = 255.1257 $[M]^+$, calcd for $C_{16}H_{17}NO_2$ 255.1259.

Data for **33e**/**34e** (85:15): R_f = 0.35 (hexane/EtOAc, 7:3). $[\alpha]_D^{22}$ = −15.7 (*c* 0.220, MeOH). IR (film): $\bar{\nu}$= 1762, 1724, 1674, 1608, 1450, 1398, 1316, 1224, 1198, 1072, 1025, 972, 760, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, C*H*$_3$C-7a), 1.74 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$C-1′), 2.20 (d, *J* = 15.9 Hz, 1 H, H-7), 2.36-2.46 (m, 2 H, C*H*$_2$C-6), 2.52-2.62 (m, 3 H, H-7, C*H*$_2$CHO), 4.71 (d, *J* = 5.2 Hz, 1 H, H-4), 5.38 (q, *J* = 7.3 Hz, 1 H, H-1′), 5.53-5.62 (m, 1 H, H-5), 7.30-7.40 (m, 5 H, Ph-H), 9.75 (t, *J* = 1.4 Hz, 1 H, C*H*O) ppm. Signals attributed to the minor isomer **34e**: 1.31 (s, C*H*$_3$C-7a), 1.78 (d, *J* = 7.2 Hz, C*H*$_3$C-1′), 4.65 (d, *J* = 5.2 Hz, H-4) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.2 (*C*H$_3$C-1′), 22.2 (*C*H$_3$C-7a), 29.2 (*C*H$_2$C-6), 38.1 (C-7), 41.8 (*C*H$_2$CHO), 51.6 (C-1′), 80.9 (C-7a), 94.4 (C-4), 119.6 (C-5), 126.9 (2 C, arom. *C*H), 127.9 (arom. *C*H), 128.8 (2 C, arom. *C*H), 130.4 (C-6), 138.5 (arom. C), 139.1 (C-3a), 157.0 (C-2), 201.8 (*C*HO) ppm. Signals attributed to the minor isomer **34e**: 24.8 (*C*H$_3$C-7a), 45.6 (*C*H$_2$CHO), 119.7 (C-5), 127.0 (arom. *C*H), 128.0 (arom. *C*H) ppm. HRMS (EI): *m/z* = 311.1531 $[M]^+$, calcd for $C_{19}H_{21}NO_3$ 311.1521.

2.2.26 | (7a*S*)-5,7a-Dimethyl-3-((*R*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (33c) and (7a*R*)-5,7a-dimethyl-3-((*R*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (34c)

A mixture of **1a** (0.120 g, 0.55 mmol), **8b** (0.193 g, 2.75 mmol), and MeI (0.157 g, 1.11 mmol) in anhydrous xylene (1.5 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. While kept in the dark, it was stirred and heated at 160°C for 48 hours. The content of the tube was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were filtered, and the solvent was removed under vacuum. The reaction crude was purified by column chromatography over silica gel (30 g/g of

crude, hexane/EtOAc, 9:1) to give **33c**/**34c** (12:88) (0.092 g, 62%) as a pale yellow oil. R_f = 0.42 (hexane/EtOAc, 7:3). $[\alpha]_D^{23}$ = +11.8 (*c* 0.400, $CHCl_3$). IR (film): $\bar{\nu}$ = 2928, 1766, 1676, 1450, 1378, 1318, 1196, 1026, 764, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, C*H*$_3$C-7a), 1.67 (s, 3 H, C*H*$_3$C-5), 1.76 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$C-1′), 2.32 (ddm, *J* = 16.0, 6.4 Hz, 1 H, H-7), 2.50 (dm, *J* = 16.0 Hz, 1 H, H-7), 4.65 (s, 1 H, H-4), 5.20-5.28 (m, 1 H, H-6), 5.37 (q, *J* = 7.2 Hz, 1H, H-1′), 7.24-7.40 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **33c**: 1.26 (s, C*H*$_3$C-7a), 1.79 (d, *J* = 7.2 Hz, C*H*$_3$C-1′), 4.61 (s, H-4) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.0 (*C*H$_3$C-1′), 21.7 (*C*H$_3$), 21.8 (*C*H$_3$), 34.0 (C-7), 51.3 (C-1′), 80.8 (C-7a), 97.7 (C-4), 113.1 (C-6), 126.6 (2 C, arom. *C*H), 127.6 (arom. *C*H), 128.6 (2 C, arom. *C*H), 132.4 (C-5), 138.9 (arom. C), 140.0 (C-3a), 156.9 (C-2) ppm. MS(70 eV): *m/z* (%) = 271 (16) $[M + 2]^+$, 116 (100), 122 (71), 107 (76), 80 (40), 78 (23). HRMS (EI): *m/z* = 269.1425 $[M]^+$, calcd for $C_{17}H_{19}NO_2$ 269.1416.

2.2.27 | (7a*S*)-5,7a-Dimethyl-3-((*S*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (33d) and (7a*R*)-5,7a-Dimethyl-3-((*S*)-1-phenylethyl)-7,7a-dihydrobenzo[*d*]oxazol-2(3*H*)-one (34d)[46]

According to the method for the preparation of **33c**/**34c**, a mixture of **1b** (0.345 g, 1.59 mmol), **8b** (0.556 g, 8.00 mmol), and MeI (0.223 g, 3.18 mmol) in anhydrous xylene (1.5 mL) was stirred and heated at 140°C for 24 hours to give **33d**/**34d** (80:20) (0.092 g, 63%) as a colorless oil. R_f = 0.45 (hexane/EtOAc, 7:3). $[\alpha]_D^{21}$ = −79.7 (*c* 0.152, MeOH). IR (film): $\bar{\nu}$ = 1763, 1677, 1608, 1450, 1401, 1382, 1318, 1197, 1026, 764, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, C*H*$_3$C-7a), 1.67 (br s, 3 H, C*H*$_3$C-5), 1.76 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$C-1′), 2.32 (ddm, *J* = 16.0, 6.3 Hz, 1 H, H-7), 2.51 (dm, *J* = 16.0 Hz, 1 H, H-7), 4.65 (s, 1 H, H-4), 5.20-5.28 (m, 1 H, H-6), 5.36 (q, *J* = 7.3 Hz, 1 H, H-1′), 7.20-7.50 (m, 5 H, Ph-H) ppm. Signals attributed to the minor isomer **34d**: 1.31 (s, C*H*$_3$C-7a), 1.64 (br s, C*H*$_3$C-5), 4.61 (s, H-4) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.0 (*C*H$_3$C-1′), 21.6 (*C*H$_3$), 21.7 (*C*H$_3$), 34.0 (C-7), 51.3 (C-1′), 80.8 (C-7a), 97.7 (C-4), 113.0 (C-6), 126.5 (2 C, arom. *C*H), 127.6 (arom. *C*H), 128.5 (2 C, arom. *C*H), 132.4 (C-5), 138.9 (arom. C), 139.9 (C-3a), 156.9 (C-2) ppm. Signals attributed to the minor isomer **34d**: 34.1, 51.9, 80.7, 97.6, 112.8, 126.4, 140.1 ppm. HRMS (EI): *m/z* = 269.1419 $[M]^+$, calcd for $C_{17}H_{19}NO_2$ 269.1416.

2.2.28 | (3a*S*,7a*R*)-3a,5,7a-Trimethyl-3-((*R*)-1-phenylethyl)-3,3a,7,7a-tetrahydrobenzo[*d*]oxazol-2(6*H*)-one (36a) and (3a*R*,7a*S*)-3a,5,7a-trimethyl-3-((*R*)-1-phenylethyl)-3,3a,7,7a-dihydrobenzo[*d*]oxazol-2(6*H*)-one (37a)

A mixture of **1a** (0.120 g, 0.55 mmol) and **35** (0.412 g, 2.77 mmol) in anhydrous xylene (1.2 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. While kept in the dark, it was stirred and heated at 160°C for 48 hours. The content of the tube was extracted with EtOAc (3 × 15 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic layers were filtered, the solvent was removed under vacuum, and the crude was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 95:5) to give **36a**/**37a** (54:46) (0.087 g, 55%) as a pale yellow solid. This mixture was separated by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 98:2) to obtain **36a** (0.044 g, 28%) as a pale yellow solid and **37a** (0.036 g, 23%) as a white solid.

Data for **36a**: R_f = 0.49 (hexane/EtOAc, 7:3); m.p. 181-182°C. $[\alpha]_D^{23}$ = −47.0 (*c* 0.100, $CHCl_3$). IR (film): $\bar{\nu}$ = 2916, 1725, 1494, 1441, 1412, 1367, 1348, 1320, 1223, 1171, 1083, 1026, 970, 759, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, C*H*$_3$C-3a), 1.30 (s, 3 H, C*H*$_3$C-7a), 1.65 (ddd, *J* = 14.0, 9.5, 5.0 Hz, 1 H, H-7), 1.69 (br s, 3 H, C*H*$_3$C-5), 1.77 (d, *J* = 7.5 Hz, 3 H, C*H*$_3$C-1′), 1.82 (br dt, *J* = 16.5, 5.0 Hz, 1 H, H-6), 2.02 (dt, *J* = 14.0, 5.0 Hz, 1 H, H-7), 2.18-2.27 (m, 1 H, H-6), 4.47 (q, *J* = 7.5 Hz, 1 H, H-1′), 5.18 (br s, 1 H, H-4), 7.22-7.26 (m, 1 H, Ph-H), 7.29-7.34 (m, 2 H, Ph-H) 7.43-7.47 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.1 (*C*H$_3$C-1′), 21.4 (*C*H$_3$C-3a), 22.0 (*C*H$_3$C-7a), 23.5 (*C*H$_3$C-5), 26.3 (C-6), 30.8 (C-7), 51.8 (C-1′), 62.9 (C-3a), 80.8 (C-7a), 122.5 (C-4), 126.9 (2 C, arom. *C*H), 127.1 (arom. *C*H), 128.4 (2 C, arom. *C*H), 136.9 (C-5), 143.0 (arom. C), 156.5 (C-2) ppm. HRMS (EI): *m/z* = 285.1725 $[M]^+$, calcd for $C_{18}H_{23}NO_2$ 285.1729.

Data for **37a**: R_f = 0.44 (hexane/EtOAc, 7:3); m.p. 119-121°C. $[\alpha]_D^{23}$ = −15.0 (*c* 0.100, $CHCl_3$). IR (film): $\bar{\nu}$ = 2927, 1738, 1447, 1404, 1317, 1169, 1026, 765, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, C*H*$_3$C-3a), 1.30 (s, 3 H, C*H*$_3$C-7a), 1.60 (br s, 3 H, C*H*$_3$C-5), 1.66 (ddd, *J* = 14.0, 7.5, 5.5 Hz, 1 H, H-7), 1.80 (d, *J* = 7.5 Hz, 3 H, C*H*$_3$C-1′), 1.81-1.87 (m, 1 H, H-6), 1.93-2.00 (m, 1 H, H-7), 2.10-2.17 (m, 1 H, H-6), 4.63 (q, *J* = 7.5 Hz, 1 H, H-1′), 5.09-5.12 (m, 1 H, H-4), 7.21-7.25 (m, 1 H, Ph-H), 7.28-7.32 (m, 2 H, Ph-H) 7.39-7.43 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.6 (*C*H$_3$C-1′), 20.9 (*C*H$_3$C-3a), 21.4 (*C*H$_3$C-7a), 23.3 (*C*H$_3$C-5), 26.7 (C-6), 31.3 (C-7), 51.5 (C-1′), 62.9 (C-3a), 80.8

(C-7a), 123.4 (C-4), 127.1 (arom. *C*H), 127.2 (2 C, arom. *C*H), 128.2 (2 C, arom. *C*H), 136.8 (C-5), 142.5 (arom. C), 156.3 (C-2) ppm. HRMS (EI): m/z = 285.1705 $[M]^+$, calcd for $C_{18}H_{23}NO_2$ 285.1729.

2.2.29 | (3a*R*,7a*S*)-3a,5,7a-Trimethyl-3-((*S*)-1-phenylethyl)-3,3a,7,7a-tetrahydrobenzo[*d*]oxazol-2(6*H*)-one (36b) and (3a*S*,7a*R*)-3a,5,7a-trimethyl-3-((*R*)-1-phenylethyl)-3,3a,7,7a-dihydrobenzo[*d*]oxazol-2(6*H*)-one (37b)

Following the method for the preparation of **36a**/**37a**, a mixture of **1b** (0.100 g, 0.46 mmol) and **35** (0.343 g, 2.30 mmol) in anhydrous xylene (1.0 mL) was stirred and heated at 140°C for 48 hours to give **36b**/**37b** (63:37) (0.121 g, 92%) as a pale yellow solid. This mixture was separated by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 98:2) to obtain **36b** (0.057 g, 44%) as a pale yellow solid and **37b** (0.052 g, 40%) as a white solid. Data for **36b**: R_f = 0.49 (hexane/EtOAc, 7:3); m.p. 181-183°C. $[\alpha]_D^{23}$ = +62.0 (*c* 0.05, $CHCl_3$). IR (film): $\bar{\nu}$ = 2916, 1725, 1413, 1349, 1321, 1224, 1171, 1083, 1027, 970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, C*H*$_3$C-3a), 1.30 (s, 3 H, C*H*$_3$C-7a),1.65 (ddd, J = 14.0, 9.5, 5.5 Hz, 1 H, H-7), 1.69 (br s, 3 H, C*H*$_3$C-5), 1.77 (d, J = 7.5 Hz, 3 H, C*H*$_3$C-1′), 1.82 (br dt, J = 17.5, 5.5 Hz, 1 H, H-6), 2.02 (ddd, J = 14.0, 5.0, 4.5 Hz, 1 H, H-7), 2.18-2.27 (m, 1 H, H-6), 4.47 (q, J = 7.5 Hz, 1 H, H-1′), 5.18 (br s, 1 H, H-4), 7.22-7.26 (m, 1 H, Ph-H), 7.30-7.34 (m, 2 H, Ph-H), 7.43-7.47 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.1 (*C*H$_3$C-1′), 21.4 (*C*H$_3$C-3a), 22.0 (*C*H$_3$C-7a), 23.5 (*C*H$_3$C-5), 26.3 (C-6), 30.8 (C-7), 51.8 (C-1′), 62.9 (C-3a), 80.8 (C-7a), 122.5 (C-4), 126.9 (2 C, arom. *C*H), 127.1 (arom. *C*H), 128.4 (2 C, arom. *C*H), 136.9 (C-5), 143.0 (arom. C), 156.5 (C-2) ppm. HRMS (EI): m/z = 285.1727 $[M]^+$, calcd for $C_{18}H_{23}NO_2$ 285.1729.

Data for **37b**: R_f = 0.44 (hexane/EtOAc, 7:3); m.p. 120-121°C. $[\alpha]_D^{23}$ = +17.0 (*c* 0.100, $CHCl_3$). IR (film): $\bar{\nu}$ = 2931, 1739, 1494, 1447, 1318, 1226, 1170, 1076, 1027, 967, 920, 766, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, C*H*$_3$C-3a), 1.30 (s, 3 H, C*H*$_3$C-7a), 1.61 (br s, 3 H, C*H*$_3$C-5),1.66 (ddd, J = 14.0, 7.5, 5.5 Hz, 1 H, H-7), 1.80 (d, J = 7.5 Hz, 3 H, C*H*$_3$C-1′), 1.81-1.87 (m, 1 H, H-6), 1.97 (ddd, J = 14.0, 6.5, 5.5 Hz, 1 H, H-7), 2.10-2.17 (m, 1 H, H-6), 4.63 (q, J = 7.5 Hz, 1 H, H-1′), 5.09-5.12 (m, 1 H, H-4), 7.21-7.25 (m, 1 H, Ph-H), 7.28-7.32 (m, 2 H, Ph-H) 7.39-7.43 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.6 (*C*H$_3$C-1′), 20.9 (*C*H$_3$C-3a), 21.4 (*C*H$_3$C-7a), 23.3 (*C*H$_3$C-5), 26.6 (C-6), 31.2 (C-7), 51.5 (C-1′), 62.9 (C-3a), 80.8 (C-7a), 123.4 (C-4), 127.1 (arom. *C*H), 127.2 (2 C, arom. *C*H), 128.2 (2 C, arom. *C*H), 136.8 (C-5), 142.5 (arom. C), 156.3 (C-2) ppm. HRMS (EI): m/z = 285.1728 $[M]^+$, calcd for $C_{18}H_{23}NO_2$ 285.1729.

2.2.30 | (*R*)-3-(1-Phenylethyl)-4,5,6,7-tetrahydrobenzo[*d*]oxazol-2(3*H*)-one (39a)

A mixture of **38** (0.228 g, 1.00 mmol) and **4a** (0.309 g, 2.10 mmol) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and heated at 140°C for 48 hours. Subsequently, it was diluted with CH_2Cl_2 (20 mL), stirred for 30 minutes, and filtered over Na_2SO_4. The solvent was removed under vacuum, and the crude mixture was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 97:3) to give 39a (0.240, 99%) as white needles. R_f = 0.73 (hexane/EtOAc, 7:3); m.p. 72-73°C. $[\alpha]_D^{26}$ = +45.0 (*c* 0.103, MeOH). IR (film): $\bar{\nu}$ = 2939, 1752, 1703, 1496, 1450, 1409, 1365, 1321, 1227, 1023, 990, 755, 709, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.53-1.91 (m, 4 H, H-5, H-6), 1.76 (d, J = 7.5 Hz, 3H, C*H*$_3$C-1′), 2.12-2.23 (m, 2 H, H-4), 2.29-2.37 (m, 2 H, H-7), 5.34 (q, J = 7.5 Hz, 1H, H-1′), 7.24-7.39 (m, 5H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.2 (*C*H$_3$C-1′), 20.3 (C-4), 20.7 (C-7), 21.5 (C-5), 21.7 (C-6), 51.5 (C-1′), 120.0 (C-3a), 126.3 (2 C, arom. *C*H), 127.4 (arom. *C*H), 128.3 (2 C, arom. *C*H), 134.4 (C-7a), 139.8 (arom. C), 155.5 (C-2) ppm. HRMS (EI): m/z = 243.1261 $[M]^+$, calcd for $C_{15}H_{17}NO_2$ 243.1259.

2.2.31 | (*S*)-3-(1-Phenylethyl)-4,5,6,7-tetrahydrobenzo[*d*]oxazol-2(3*H*)-one (39b)

According to the method for the preparation of **39a**, a mixture of **38** (0.228 g, 1.00 mmol) and **4b** (0.309 g, 2.10 mmol) provided **39b** (0.240, 99%) as a white solid. R_f = 0.72 (hexane/EtOAc, 7:3); m.p. 75-76°C. $[\alpha]_D^{24}$ = −42.6 (*c* 0.123, MeOH). IR (film): $\bar{\nu}$ = 2939, 1749, 1703, 1496, 1450, 1409, 1363, 1321, 1227, 1023, 990, 755, 709, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.55-1.85 (m, 4 H, H-5, H-6), 1.77 (d, J = 7.3 Hz, 3H, C*H*$_3$C-1′), 2.10-2.23 (m, 2 H, H-4), 2.31-2.43 (m, 2 H, H-7), 5.36 (q, J = 7.3 Hz, 1H, H-1′), 7.26-7.40 (m, 5H, Ph-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.4 (*C*H$_3$C-1′), 20.6 (C-4), 20.9 (C-7), 21.8 (C-5), 22.0 (C-6), 51.7 (C-1′), 120.2 (C-3a), 126.6 (2 C, arom. *C*H), 127.7 (arom. *C*H), 128.6 (2 C, arom. *C*H), 134.8 (C-7a), 140.1 (arom. C), 155.6 (C-2) ppm. HRMS (EI): m/z = 243.1267 $[M]^+$, calcd for $C_{15}H_{17}NO_2$ 243.1259.

2.2.32 | (4a*R*,8a*S*)-9-((*R*)-1-phenylethyl)-5,6,7,8-tetrahydro-4*H*-4a,8a-(epoxymethanoimino)chromen-10-one (40a) and (4a*S*,8a*R*)-9-((*R*)-1-phenylethyl)-5,6,7,8-tetrahydro-4*H*-4a,8a-(epoxymethanoimino)chromen-10-one (41a)

A mixture of **39a** (0.100 g, 0.41 mmol) and **8a** (0.115 g, 2.06 mmol) in anhydrous toluene (5.0 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2 atmosphere. It was stirred and heated at 80°C for 120 hours. The solvent was removed under vacuum, and the crude mixture was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 97:3) to give a mixture of **40a**/**41a** (84:16) (0.119 g, 97%) as a white solid. R_f = 0.23 (hexane/EtOAc, 8:2); m.p. 130-132°C. $[\alpha]_D^{20}$ = +44.6 (*c* 0.107, MeOH). IR (film): $\bar{\nu}$ = 2960, 1734, 1416, 1353, 1224, 1050, 995, 881, 753, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86-0.96 (m, 1 H, H-7), 1.30-1.36 (m, 1 H, H-6), 1.36-1.44 (m, 1 H, H-7), 1.44-1.54 (m, 1 H, H-6), 1.63-1.67 (m, 1 H, H-8), 1.67-1.71 (m, 1 H, H-5), 1.76 (d, *J* = 7.5 Hz, 3H, C*H*$_3$C-1′), 1.81 (dddd, *J* = 14.0, 6.5, 4.0, 1.0 Hz, 1 H, H-5), 2.00 (dt, *J* = 15.0, 4.5 Hz, 1 H, H-8), 2.21 (dt, *J* = 17.5, 2.5 Hz, 1 H, H-4), 2.29 (ddd, *J* = 17.5, 5.5, 0.5 Hz, 1 H, H-4), 4.46 (q, *J* = 7.5 Hz, 1 H, H-1′), 4.86 (td, *J* = 5.5, 3.0 Hz, 1 H, H-3), 6.28 (ddd, *J* = 6.0, 3.0, 0.5 Hz, 1 H, H-2), 7.16-7.20 (m, 1 H, Ph-H), 7.23-7.28 (m, 2 H, Ph-H), 7.40-7.44 (m, 2 H, Ph-H) ppm. Signals attributed to the minor isomer **41a**: 1.75 (d, *J* = 7.0 Hz, C*H*$_3$C-1′), 2.14 (dt, *J* = 17.5, 3.0 Hz, 1 H, H-4), 4.75 (td, *J* = 5.5, 3.0 Hz, H-3), 4.77 (q, *J* = 7.0 Hz, H-1′), 5.96 (ddd, *J* = 6.0, 3.0, 0.5 Hz, H-2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5 (C-6), 20.1 (*C*H$_3$C-1′), 20.2 (C-7), 26.9 (C-4), 29.3 (C-8), 35.3 (C-5), 52.0 (C-1′), 80.7 (C-4a), 93.2 (C-8a), 100.4 (C-3), 126.9 (2 C, arom. *C*H), 127.2 (arom. *C*H), 128.5 (2 C, arom. *C*H), 141.9 (C-2), 142.7 (arom. C), 156.6 (C-10) ppm. HRMS (EI): *m/z* = 299.1521 $[M]^+$, calcd for $C_{18}H_{21}NO_3$ 299.1521.

2.2.33 | (4a*S*,8a*R*)-9-((*S*)-1-phenylethyl)-5,6,7,8-tetrahydro-4*H*-4a,8a-(epoxymethanoimino)chromen-10-one (40b) and (4a*R*,8a*S*)-9-((*S*)-1-phenylethyl)-5,6,7,8-tetrahydro-4*H*-4a,8a-(epoxymethanoimino)chromen-10-one (41b)

Following the method for the preparation of **40a**/**41a**, the reaction of **39b** (0.100 g, 0.41 mmol) and **8a** (0.115 g, 2.06 mmol) provided a mixture of **40b**/**41b** (88:12) (0.117 g, 95%) as colorless needles. R_f = 0.24 (hexane/EtOAc, 8:2); m.p. 139-141°C. $[\alpha]_D^{20}$ = −40.5 (*c* 0.111, MeOH). IR (film): $\bar{\nu}$ = 2960, 1733, 1416, 1353, 1330, 1223, 1050, 995, 882, 752, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.93-1.03 (m, 1 H, H-7), 1.28-1.37 (m, 1 H, H-6), 1.43-1.51 (m, 1 H, H-7), 1.51-1.60 (m, 1 H, H-6), 1.69-1.75 (m, 1 H, H-8), 1.75-1.78 (m, 1 H, H-5), 1.83 (d, *J* = 7.0 Hz, 3H, C*H*$_3$C-1′), 1.88 (dddd, *J* = 14.0, 6.5, 4.0, 1.0 Hz, 1 H, H-5), 2.07 (dm, *J* = 15.0 Hz, 1 H, H-8), 2.23 (dt, *J* = 17.5, 2.5 Hz, 1 H, H-4), 2.37 (ddd, *J* = 17.5, 5.5, 1.0 Hz, 1 H, H-4), 4.53 (q, *J* = 7.0 Hz, 1 H, H-1′), 4.93 (td, *J* = 5.5, 2.5 Hz, 1 H, H-3), 6.35 (ddd, *J* = 5.5, 2.5, 0.5 Hz, 1 H, H-2), 7.25 (tt, *J* = 7.0, 2.0 Hz, 1 H, Ph-H), 7.30-7.35 (m, 2 H, Ph-H), 7.47-7.51 (m, 2 H, Ph-H) ppm. Signals attributed to the minor isomer **41b**: 1.82 (d, *J* = 7.5 Hz, C*H*$_3$C-1′), 4.81 (td, *J* = 5.5, 3.0 Hz, H-3), 4.85 (q, *J* = 7.5 Hz, H-1′), 6.03 (ddd, *J* = 6.0, 2.5, 1.0 Hz, H-2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5 (C-6), 20.1 (*C*H$_3$C-1′), 20.2 (C-7), 26.8 (C-4), 29.2 (C-8), 35.3 (C-5), 51.9 (C-1′), 80.6 (C-4a), 93.2 (C-8a), 100.3 (C-3), 126.9 (2 C, arom. *C*H), 127.1 (arom. *C*H), 128.4 (2 C, arom. *C*H), 141.9 (C-2), 142.6 (arom. C), 156.6 (C-10) ppm. HRMS (EI): *m/z* = 299.1520 $[M]^+$, calcd for $C_{18}H_{21}NO_3$ 299.1521.

2.3 | Single-crystal X-ray crystallography

Colorless single-crystals of **30a**, **29b**, and **29d** were obtained by recrystallization from CH_2Cl_2/hexane (7:3), of **36b** from CH_2Cl_2/hexane (1:6), and of **40b** from $CHCl_3$. The crystals were mounted on glass fibers. For **29b**, crystallographic measurements were performed at room temperature with Cu Kα radiation (graphite monochromator, λ = 1.5418 Å) and a scintillation detector. Unit cell parameters were calculated from least-squares refinement of 41 reflections in the range of $10.7 < 2\theta < 28.2°$. Three standard reflections were monitored periodically, showing little change during data collection. Empirical (psi-scan) absorption corrections were utilized. The crystal structures of **30a**, **29d**, **36b**, and **40b** were obtained at room temperature with Mo Kα radiation (graphite monochromator, λ = 0.7107 Å) with a CCD detector. Empirical (multi-scan) absorption corrections were applied. In all cases, intensities were corrected for Lorentz and polarization effects. Anisotropic temperature factors were introduced for all nonhydrogen atoms, while hydrogen atoms were placed in idealized positions and their atomic coordinates refined, using unit weights in the refinement (Table 1). Structures were solved with the SHELXS,[50] SHELXT,[50] or SIR92[51] program as implemented in the WinGX suite,[52] and refined within WinGX using SHELXL.[53] In

TABLE 1 Crystal data and structure refinement for **29b**, **29d**, **30a**, **36b**, and **40b**

Structure	29b	29d	30a	36b	40b
CCDC number	1882055	1882058	1882057	1882056	1922326
Empirical formula	$C_{16}H_{19}NO_3$	$C_{17}H_{21}NO_3$	$C_{16}H_{19}NO_3$	$C_{18}H_{23}NO_2$	$C_{18}H_{21}NO_2$
Molecular weight	273.32	287.35	273.32	285.27	299.36
Temperature	292(2) K	293(2) K	294(2) K	294(2) K	291(2) K
Crystal size	0.40 × 0.24 × 0.20 mm^3	0.57 × 0.52 × 0.23 mm^3	0.36 × 0.24 × 0.23mm^3	0.30 × 0.28 × 0.26 mm^3	0.41 × 0.32 × 0.28 mm^3
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_1$
Unit cellvparameters	a = 6.5262(6) Å, α = 90° b = 7.4398(5) Å, β = 93.175(8)° c = 14.9732(11) Å, γ = 90°	a = 6.5333(3) Å, α = 90° b = 7.4983(4) Å, β = 90° c = 31.0603(19) Å, γ = 90°	a = 6.5214(2) Å, α = 90° b = 7.4404(2) Å, β = 93.180(3)° c = 14.9715(4) Å, γ = 90°	a = 6.74050(10) Å, α = 90° b = 14.7626(2) Å, β = 90° c = 15.9444(2) Å, γ = 90°	a = 6.5392(3) Å, α = 90° b = 7.4597(3) Å, β = 90.347(4)° c = 15.7724(6) Å, γ = 90°
Volume	725.89(10) $Å^3$	1521.60(14) $Å^3$	725.33(4) $Å^3$	1586.58(4) $Å^3$	769.37(6) $Å^3$
Z	2	4	2	4	2
Density	1.250 mg/m^3	1.254 mg/m^3	1.251 mg/m^3	1.195 mg/m^3	1.292 mg/m^3
Absorption coefficient	0.699 mm^{-1}	0.086 mm^{-1}	0.086 mm^{-1}	0.077 mm^{-1}	0.088 mm^{-1}
Theta range	2.956-56.860°	3.186-32.634°	2.725-32.400°	2.555-32.583°	3.365-32.347°
Reflections collected	1604	9353	7545	12867	4872
Independent reflections	1233	4313	4110	5001	3626
Observed reflections	1026	3896	3116	3902	3951
Final R indices	R_1 = 0.0671; wR_2 = 0.1719	R_1 = 0.0459; wR_2 = 0.1111	R_1 = 0.0407; wR_2 = 0.0923	R_1 = 0.0412; wR_2 = 0.1026	R_1 = 0.0413; wR_2 = 0.0946
Goodness-of-fit on F^2	1.052	1.094	1.041	0.994	1.051

all cases, ORTEP and packing diagrams were made with ORTEP3[54] or MERCURY.[55]

2.4 | Theoretical calculations

All ab initio and DFT calculations were carried out with the Gaussian 09 program package.[56] Optimizations of the stationary points were initially made at the HF/6-31G(d) level of theory. The optimized geometries served as starting points for further optimizations at the ωB97X-D/6-31G(d) and ωB97X-D/6-31 + G(d,p) levels of DFT theory. For all optimizations, the OPT = TIGHT optimization option was employed. For all DFT calculations, the INT (GRID = ULTRAFINE) option was used. The TSs were located with the QST2, QST3, or TS optimization option. All stationary points were characterized by frequency calculations. All minima (starting materials and adducts) showed only real vibrational frequencies, while each TSs displayed a single negative eigenvalue of the Hessian matrix. Through visual inspection of the normal mode associated with the imaginary vibrational frequency, it was confirmed that the TSs corresponded to motion along the expected reaction coordinate.

3 | RESULTS AND DISCUSSION

3.1 | Functionalization of enantiopure 1,3-oxazolidin-2-ones 1a-b

An efficient methodology was previously developed for the preparation of enantiopure (*S*)-4,5-dimethyl-3-(1-phenylethyl)-4-oxazolin-2-one (**1b**) through solvent-free thermal conditions by mixing **3a** and isocyanate **4b** (Table 2, entry 4).[49] The same procedure was carried out in the current work for the preparation of (*R*) enantiomer **1a** by reacting **3a** with isocyanate **4a** (entry 1), resulting in good yield (Scheme 2). Under these reaction conditions, 4-methylene-2-oxazolidinones **2a-b** were observed in trace amounts. Solvent-free MW irradiation was explored to determine whether the proportion of these compounds could be improved (entries 2, 3, and 5) during the synthesis of the regioisomeric 4-oxazolin-2-ones **1a-b**. Thus, heterocycles **2a-b** were obtained in low yields along with the corresponding isomers **1a-b**, respectively (entries 3 and 5). However, the reaction was not diastereoselective and provided a low ratio of the C-5 epimers. Hence, the reaction process likely involves the hemiaminal intermediates **12** and **13** without causing any significant change in the configuration of the C-3 carbon of **3a**. Indeed, a mixture of **12/13** (61:39) was generated by heating the starting mixture of **3a** and **4b** under MW irradiation at a lower temperature (120°C) for 90 minutes. The absolute configurations of the C-4 and C-5 centers could not be unambiguously established but were assumed to be in accordance with the previous[44-46] and the current studies. Interestingly, a mixture of only two of the four possible diastereoisomers was obtained, presumably by a chiral auxiliary-controlled cyclization at the stage of the I and II carbamate species,[44] in which the epimerization of the C-4 diastereoisomeric center did not take place.

In the interest of exploring the reactivity and diastereoselectivity of the exocyclic double bond in 4-methylene-2-oxazolidinones, as was done with compounds **2** (Scheme 2), derivatives **14a-b** were synthesized under similar reaction conditions. Thus, under MW irradiation (60 W) at 200°C for 20 minutes, the reaction of α-ketol **3b** and isocyanate **4a** led to enantiopure 3-substituted 4-methylene-1,3-oxazolidin-2-one **14a** in 66% yield (Scheme 3). Enantiomer **14b** was prepared by using isocyanate **4b** under thermal (130°C, 24 h) or MW (300 W, 140°C, 3 h) protocols to give 78% and 84% yields, respectively.

Upon Pd-catalyzed hydrogenation of **1b**, the expected mixture of 2-oxazolidinones **15**/**16** was obtained in good diastereoisomeric ratios (*dr*) and high yields (Table 3, entries 1-3). The use of high pressures decreased the *dr* (entry 3). The diastereoselectivity increased with palladium hydroxide as the catalyst, although the products in the mixture were obtained in low yield (entry 4). In contrast, the highest *dr* with this catalyst was found with **14b** as the substrate (Scheme 3), generating a mixture of **17**/**18** in high yield (entry 7).

The Michael addition of **1a** to **8b** at elevated temperatures afforded a moderate yield of adducts **19a**/**20a** (72:28) (Scheme 4). Whereas the reaction under milder thermal conditions between **1b** and **8b** led to improve diastereoselectivity, yielding a mixture of adducts **19b**/**20b** (91:9).[49]

TABLE 2 Preparation of compounds **1a-b** and **2a-b**, obtained by condensation of α-ketol **3a** and isocyanates **4a-b**[a]

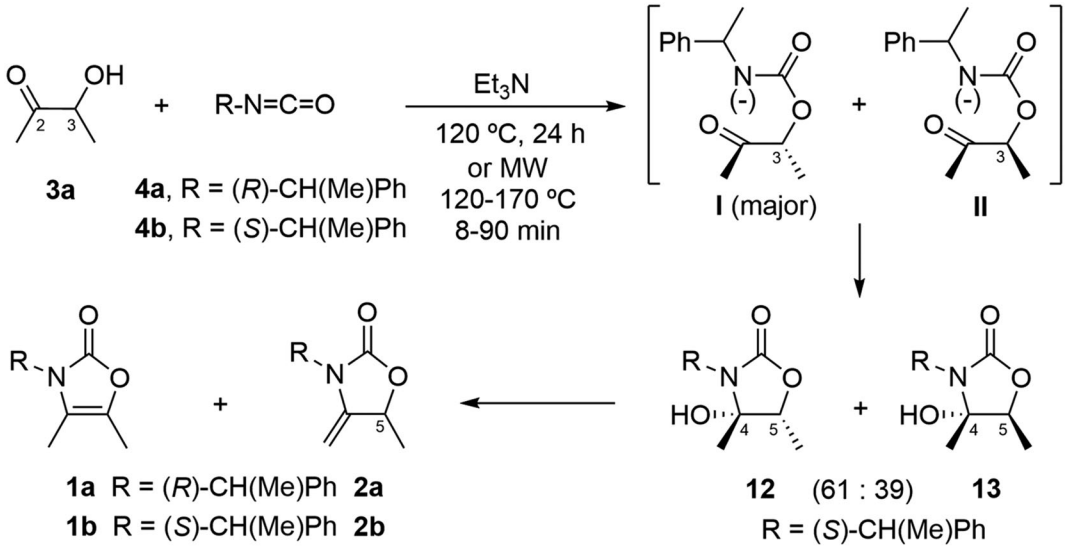
Entry	4	Base	MW, W	T, °C	*t*	1 (%)[b]	2 (%)[b]
1	**4a**	Et_3N	___	120	24 h	**1a** (75)	**2a** (0)
2	**4a**	___	70	200	15 min	**1a** (85)	**2a** (0)
3	**4a**	___	200	170	8 min	**1a** (55)	**2a** (29)[c]
4	**4b**	Et_3N	___	120	24 h	**1b** (75)	**2b** (0)
5	**4b**	Et_3N	200	140	8 min	**1b** (16)	**2b** (39)[d]

[a]In the presence of 3a/4 and Et_3N (2.0 mol equiv).

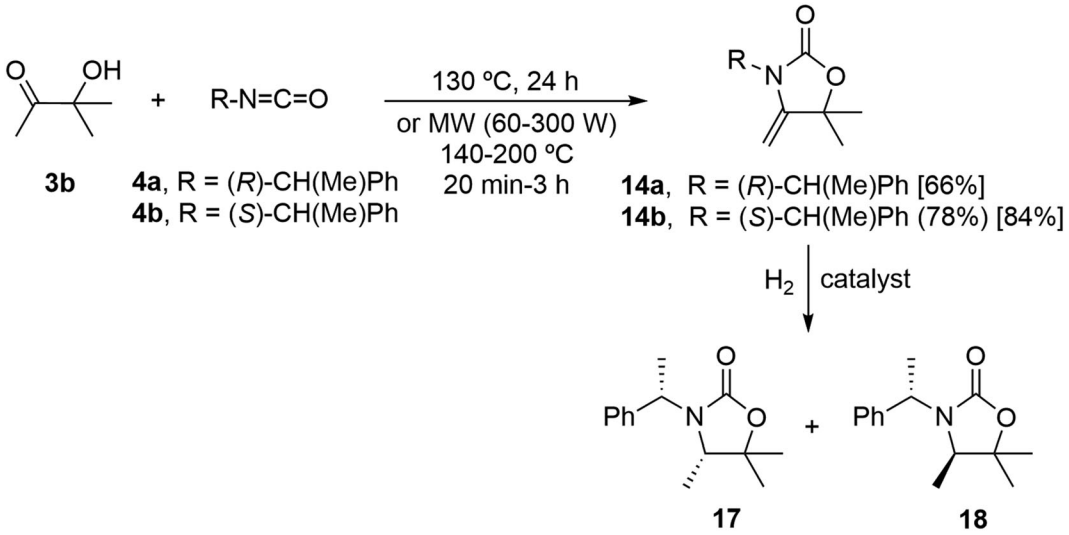
[b]After recrystallization or column chromatography.

[c]As a mixture of diastereoisomers (65:35).

[d]As a mixture of diastereoisomers (54:46).



SCHEME 2 Thermal- and MW-promoted synthesis of oxazolin-2-ones **1a-b** and oxazolidin-2-ones **2a-b**, and hemiaminals **12** and **13**



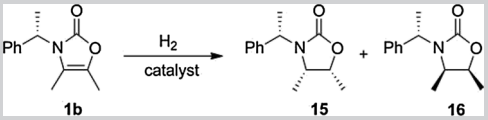
SCHEME 3 Thermal- and MW-promoted synthesis of 4-methylene oxazolidin-2-ones **14a-b**, and diastereoselective hydrogenation leading to oxazolidin-2-ones **17** and **18**

In the case of 4-methylene 2-oxazolidinones **14a** and **14b**, the Michael addition to **8b** proceeded better under iodine catalysis at 0°C to yield mixtures of *E/Z* diastereoisomers **21a**/**22a** and **21b**/**22b**, respectively (Scheme 5). The presence of a mixture of the latter compounds is probably due to the longer reaction time (6 h), which may favor the isomerization of the double bond, as was observed after monitoring the reaction.

Interestingly, when the **21b**/**22b** (81:19) mixture was hydrogenated, the ^{1}H NMR spectrum of the mixture crude displayed a set of signals corresponding to diastereoisomers **23a**/**24a** (98:2). Hence, not only was the reaction highly diastereoselective but also the *E/Z* geometry of the starting material did not influence the diastereoselection of the hydrogenation.

To test the control of the *E/Z* functionalization of the exocyclic double bond of enantiomers **14a-b**, the formylation and bromination reactions were explored (Scheme 5). Thus, the Vilsmeier-Haack method of formylation was applied to both of the enantiopure 2-oxazolidinones to give high yields of the respective *E* diastereoisomers **25a-b**. No signals of the *Z* isomers were detected by ^{1}H NMR analysis of the crude mixtures. The *E* geometry was established by NOE experiments, which showed an enhancement of the singlets attributed to the methyl groups when the formyl proton was irradiated. A reciprocal effect was found when the former signals were irradiated. A similar diastereoselectivity was observed after bromination of **14b** with NBS to furnish the single *E* isomer **26**.

TABLE 3 Diastereoselective hydrogenation of 4-oxazolin-2-one **1b** and 4-methylene-2-oxazolidinone **14b**[a]



Entry	Substrate	Cat. (%)	P, psi	Solvent	*t*, h	Products[b] [%][c]
1[d]	**1b**	Pd/C (10)	750	EtOAc	24	15/16 (84:16) [73]
2	**1b**	Pd/C (10)	1000	MeOH	24	15/16 (87:13) [94]
3	**1b**	Pd/C (10)	1300	MeOH	48	15/16 (69:31) [92]
4	**1b**	Pd $(OH)_2$ (20)	(e)	MeOH	18	15/16 (89:11) [34]
5	**14b**	Pd/C (5)	1250	MeOH	48	17/18 (69:31) [88]
6	**14b**	Pd/C (10)	1500	MeOH	24	17/18 (72:28) [90]
7	**14b**	Pd $(OH)_2$ (20)	(e)	MeOH	24	17/18 (96:4) [99]

[a]The reactions were heated at rt.

[b]Ratio calculated from the ^{1}H NMR spectra of the crude mixtures.

[c]After recrystallization or column chromatography.

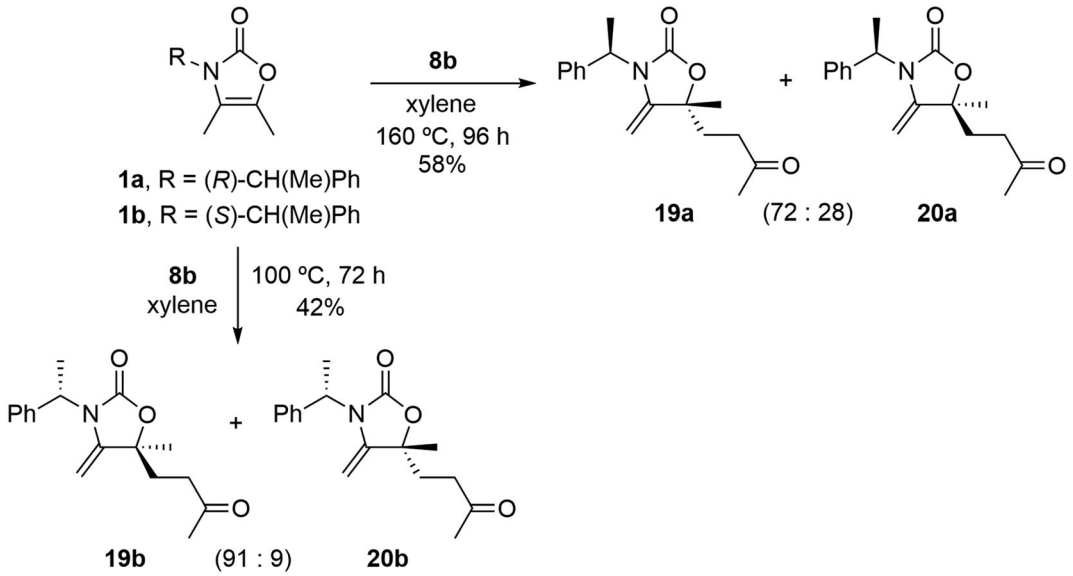
[d]AcOH was added and heated at 60°C.

[e]Under atmospheric pressure with a balloon.

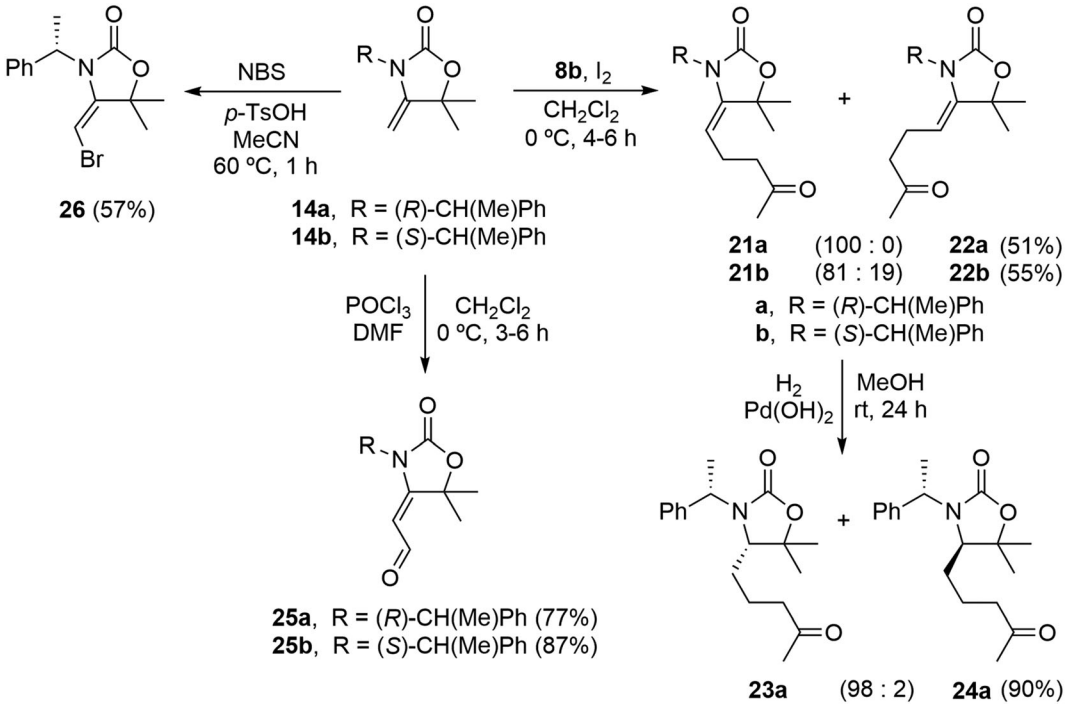
We previously described a new synthetic approach for the preparation of 1,3-oxazolidin-2,4-diones starting from 4-methylene 1,3-oxazolidin-2-ones via an oxidative cleavage by treatment with MCPBA.[49] To evaluate the scope of this methodology, epimeric mixtures of derivatives **2a** and **2b** were treated under optimized conditions (Scheme 6). The epimeric ratios of the starting materials were roughly maintained during the process, to yield similar epimeric ratios of 2,4-diones 27 and 28, which suggests that the mechanism of the oxidative cleavage does not affect the epimeric center vicinal to the exocyclic double bond.

3.2 | Enantiopure 1,3-oxazolin-2-ones 1a-b as synthons in the construction of fused hetero- and carbocyclic scaffolds

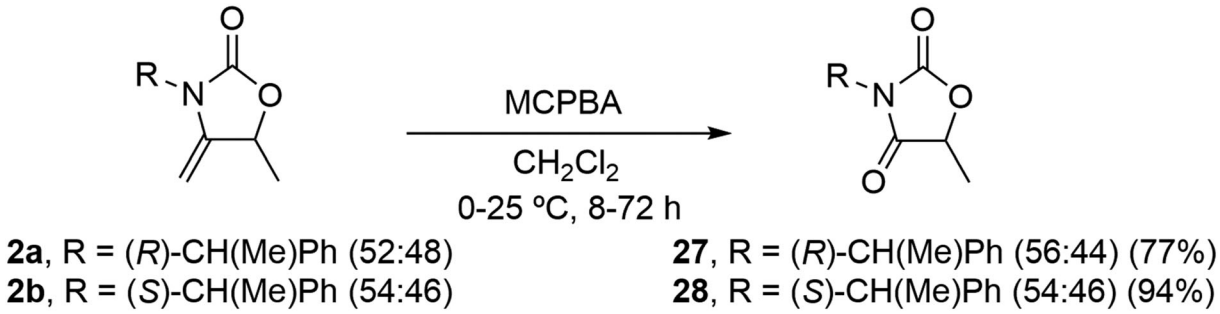
Preliminary results have demonstrated the potential of enantiopure 4-oxazolin-2-one **1b** in Michael/cyclization cascade reactions with acrolein (**8a**) to yield the fused *bis*-heterocyclic compounds **29b**/**30b** in high *dr* (91:9)[46] (Table 4, entry 3) (Scheme 1). The *dr* was slightly improved by reducing the reaction temperature to 60°C for 5 days, maintaining **29b** as the major isomer (entry 2). This procedure was even more efficient for enantiomer



SCHEME 4 Preparation of 4-methylene oxazolidin-2-ones **19a**/**20a** and **19b**/**20b** by thermal Michael addition of **1a** or **1b** to **8b**, respectively



SCHEME 5 Reactivity and stereoselectivity of 4-methylene oxazolidin-2-ones **14a** and **14b** in diverse reactions



SCHEME 6 Oxidative cleavage of epimeric mixtures of 4-methylene oxazolidin-2-ones **2a-b**

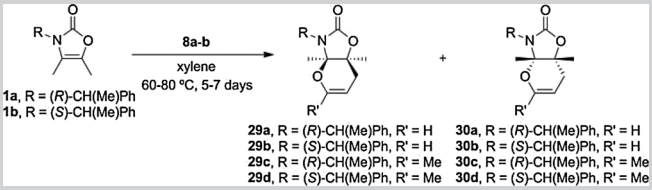
1a, producing the single diastereoisomer **29a** (entry 1). To further explore the possibility of improving the diastereoselectivity in the reaction of **1b** with **8a**, microwave (MW) irradiation was applied (entry 4). The *dr* was similar to that found under thermal conditions but the chemical yield significantly decreased (entry 2).

The reactivity with methyl vinyl ketone (**8b**) was lower, as were the yields of the bicyclic pyranyl analogs **29c-d**/**30c-d**. Nevertheless, the diastereoselectivity remained high (Table 4, entries 5-8), improving at a low temperature or under MW irradiation.

The Pd $(OH)_2$-catalyzed hydrogenation of a mixture of **29b**/**30b** (93:7) under mild conditions (1 atm, rt, 18 h) led to a total conversion into the corresponding mixture of fused hexahydro-2*H*-pyrano[2,3-*d*]oxazol-2-ones **31a**/**32a** (92:8) (Scheme 7). Interestingly, when the hydrogenation was carried out on a mixture of **29d**/**30d** (>99:1) under the same reaction conditions, a single isomer was obtained at the C-5 chiral center of the resulting mixture of products **31b**/**32b** (>99:1). The C-5 configuration was tentatively assigned in accordance with the crystal structure of **29d** (see Figure 1). Since the front face (*si* face) of the dihydropyrane moiety is concave (as depicted in Scheme 7), the *re* face is available for the entry of the catalyst and hydrogen atoms, giving rise to the major diastereoisomer **31b**.

As expected,[45] when 4-oxazolin-2-ones **1a-b** were submitted to more severe conditions in the presence of the same Michael acceptors **8a-b**, and with methyl iodide as the promoting agent, mixtures of dihydrobenzo[*d*]oxazol-2(3*H*)-ones **33a-e**/**34a-e** were generated (Table 5). The diastereoselectivity was lower than that of the fused tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-ones **29**/**30**, presumably because of the higher temperature applied. It is

TABLE 4 Diastereoselective construction of bicyclic dihydropyranyl compounds **29a-d**/**30a-d**[a]



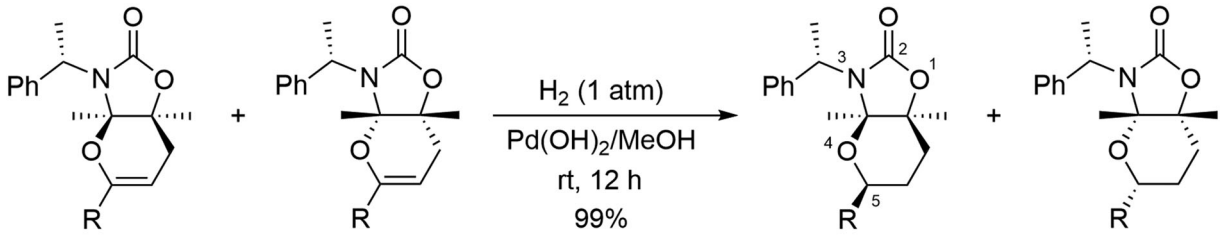
Entry	Substrate	8	T, °C	*t*, days	Products[b] [%][c]
1	**1a**	**8a**	60	5	29a/30a (<1:99) [92]
2	**1b**	**8a**	60	5	29b/30b (93:7) [74]
3	**1b**	**8a**	100	1	29b/30b (91:9) [66]
4[d]	**1b**	**8a**	110	0.2	29b/30b (92:8) [48]
5	**1a**	**8b**	80	5	29c/30c (19:81) [14]
6	**1a**	**8b**	60	5	29c/30c (<1:99) [45]
7	**1b**	**8b**	60	7	29d/30d (>99:1) [14]
8[d]	**1b**	**8b**	110	0.2	29d/30d(98:2) [42]

[a]In the presence of **1a-b**/**8a-b** (1:1 to 1:5 mol equiv) in xylene.

[b]Ratio calculated from the ^{1}H NMR spectra of the crude mixtures.

[c]After recrystallization or column chromatography.

[d]Irradiated with MW (100 W).



SCHEME 7 Hydrogenation of mixtures of fused tetrahydro-2*H*-pyrano[2,3-*d*]oxazol-2-ones **29b**/**30b** and **29d**/**30d**

worth noting that the reaction of **1b** with an excess of acrolein (**8a**) at 160°C yielded the corresponding dienes **33b**/**34b** along with derivatives **33e**/**34e**, which resulted from the subsequent Michael addition of the dienes to the excess of **8a** (entry 2). However, cascade products analogous to **33e**/**34e** were not observed upon using **8b** instead of **8a**, even after heating for 48 hours (entry 3). Derivatives **33e**/**34e** could also be prepared by direct addition of dienes **33b**/**34b** to acrolein (**8a**), finding similar diastereoselectivity (entry 5).

Furthermore, the diastereoselectivity in reactions was analyzed with alkyl halides as the electrophile. Thus, the reaction was carried out with prenyl bromide (**35**), yielding mixtures of trimethyl tetrahydrobenzo[*d*] oxazol-2(6*H*)-ones **36a-b**/**37a-b** in low diastereoselectivity (Scheme 8). By reducing the reaction temperature (140°C), a slight enhancement of selectivity was observed. As suggested in a previous report,[45] the reaction mechanism probably proceeds via nucleophilic substitution at the C-5 center of the heterocycle to give intermediate I, which undergoes isomerization of the prenyl double bond and protonation of the enamide moiety to furnish active species II. Cyclization of the latter was followed by isomerization of the endocyclic double bond formed, providing mixtures of diastereoisomers **36b**/**37b** (Scheme 8).

3.3 | Synthesis of enantiopure bicyclic 1,3-oxazolidin-2-ones 39a-b as synthons in the construction of propellanes

The aforementioned results reveal the versatility of (*R*)- and (*S*)-4,5-dimethyl-3-(1-phenylethyl)-4-oxazolin-2-ones

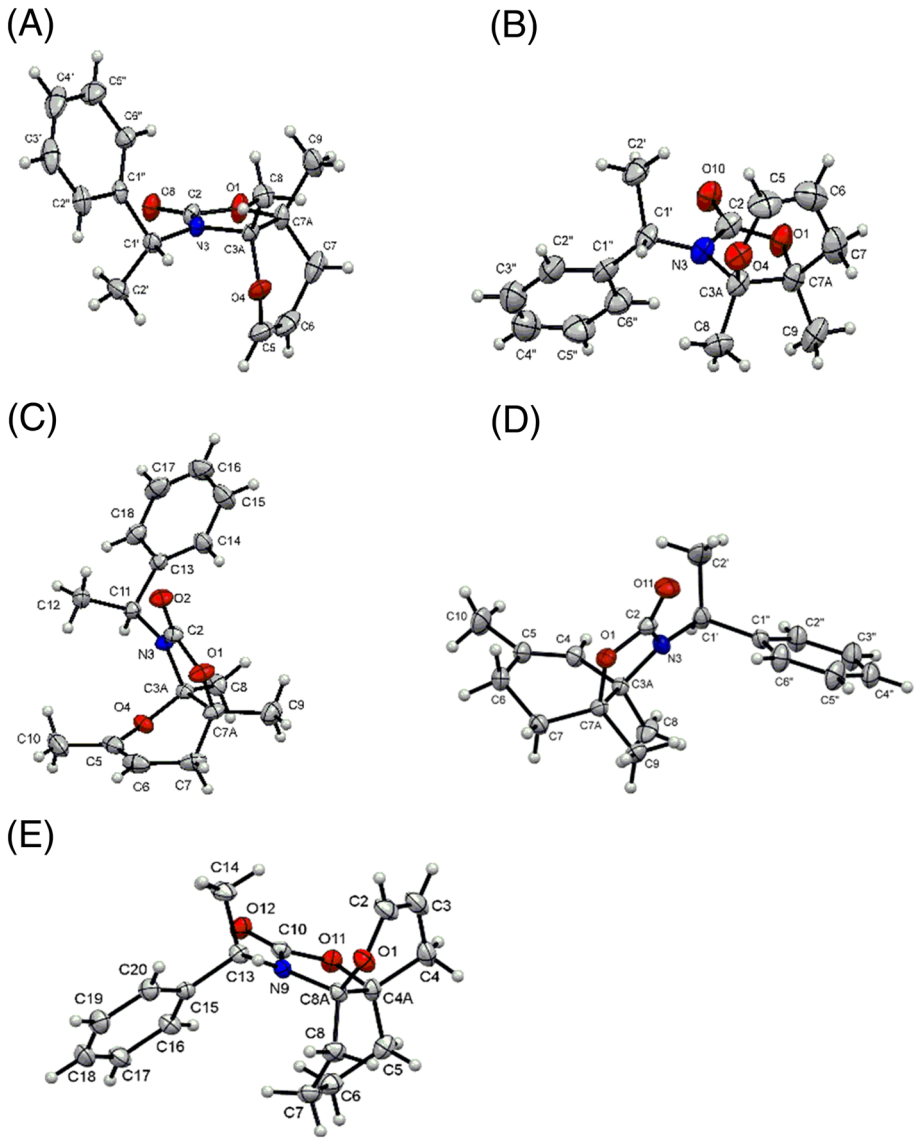
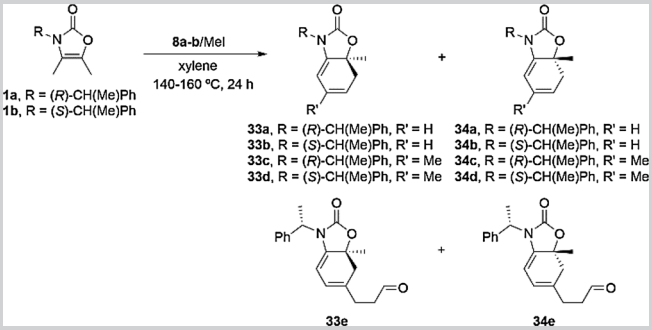


FIGURE 1 Structures of (A) **30a**, (B) **29b**, (C) **29d**, (D) **36b**, and (E) **40b** as determined by single-crystal X-ray diffraction (ellipsoids at the 30% probability level)

1a-b for the diastereoselective functionalization of their skeleton through the induction of the chiral moiety. The presence of the C-4 and C-5 methyl groups also plays a key role in improving such versatility and perhaps the diastereoselectivity as well. For example, the generation of dienes **33a-d**/**34a-d** stems from the direct cooperation of the C-4 methyl group. Therefore, it may be attractive to integrate the tetrasubstituted heterocyclic double bond of the 4-oxazolin-2-one heterocycle within a six-membered ring and explore its reactivity with Michael acceptors (eg, **8a**). Accordingly, enantiopure tetrahydrobenzo[*d*]oxazol-2(3*H*)-ones **39a-b** were prepared by reacting adipoin (**38**) with chiral isocyanates **4a-b** under solvent free conditions in quantitative yields (Scheme 9).

Similar to 4-oxazolin-2-ones **1a-b**, the thermal addition of **39a-b** to **8a** efficiently proceeded to provide the dihydropyran cycloadducts **40a-b**/**41a-b**. However, there was a lower diastereoselectivity in the formation of these heterocyclic [4.4.3]propellanes than that found with the dihydropyrans **29**/**30** (Table 4). The reaction of **39a** with **8a** was carried out under MW irradiation (100 W, 120°C) to try to improve the *dr*,[57-60] which turned out to be even lower for **40a/41a** (75:25). It appears that the conformational motion of the cyclohexenyl moiety of the bicyclic 4-oxazolin-2-ones **39a-b** sterically counteracts the effect of the chiral inductor. Hence, the entry of the Michael acceptor (or heterodiene, see below) occurs with a lower diastereoselectivity than in the reaction with **1a-b** (Table 4).

TABLE 5 Diastereoselective synthesis of dihydrobenzo[*d*]oxazol-2(3*H*)-ones **33a-e**/**34a-e**[a]

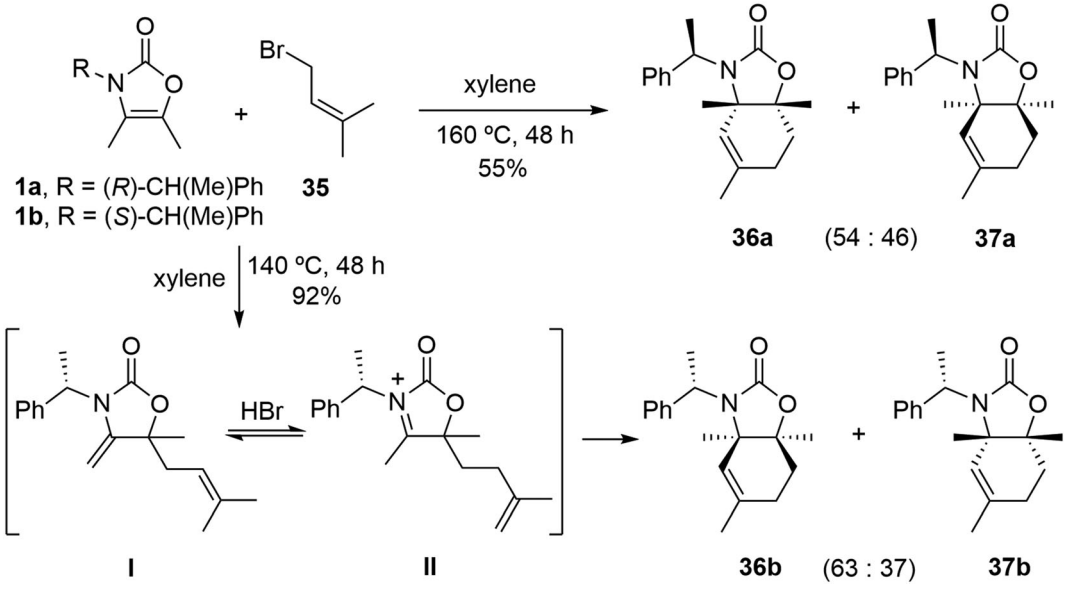


Entry	Substrate	8 (mol equiv)	T, °C	*t*, h	Products[b] [%][c]
1	**1a**	**8a** (18.0)	140	24	33a/34a (20:80) [60]
2	**1b**	**8a** (15.0)	160	24	33b/34b (83:17) [61] 33e/34e (86:14) [32]
3	**1a**	**8b** (5.0)	160	48	33c/34c (12:88) [62]
4	**1b**	**8b** (5.0)	140	24	33d/34d (80:20) [63]
5	**33b/34b** (83:17)	**8a** (3.0)	160	24	33e/34e (85:15) [41]

[a]In the presence of **1a-b**/**8a-b** (1:3 to 1:18 mol equiv) and MeI (2.0 mol equiv) in xylene.

[b]Ratio calculated from the ^{1}H NMR spectra of the crude mixtures.

[c]After column chromatography.

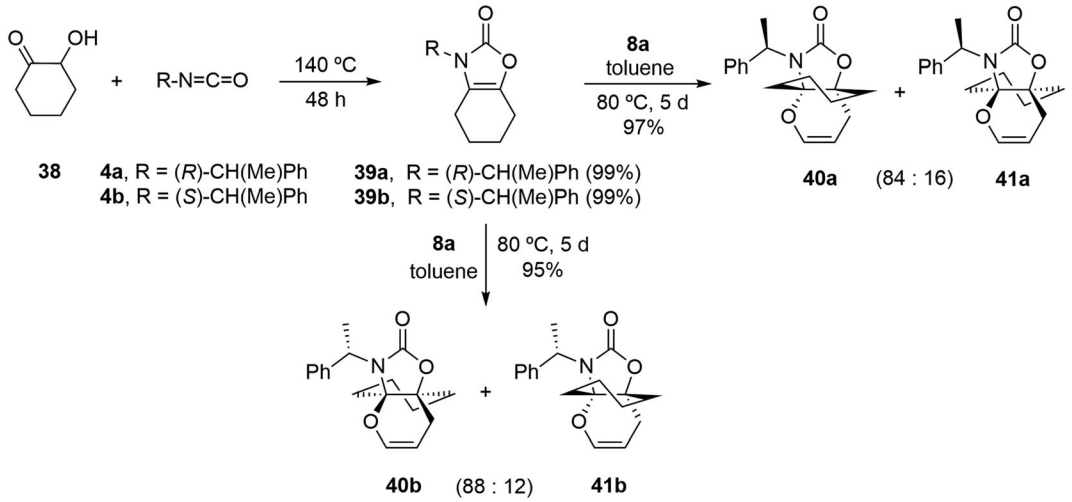


SCHEME 8 Formation of trimethyl tetrahydrobenzo[*d*]oxazol-2(6*H*)-ones **36a-b**/**37a-b**

3.4 | Assignment of the absolute configuration of the products derived from 4-oxazolin-2-ones 1a-b and 39b

The assignment of the absolute stereochemistry of all the products derived from the simple functionalization of 4-oxazolin-2-ones **1a-b** was made on the basis of the single-crystal X-ray diffraction analysis of oxazolidin-2-one-based *bis*-heterocycles **30a**, **29b**, and **29d**, of trimethyl tetrahydrobenzo[*d*]oxazol-2(6*H*)-one **36b**, and of propellane **40b** (Figure 1).[61]

In the case of the first three bicycles, the conformation of the dihydropyran ring is bent towards the oxazolidin-2-one ring, keeping the double bond far away from the



SCHEME 9 Synthesis of enantiopure tetrahydrobenzo[*d*]oxazol-2(3*H*)-ones **39a-b**, and diastereoselective cycloaddition with acrolein (**8a**) to give heterocyclic propellanes **40a-b**/**41a-b**

methyl groups. This conformational preference may control the highly diastereoselective hydrogenation of the double bond of **29d**, in which the hydrogen-activated catalyst (Pd $(OH)_2$) approaches from the convex and less hindered face to yield the tetrahydropyran derivative **31b** as the major isomer (Scheme 7).

Interestingly, the vicinal quaternary centers C-3a and C-7a maintained the O(4) and C(7) atoms almost coplanar in the dihydropyran fused ring, with the C(7)-C(7a)-C(3a)-O(4) dihedral angle being 0.3(2) for **30a**, 0.5(9) for **29b**, 2.2(2) for **29d**, and 1.0(3)[C(4)-C(4A)-C(8A)-O(1)] for **40b**. Moreover, the O(1) and N(3) atoms in the oxazolidin-2-one ring are also almost coplanar, with the N(3)-C(3a)-C(7a)-O(1) dihedral angle being −3.00(15) for **30a**, 2.1(6) for **29b**, 4.94(18) for **29d**, and 3.81(19) [O(11)-C(4A)-C(8A)-N(9)] for **40b**. However, the C(8) and C(9) methyl groups adopt a noneclipsed conformation. The C(8)-C(3a)-C(7a)-C(9) dihedral angle is −9.4(2)

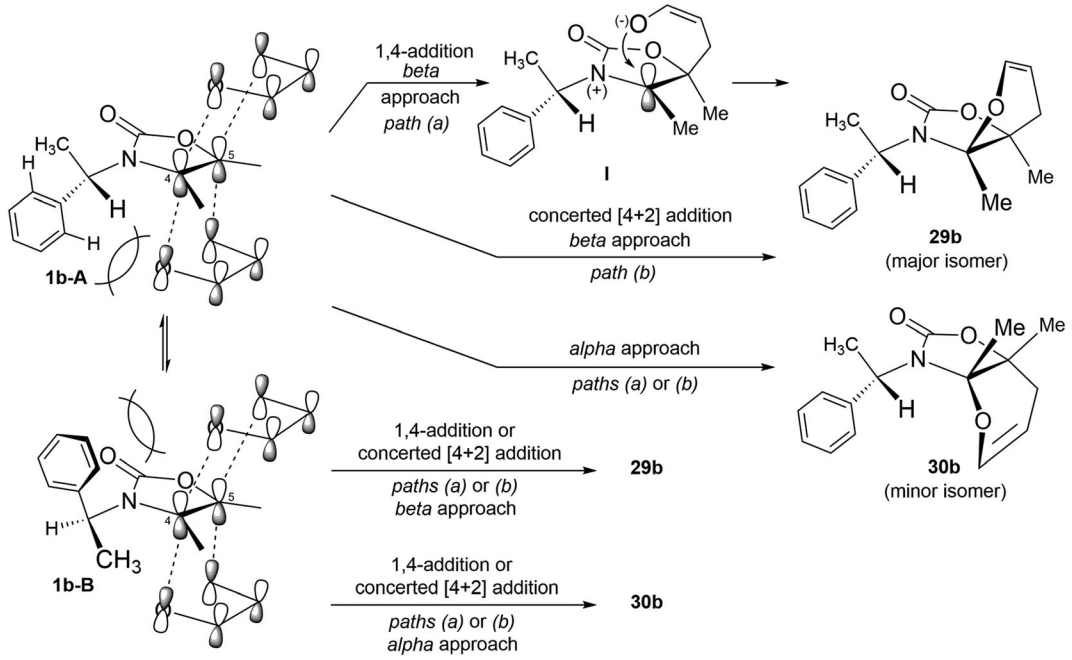


FIGURE 2 Rotamers **1b-a** and **1b-B** of the chiral auxiliary of **1b**. Representation of the preferential *beta* 1,4-addition of 1b-a to electrophile **8a**, or *beta-exo* concerted [4 + 2] cycloaddition to heterodiene **8a**, to yield major diastereoisomer **29b** and minor **30b** (upper three arrows). Portrayal of the preferential *alpha* 1,4-addition of **1b-B** to electrophile **8a**, or *alpha-exo* concerted [4 + 2] cycloaddition to heterodiene **8a**, to yield diastereoisomers **29b** and **30b** (below). For a clearer view, only the *exo* approaches are included, although the *endo* approaches are the most favored (see Table 7)

for **30a**, −10.4(9) for **29b**, 9.6(2) for **29d**, and 9.3(2) [C(5)-C(4A)-C(8A)-C(8)] for the dihedral angle including the quaternary carbons and the methylene groups of the cyclohexane moiety for **40b**. In contrast, the torsion angles are larger for the structure of compound **36b**. For **36b**, the dihedral angle is 31.66(17) for C(7)-C(7a)-C(3a)-C(4), 29.81(13) for N(3)-C(3a)-C(7a)-O(1) and 34.82(18) for C(9)-C(7a)-C(3a)-C(8). This is likely due to the position of the double bond in the cyclohexene ring, vicinal to the C(3a) angular carbon, which causes the fused rings and the methyl groups to twist.

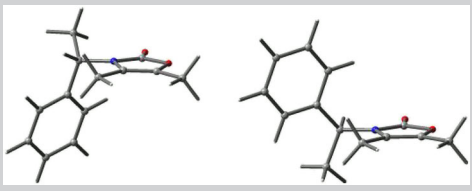
3.5 | Reaction mechanisms and diastereoselectivity of the processes between 4-oxazolin-2-ones 1a-b and electrophiles 8a-b

Regio- and diastereoselective reaction pathways can be suggested for the formation of major adducts **30a** and **29b** from the addition of 4-oxazolin-2-ones **1a** and **1b**, respectively, to acrolein (**8a**). Such pathways may also be involved in the formation of **30c** and **29d** from the addition of **1a** and **1b**, respectively, to methyl vinyl ketone (**8b**) (Table 4). It is possible to rationalize the regioselectivity as a consequence of the polarization of the double bond of heterocycles **1a-b** by the lone-pair of the nitrogen atom, which would increase the electron density at C-5.[44] Consequently, the latter position is more nucleophilic than C-4, attacking the electrophilic β-carbon center of the conjugate carbonyl compounds **8a-b**.

Diastereoselectivity should of course be explained by considering the conformational effect of the chiral auxiliary group of 4-oxazolin-2-ones **1a** and **1b**. This group must certainly control the additions of the electrophilic substrates. Thus, the addition of **8a** to these compounds affords derivatives **30a** and **29b**, respectively. Likewise, the addition of **8b** to the same compounds yields the corresponding major isomers **30c** and **29d**, respectively (Table 4).

Two possible mechanisms can be proposed for the reaction of **1b** with **8a** to form diastereoisomers **29b** and **30b** (Figure 2). The first is a two-step pathway, including the formation of zwitterionic intermediate I from the 1,4-conjugated addition of **1b** to **8a** (path a).[62,63] The second one may occur through a concerted hetero-Diels-Alder cycloaddition (path b).[64-66]

TABLE 6 The conformational analysis of **1b** provides the absolute (E_0) and relative (ΔE_0) energies of **1b-A** in relation to conformer **1b-B**, including zero-point energies (ωB97X-D/6-31 + G(d, p))



Conformer	E_0, a.u.	ΔE_0, kcal/Mol	$\theta_{(H\text{-}C\text{-}N\text{-}C4)}$, °
1b-A	−709.19572	1.2	30.9
1b-B	−709.19761	0.0	169.7

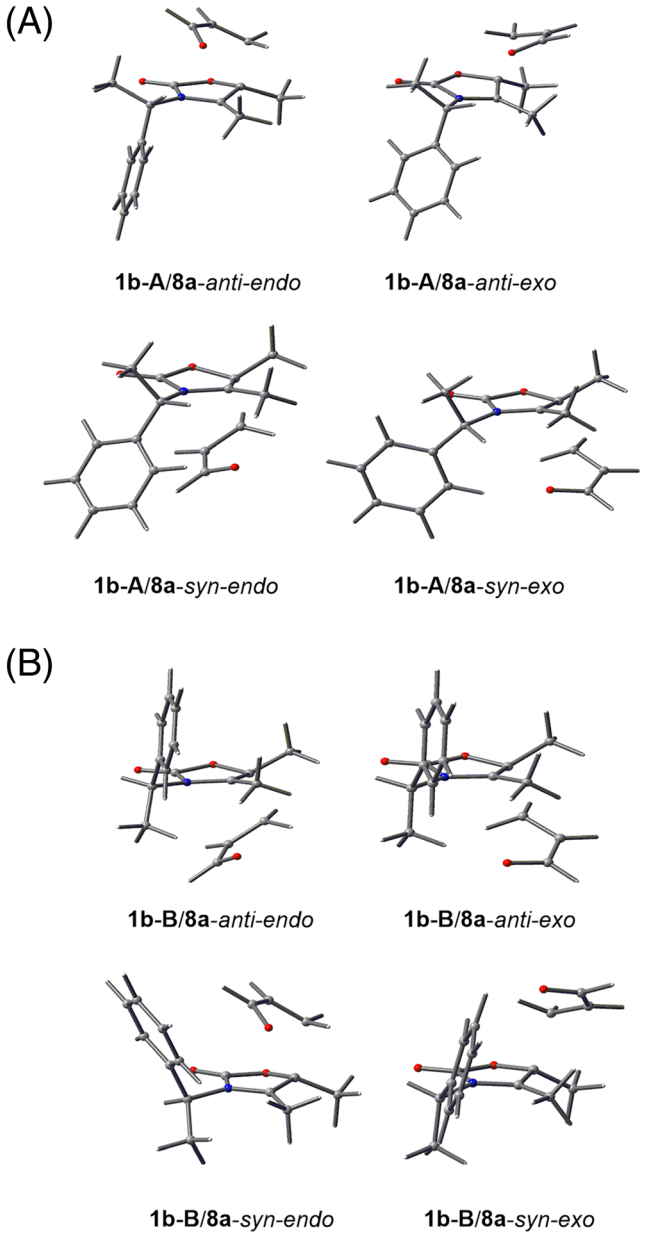


FIGURE 3 TSs calculated (ωB97X-D/6-31 + G(d,p))for the cycloaddition between **1b** and **8a**, starting from conformers (A) **1b-a** and (B) **1b-B**

Figure 2 depicts rotamers **1b-A** and **1b-B** of the chiral auxiliary **1b**. The former corresponds to the conformation observed in the X-ray structure of **29b**, in which the benzylic proton is quasi coplanar in relation to the plane of the heterocycle, leaving the methyl and phenyl groups at the *beta* and *alpha* positions, respectively. For the case of path (a), therefore, electrophile **8a** prefers to approach the C-5 nucleophilic center from the *beta* side, as the approach from the *alpha* side would be destabilized by repulsive van der Waals interactions created by the bulkier phenyl group. Thus, zwitterionic intermediate I is selectively formed, followed by cyclization of the negatively charged oxygen to the iminium C-4 carbon atom to give major isomer **29b**. The same reasoning fits well for the opposite configuration of the chiral auxiliary of **1a** to preferentially carry out the nucleophilic attack on **8a** from the *alpha* side (the side of the methyl group) to afford **30a** as the major isomer (Table 4, entry 1; Figure 1A).

A similar explanation can be proposed in an alternative concerted [4 + 2] hetero-Diels-Alder cycloaddition, where **8a** is the heterodiene species also preferentially approaching the *beta* side (Figure 2 shows only the *exo* approach). In principle, this second mechanism can be discarded, considering that Michael addition products **19a/20a** were isolated from the reaction between **1b** and MVK (**8b**) as presumable reaction intermediates (Scheme 4). On the other hand, the corresponding Michael addition epimeric products coming from the reaction with acrolein (**8a**) were never isolated or detected.

Due to the conformation displayed by the chiral fragment in the X-ray structures (Figure 1), a systematic conformational analysis of **1b** was conducted at the ωB97X-D/6-31 + G(d,p))[67] level of DFT theory (Table 6) using Gaussian 09.[55] The analysis involved rotation of the bond between the chiral auxiliary and the nitrogen. Only two conformers were found: **1b-A** and **1b-B**. In the former, the C–H bond of the chiral fragment is *syn* in regard to the N(3)-C(4) bond in the heterocycle. In the latter, the C–H bond is *anti* with respect to the N(3)-C(4) bond (see Table 6 for dihedral angles). From the 1.2 kcal/mol energy difference between these conformers, a 12:88 mixture of **1b-A**/**1b-B** would be expected at room temperature. If the conformation of **1b** were the only factor determining the stereoselectivity, the addition of **8a** to **1b** would take place on the least hindered *alpha* face of **1b-B** to yield **30b** (Figure 2). However, this compound was the minor isomer in the actual reaction.

As is well known, the stereoselectivity of a reaction such as the one under consideration does not necessarily depend on conformational preferences.[68] Hence, a theoretical analysis was conducted for the addition reaction of oxazolidinone **1b** to **8a** at the ωB97X-D/6-31 + G(d,p) level of DFT theory (see details of quatum calculations in Supporting Information). Attempts to optimize a zwitterionic intermediate such as I (Figure 2) in the gas phase were unsuccessful, leading to its dissociation into the starting materials. Unexpectedly, the transition states (TSs) for concerted hetero-Diels-Alder cycloadditions could be located, allowing for the calculation of the TSs for all possible

TABLE 7 Absolute ($E_0^{\ddagger}$) and relative ($\Delta E_0^{\ddagger}$) energies (with respect to the **1b-a**/**8a**-anti-endo TS) for the eight TSs of the [4 + 2] cycloaddition between **1b** and **8a**, including zero-point energies (ωB97X-D/6-31 + G(d,p))[a]

TS	$E_0^{\ddagger}$, u.a.	$\Delta E_0^{\ddagger}$, kcal/Mol	$d_{(O\cdots C)}$, Å[b]	$d_{(C\cdots C)}$, Å[b]	Product Fraction[c]	*dr*, %[d]
1b-A/8a-*anti-endo*	−900.97344	0.0	3.038	1.914	0.946	94.7
1b-A/8a-*anti-exo*	−900.96679	4.2	2.881	1.933	0.001	
1b-B/8a-*syn-endo*	−900.96600	4.7	2.778	1.931	0.000	
1b-B/8a-*syn-exo*	−900.96254	6.8	3.599	1.899	0.000	
1b-A/8a-*syn-endo*	−900.96888	2.9	2.753	1.936	0.010	5.3
1b-A/8a-*syn-exo*	−900.96418	5.8	2.954	1.949	0.000	
1b-B/8a-*anti-endo*	−900.97043	1.9	2.848	1.958	0.042	
1b-B/8a-*anti-exo*	−900.96664	4.3	3.000	1.930	0.001	

[a]The first four TSs lead to **29b**, the last four to **30b**.

[b]Distances between the atoms forming the new bonds in the cycloaddition.

[c]Product fraction assuming kinetic control of the cycloaddition and the Boltzmann distribution ($\Delta E_0^{\ddagger}$, 25°C) of the TSs, based on the activation energies.

[d]Diastereoisomeric ratios considering all the contributions to the TSs for each of the two final products.

diastereoisomeric approaches between the two reactants that give rise to the formation of **29b**/**30b**. After considering the two conformers of the chiral fragment in **1b** (**1b-A** and **1b-B**), the *anti* and *syn* approximations with regard to the phenyl group, and the *endo*/*exo* orientations of the heterodiene that promote the formation of **29b**/**30b**, eight TSs were obtained. The TSs leading to the other possible regioisomers were not studied. The geometries of these stationary points are shown in Figure 3, while the corresponding energies are summarized in Table 7. Notice that out of the eight TSs, four lead to **29b** (the first four TSs in Table 7) and four to **30b**.

All the TSs are very asynchronic (Figure 3 and Table 7), as the distance between the C-5 carbon atom of 1b and the C-3 carbon of 8a is shorter than that between the C-4 carbon atom of the heterocycle and the oxygen atom of the heterodiene. This agrees with the expected polarization of the π systems for both cycloaddends. The conformations of the chiral *N*-phenylethyl moiety are very similar to those of the isolated heterocycle, with slight changes in the orientation adopted by the benzene ring. In the *exo* TSs, significant steric interactions between the heterodiene and the methyl groups of the dienophile are readily apparent, leading to higher energies than those found for the *endo* TSs (Table 7).

Due to their higher energy, the *exo* TSs do not contribute to the formation of the final products **29b** and **30b** (Table 7) under conditions of kinetic control. In particular, **1b-B**-*syn-exo* is the most energetic and asynchronous TS, probably because of the stronger steric interactions of the heterodiene not only with the methyl groups at C-4 and C-5 but also with the phenyl group of the chiral fragment that is oriented towards it. Out of the four *endo* TSs, **1b-A**-*anti-endo* and **1b-B**-*anti-endo* are the significant ones, both involving the approach of the heterodiene to the dienophile from the same side of the methyl group in the chiral fragment of the oxazolinone (Table 7). Among these TSs, the main factor in controlling the selectivity in this cycloaddition seems to be the steric effect of the methyl group, which is oriented away from the reacting centers of the oxazolidinone in the **1b-A**-*anti-endo* TS. Contrarily, the methyl group is oriented towards the heterodiene in the **1b-B**-*anti-endo* TS, blocking its approach to the dienophile. In conclusion, the least hindered approach of the heterodiene to the oxazolinone dienophile appears to take place on the beta face of the latter. Interestingly, the diastereoisomeric ratio of **29b/30b** (95:5) obtained from the analysis of the energies of the TSs is in close agreement with that determined experimentally (93:7).

Since the above theoretical evaluation fits well with the experimental results, calculations were made for the addition of **1b** to MVK (**8b**). By taking the same factors into account, a set of eight TSs were located (Figure 4), similar to those found for acrolein (**8a**), indicating that this is also a concerted process.

The relative energies of the TSs (Figure 4 and Table 8) are very similar to those found for the cycloadditions with **8a** (Table 7), suggesting that the introduction of the methyl group of **8b** does not significantly increase the repulsive interactions for most of the approaches. The highest energy values are those for the TSs *syn* to the phenyl group in conformer **1b-B**, in which the methyl group of **8b** is close to the phenyl ring of the auxiliary, either for the *endo* or *exo* approaches (Figure 4).

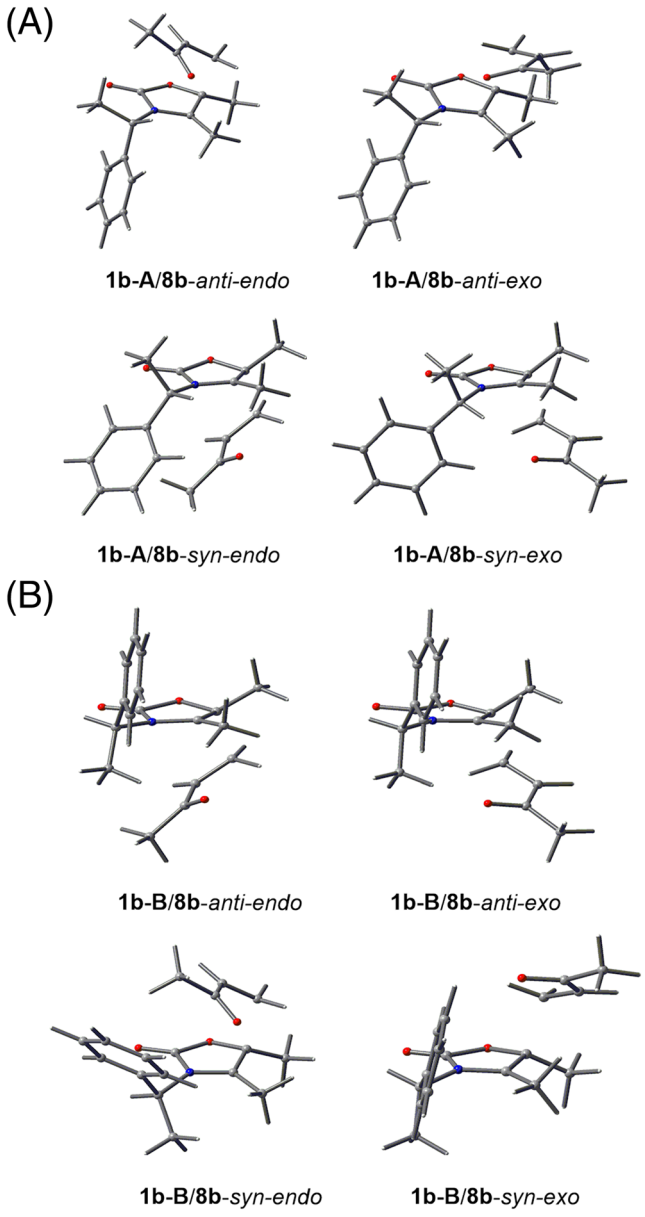


FIGURE 4 TSs calculated (ωB97X-D/6-31 + G(d,p))for the cycloaddition between **1b** and **8b**, starting from conformers (A) **1b-a** and (B) **1b-B**

TABLE 8 Absolute ($E_0^{\ddagger}$) and relative ($\Delta E_0^{\ddagger}$) energies (with respect to the **1b-a**/**8b**-anti-endo TS) for the eight TSs of the [4 + 2] cycloaddition between **1b** and **8b**, including zero-point energies (ωB97X-D/6-31 + G(d,p))[a]

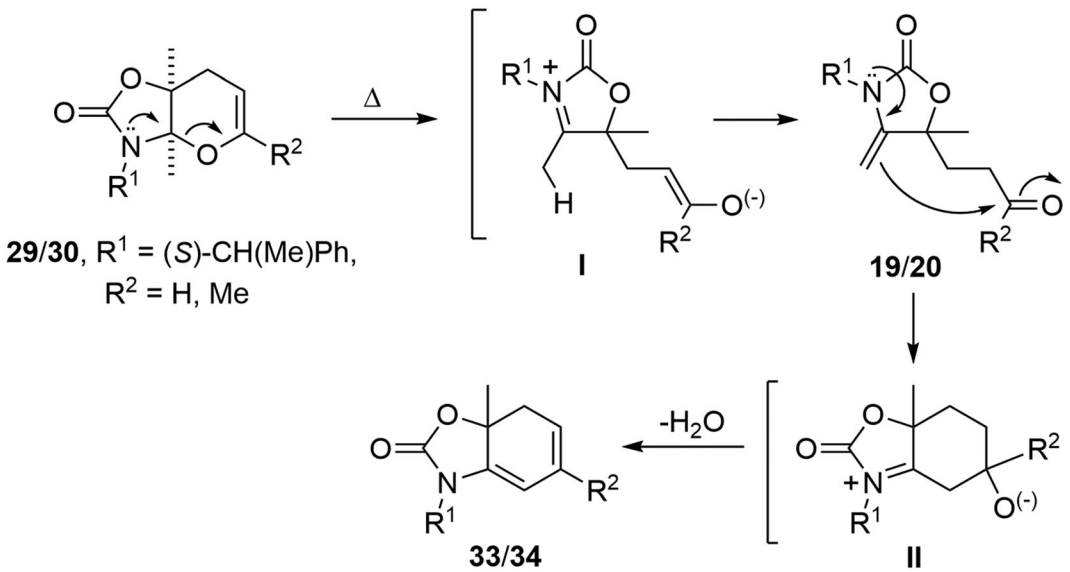
TS	$E_0^{\ddagger}$, u.a.	$\Delta E_0^{\ddagger}$, kcal/Mol	$d_{(O\cdots C)}$, Å[b]	$d_{(C\cdots C)}$, Å[b]	Product Fraction[c]	*dr*, %[d]
1b-A/8b-*anti-endo*	−940.26130	0.0	3.004	1.882	0.958	95.9
1b-A/8b-*anti-exo*	−940.25444	4.3	2.817	1.920	0.001	
1b-B/8b-*syn-endo*	−940.25241	5.6	2.780	1.906	0.000	
1b-B/8b-*syn-exo*	−940.24980	7.2	3.498	1.885	0.000	
1b-A/8b-*syn-endo*	−940.25670	2.9	2.762	1.890	0.007	4.1
1b-A/8b-*syn-exo*	−940.25174	6.0	2.856	1.941	0.000	
1b-B/8b-*anti-endo*	−940.25815	2.0	2.844	1.918	0.034	
1b-B/8b-*anti-exo*	−940.25408	4.5	2.894	1.927	0.000	

[a]The first four TSs lead to **29b**, the last four to **30b**.

[b]Distances between the atoms forming the new bonds in the cycloaddition.

[c]Product fraction assuming kinetic control of the cycloaddition and the Boltzmann distribution ($\Delta E_0^{\ddagger}$, 25°C) of the TSs, based on the activation energies.

[d]Diastereoisomeric ratios considering all the contributions to the TSs for each of the two final products.



SCHEME 10 Mechanism of conversion of fused pyranyl compounds **29**/**30** into dienes **33**/**34** via the formation and cyclization of intermediates **19a**/**20a**

The diastereoselectivity theoretically predicted (Table 8) for the Diels-Alder cycloaddition of **8b** is not as high as experimentally observed (Table 4). Nevertheless, a higher diastereoselectivity should theoretically be expected from **8b** than from **8a** (Tables 7 and 8), and this is in agreement with the trend in the experimental data.

Since the formation of fused-pyranyl derivatives **29** and **30** is favored by a concerted TS, the Michael conjugated addition products **19a**/**20a** (Scheme 4) probably result from the pyranyl ring opening of derivatives **29**/**30**, which occurs as a consequence of raising the temperature of the reaction mixture (Scheme 10). Furthermore, we have established that dienes **33**/**34** can be formed by heating the 1,4-addition products **19a**/**20a**. Hence, these dienes would also be formed by conversion of derivatives **29**/**30** through a cascade pyranyl ring opening/intramolecular cyclization process of **19a**/**20a** via intermediates I and II.[69]

Regarding the behavior of chiral bicyclic oxazolidinones **39a-b**, it is possible to use a similar analysis to propose the structures of the major isomers (Scheme 9).[70] Assuming that the electronic, steric, and conformational properties of the structures of oxazolidinones **39a-b** are analogous to those of oxazolidinones **1a-b**, the generation of

heterocyclic [4.4.3]propellanes **40a-b**/**41a-b** may also take place through a concerted hetero-Diels-Alder reaction. Therefore, their diastereoselectivity should be controlled by a preferential approach of the heterodiene from the face opposite to the position of the phenyl ring of the chiral auxiliary. As a result, the structures of diastereoisomers **40a-b** are assigned to the major adducts, which are supported by the X-ray structure of **40b** (Figure 1E).

4 | CONCLUSION

Enantiopure 3-((*R*)- and 3-((*S*)-1-phenylethyl)-4-oxazoline-2-ones **1a-b** are useful diastereoselective chiral synthons for the construction of diverse hetero- and carbocyclic-fused polycyclic systems constituted by two quaternary centers, each containing one heteroatom. For most of the evaluated processes, the *N*-((*R*) or (*S*)-1-phenylethyl) chiral auxiliary efficiently induced the highly diastereoselective functionalization of the 4-oxazolin-2-one scaffold at the C-4 and C-5 stereocenters. Thus, hydrogenation, electrophilic additions, and hetero-Diels-Alder reactions were carried out either under mild reaction conditions or thermal or microwave heating, providing the corresponding products in good yields and high *dr*. In particular, the reaction between compounds **1a-b** and conjugated carbonyl compounds **8a-b** generated the diastereoselective formation of **29a-d**/**30a-d**, which according to the DFT calculations are the result of concerted hetero-Diels-Alder cycloadditions. The relative energies of the possible diastereoisomeric TSs indicate that the most favorable approach of the heterodiene to the oxazolinone is controlled by the orientation of the substituents in the stereogenic center of the chiral auxiliary, leading to the observed configuration of the quaternary carbon centers of the major products. The stereoselectivity estimated from the theoretical calculations matches the experimental *dr* very closely. It has been reported that the chiral α-phenylethyl auxiliary is readily removed by hydrogenolysis after acting as a valuable inductor for asymmetric synthesis[36-43,71] Hence, it is expected that such auxiliary can be removed in a like manner for most of the products obtained in the current study without affecting their functionalities. Experimental studies are being carried out to test this idea, and the results will be reported in due course.

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ORCID

Joaquín Tamariz https://orcid.org/0000-0002-0600-3857

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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