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TETRAHEDRON: *ASYMMETRY*

Stereocontrolled cyclopropanation of Garner's aldehyde derived enones

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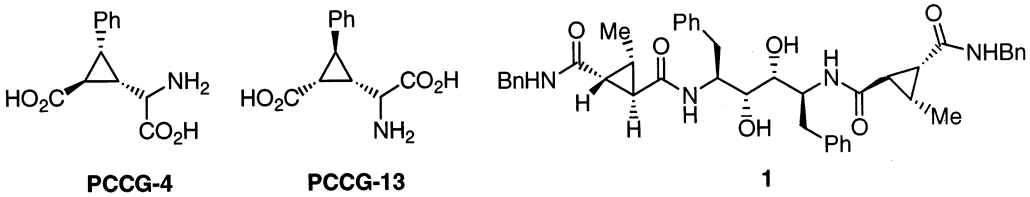
Abstract

The reaction of sulfonium ylides with enones **5** derived from (*S*)-Garner's aldehyde in toluene provides 1,2,3-trisubstituted cyclopropanes. The configuration of the major isomer is 2*R*,1′*R*,2′*R*,3′*R*. Using this reaction a 3-benzyl analogue of the CCG family compounds was synthesized.

1. Introduction

Recently, several classes of compounds that possess the 1,2,3-trisubstituted cyclopropane subunit were reported to have promising biological activities.[1–9] These compounds include PCCG-4 and PCCG-13,[4] the subtype-selective antagonists for metabotropic glutamate receptor, and peptide **1**, a potent inhibitor of HIV-1 protease (Scheme 1).[1a] Although the enantioselective construction of cyclopropanes has attracted significant attention in the past two decades,[10] few examples have been reported for synthesis of enantiopure 1,2,3-trisubstituted cyclopropanes.[11] We have demonstrated that the reaction of ethyl dimethylsulfonium acetate bromide with



Scheme 1.

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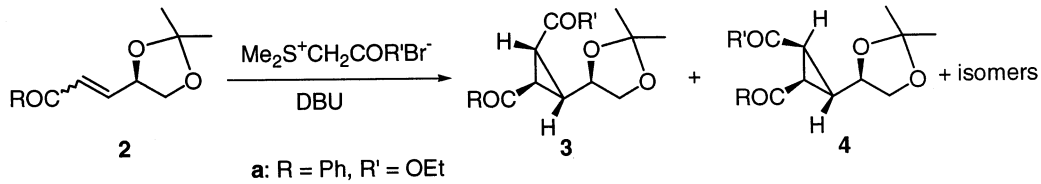
aromatic enones **2** derived from (*S*)-glyceraldehyde acetonide under the action of DBU provided 1,2,3-trisubstituted cyclopropanes **3** and **4** in excellent yield and good diastereoselectivity (Scheme 2).[12] It was then found that a similar strategy could be extended to Garner aldehyde-derived enones. Herein we wish to detail the result.



Scheme 2.

2. Results and discussion

Initially, the reaction of enone **5a** with ethyl (dimethylsulfuranylidene)acetate (EDSA) generated in situ by treatment of ethyl dimethylsulfonium acetate bromide with DBU was studied as our model reaction. We found that this reaction worked at 0°C and gave the cyclopropanation product **6a** in 72% yield, together with an inseparable mixture of **7a** and **8a**. The stereochemistry of **6a** was assigned as the (2*R*,1′*R*,2′*R*,3′*R*)-form by a single-crystal X-ray analysis which is shown in Fig. 1. This configuration is the same as **3**, the major isomer of the reaction of **2a** with EDSA. Selective deprotection of the mixture of **7a** and **8a** by treatment with Dowex-50W in methanol provided a separable mixture of **9a** and **10a** (Schemes 3 and 4). By NOESY studies the structures of **9a** and **10a** were assigned as the (2*R*,1′*R*,2′*R*,3′*S*)- and (2*R*,1′*R*,2′*S*,3′*S*)-forms, respectively, because marked NOE correlation between 2′-H and 3′-H but not 1′-H and 2′-H or

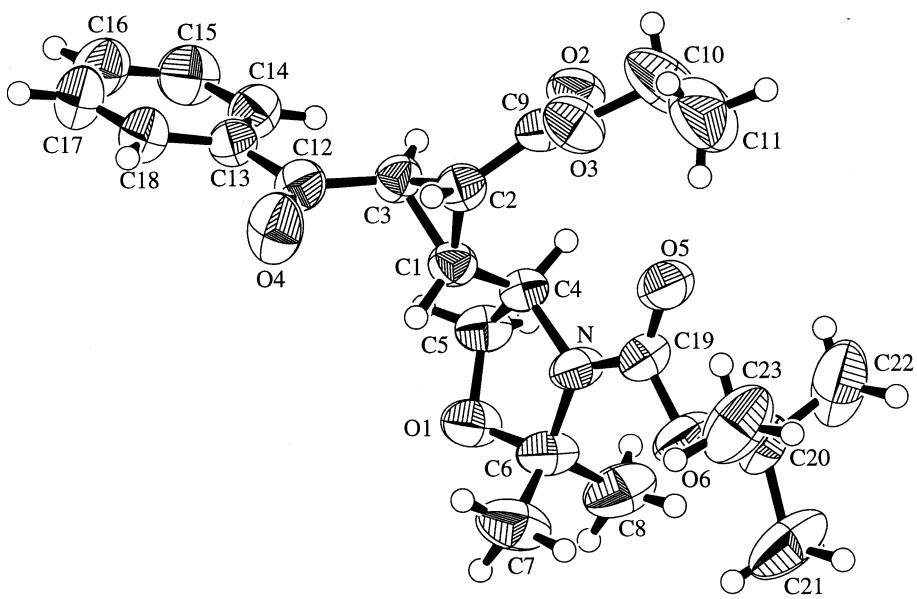
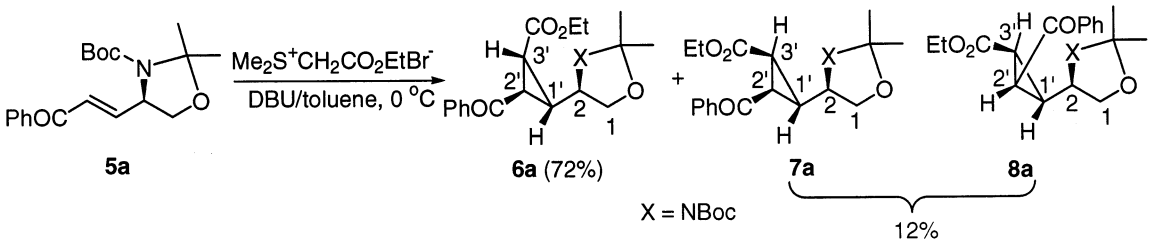
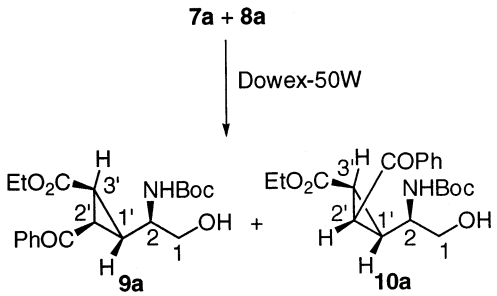


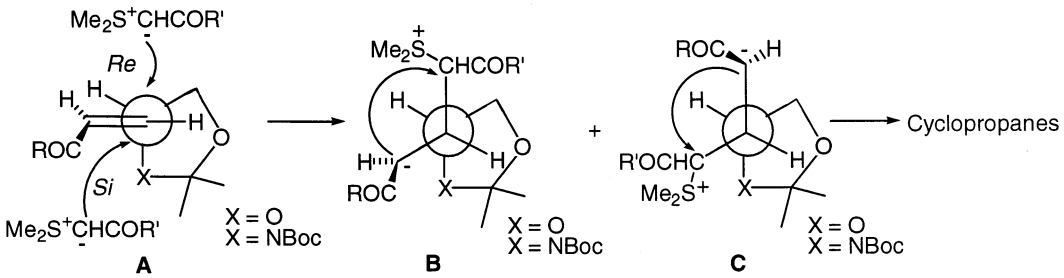
Figure 1. X-ray structure of **6a**



Scheme 3.



Scheme 4.

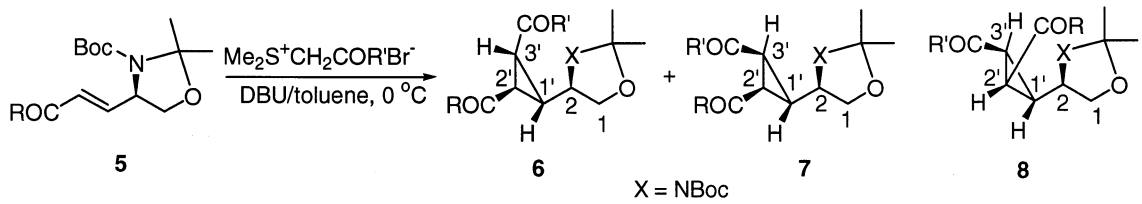


Scheme 5.

1′-H and 3′-H was observed in the NOESY spectra of **9a**, while marked NOE correlation between 2′-H and 1′-H but not 3′-H and 2′-H or 1′-H and 3′-H was observed in the NOESY spectra of **10a**. This stereochemical outcome is quite similar to that of the reaction of **2a** with EDSA or related sulfonium ylides. However, unlike the reaction of **2a** with EDSA, no other minor isomers such as the (2*R*,1′*S*,2′*S*,3′*S*)-isomer were detected in the present reaction. This difference is explained by Scheme 5. The ylides attacked the enones from either *Re*- or *Si*-face to give intermediates **B** or **C**, which delivered the corresponding cyclopropanation products [(1′*R*)- and (1′*S*)-isomers, respectively] after an elimination–cyclization reaction. Because the *N*-Boc group in **5a** is much more bulky than the corresponding oxygen moiety in **2a**, the possibility of forming the intermediate **C** in the present case is much smaller than that of the reaction of **2a** with EDSA and the (1′*S*)-isomers were therefore not obtained.

In order to explore the scope of this reaction, other enones, sulfonium ylides, and reaction conditions were studied and the results were summarized in Table 1. Methylene chloride and acetonitrile were also suitable solvents for this reaction, but the stereoselectivity in these cases was poor (compare entries 1–3). The sulfonium ylides derived from ketones or amides could also

Table 1
Cyclopropanation of enones **5** with sulfonium ylides

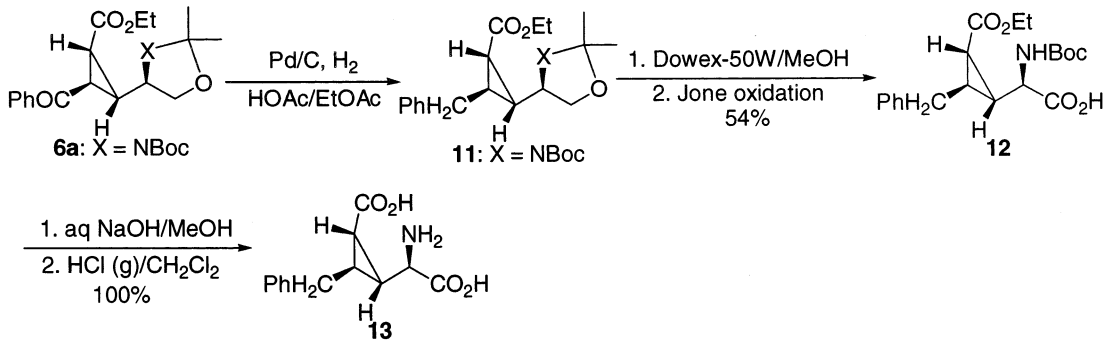


Entry	R	R′	Solvent	Time (h)	Product ((yield (%))[a]
1	Ph	OEt	Toluene	7	**6a** (72) **7a**+**8a** (12)
2	Ph	OEt	CH_2Cl_2	5	**6a** (32) **7a**+**8a** (33)
3	Ph	OEt	CH_3CN	7	**6a** (25) **7a**+**8a** (44)
4	Ph	*t*-OBu	Toluene	24	**6b** (72) **7b**+**8b** (10)
5	Ph	Me	Toluene	24	**6c** (68) **7c**+**8c** (23)
6	Ph	Ph	Toluene	24	**6d** (30) **7d**+**8d** (10)
7	Ph	$N(CH_2CH_2)_2O$	Toluene	24	**6e** (8) **7e**+**8e** (0)
8	Ph	$N(CH_2CH_2)_2O$	CH_3CN	24	**6e** (24) **7e**+**8e** (13)
9	Me	OEt	Toluene	24	**6f** (54) **7f**+**8f** (6)
10	Me	*t*-OBu	Toluene	24	**6g** (60) **7g**+**8g** (6)

[a] Isolated yield.

be reacted with enone **5a** to provide the corresponding cyclopropanation products (entries 5–8). The results demonstrated in entries 9 and 10 indicated that the aliphatic enone could be used as the reaction substrate. Taking these results together, we could conclude that the present reaction would allow us to assemble 1,2,3-trisubstituted cyclopropanes with great diversity.

Obviously, 3-benzyl analogues of CCG family compounds[4,5] could be synthesized starting from the present reaction products. An example is illustrated in Scheme 6. Under Pd/C-catalyzed hydrogenation conditions, the phenyl ketone moiety in **6a** was reduced to afford the corresponding benzyl derivative **11**. Treatment of **11** with Dowex-50W in methanol, followed by Jones oxidation provided monoacid **12**. After hydrolysis of **12** with aqueous NaOH, the dicarboxylic acid generated was deprotected with gaseous hydrogen chloride in methylene chloride to give amino acid **13** as a hydrochloride salt.



Scheme 6.

In conclusion, we observed that the enones derived from Garner's aldehyde gave better stereoselectivity than the enones derived from (*S*)-glyceraldehyde acetonide in the cyclopropanation reactions with sulfonium ylides. The present reaction is promising to synthesize some biologically important 1,2,3-trisubstituted cyclopropanes such as CCG analogues.

3. Experimental

3.1. General procedure for synthesis of enone **5**

To a solution of L-Garner's aldehyde (3.89 g, 17 mmol) in dry benzene (150 mL) was added 1-phenyl-2-(triphenylphosphoranylidene)ethanone (13 g, 34 mmol) at rt with stirring, then the mixture was heated to reflux and stirring was maintained until the reaction was completed (monitored by TLC). The solvent was evaporated in vacuo and the residue was purified by flash chromatography (1:8 ethyl acetate/petroleum ether as eluent) to give **5a**.

5a: 98% yield; $[\alpha]_D^{20}=-48.4$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, $J=7.8$ Hz, 2H), 7.54 (m, 1H), 7.46 (m, 2H), 6.91–6.89 (m, 2H), 4.64–4.52 (m, 1H), 4.13 (dd, $J=6.7$, 6.5 Hz, 1H), 3.84 (dd, $J=9.2$, 2.2 Hz, 1H), 1.54–1.41 (m, 15H); MS *m*/*z* 331 (M^+), 316 (M^+-CH_3), 216, 115, 105, 57, 41; anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86, H, 7.60, N, 4.23, found: C, 68.83, H, 7.73, N, 4.10.

5b: 87% yield; $[\alpha]_D^{20}=-55.2$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.68–6.65 (m, 1H), 6.19 (t, $J=15.9$ Hz, 1H), 4.55–4.48 (m, 1H), 4.12 (dd, $J=6.7$, 6.5 Hz, 1H), 3.8 (dd, $J=9.2$, 2.0 Hz, 1H), 2.3 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H), 1.47–1.41 (m, 9H); MS *m*/*z* 270 (M^++H^+), 254, 154, 57, 43, 41.

3.2. General procedure for cyclopropanation

To an ice-cold solution of enone **5** (1.2 mmol) and corresponding sulfonium ylide (3.6 mmol) in toluene was added DBU (3.6 mmol) with stirring, and the mixture was stirred at 0°C for 0.5 h. After the mixture was allowed to slowly warm to room temperature, the stirring was continued until the reaction was completed (monitored by TLC). Water was added and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was purified by flash chromatography to give **6**, **7** and **8**.

3.2.1. (1R,2R,3R)-2-Benzoyl-3-[(R)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid, ethyl ester **6a**

$[\alpha]_D^{20}=-1.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J=7.2$ Hz, 2H), 7.61 (t, $J=7.4$ Hz, 1H), 7.45 (t, $J=7.6$ Hz, 2H), 4.31–4.21 (m, 3H), 4.05 (dd, $J=8.8$, 6.0 Hz, 1H), 3.85 (m, 1H), 3.21 (m, 1H), 2.68 (dd, $J=9.3$, 4.5 Hz, 1H), 2.21 (m, 1H), 1.55 (s, 3H), 1.51–1.45 (m, 12H), 1.3 (t, $J=7.1$ Hz, 3H); MS *m*/*z* 418 (M^++H^+), 362, 302, 256, 105, 77, 57, 41; anal. calcd for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N, 3.35; found: C, 66.18; H, 7.51; N, 3.38.

*3.2.2. (1*S,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid, ethyl ester* ***7a*** *and (1*S,*2*S,*3*R*)-2-benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid, ethyl ester* ***8a***

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J=7.4$ Hz, 2H), 7.55 (t, $J=6.9$ Hz, 1H), 7.45 (t, $J=7.6$ Hz, 2H), 4.05–3.95 (m, 4H), 3.95–3.88 (m, 1H), 2.72–2.65 (m, 2H), 2.61–2.52 (m, 1H), 1.65 (s, 3H), 1.53–1.45 (m, 12H), 1.1 (t, $J=7.1$ Hz, 3H); MS m/z 418 (M^++H^+), 362, 302, 256, 105, 77, 57, 41; anal. calcd for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N, 3.35; found: C, 66.10; H, 7.54; N, 3.27.

*3.2.3. (1*R,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid,* tert*-butyl ester* ***6b***

$[\alpha]_D^{20}=-33.2$ (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $J=7.5$ Hz, 2H), 7.61 (t, $J=7.1$ Hz, 1H), 7.47 (t, $J=7.5$ Hz, 2H), 4.27 (m, 1H), 4.02 (dd, $J=8.2$, 6.1 Hz, 1H), 3.87 (m, 1H), 3.12 (m, 1H), 2.6 (dd, $J=9.3$, 4.5 Hz, 1H), 2.13 (m, 1H), 1.53–1.42 (m, 24H); MS m/z 446 (M^++H^+), 390, 334, 290, 274, 256, 105, 57, 41; anal. calcd for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14; found: C, 67.26; H, 7.97; N, 3.04.

*3.2.4. (1*S,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid,* tert*-butyl ester* ***7b*** *and (1*S,*2*S,*3*R*)-2-benzoyl-3-[(R)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid,* tert*-butyl ester* ***8b***

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J=7.5$ Hz, 2H), 7.53 (m, 1H), 7.45 (m, 2H), 4.01–3.88 (m, 2H), 3.28–2.79 (m, 1H), 2.43 (m, 1H), 2.1 (m, 1H), 1.6 (s, 3H), 1.47 (s, 3H), 1.43 (s, 9H), 1.21 (s, 9H); MS m/z 446 (M^++H^+), 390, 334, 290, 274, 105, 57, 41; anal. calcd for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14; found: C, 67.26; H, 7.89; N, 3.19.

*3.2.5. (1*R,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropyl methyl ketone* ***6c***

$[\alpha]_D^{20}=-88.8$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, $J=7.2$ Hz, 2H), 7.55 (t, $J=7.4$ Hz, 1H), 7.45 (t, $J=7.7$ Hz, 2H), 4.05–3.95 (m, 2H), 3.86–3.73 (m, 1H), 3.31 (dd, $J=6.0$, 4.6 Hz, 1H), 2.95 (dd, $J=9.5$, 4.5 Hz, 1H), 2.45 (s, 3H), 2.3 (m, 1H), 1.57 (s, 3H), 1.45 (s, 9H), 1.41 (s, 3H); MS m/z 388 (M^++H^+), 332, 288, 272, 256, 105, 77, 57, 41; anal. calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61; found: C, 67.56; H, 7.28; N, 3.73.

*3.2.6. (1*S,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropyl methyl ketone* ***7c*** *and (1*S,*2*S,*3*R*)-2-benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropyl methyl ketone* ***8c***

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, $J=7.3$ Hz, 2H), 7.55 (m, 1H), 7.45 (t, $J=7.5$ Hz, 2H), 4.05 (dd, $J=9.1$, 5.6 Hz, 1H), 3.97–3.80 (m, 2H), 2.99–2.49 (m, 3H), 2.2 (s, 3H), 1.65–1.61 (m, 6H), 1.5 (s, 9H); MS m/z 388 (M^++H^+), 332, 288, 272, 256, 105, 77, 57, 41; anal. calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61; found: C, 68.27; H, 7.59; N, 3.47.

*3.2.7. (1*R,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropyl phenyl ketone* ***6d***

$[\alpha]_D^{20}=-4.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13–8.02 (m, 4H), 7.62 (m, 2H), 7.59–7.43 (m, 4H), 4.19 (m, 1H), 4.12 (m, 1H), 3.92 (m, 1H), 3.62 (m, 2H), 2.50 (m, 1H), 1.45

(s, 3H), 1.3–1.2 (m, 12H); MS m/z 450 (M^++H^+), 376, 350, 334, 244, 105, 77, 57, 41; anal. calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12; found: C, 72.03; H, 6.98; N, 3.03.

*3.2.8. (1*S,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropyl phenyl ketone* ***7d*** *and (1*S,*2*S,*3*R*)-2-benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropyl phenyl ketone* ***8d***

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–7.95 (m, 4H), 7.61–7.55 (m, 2H), 7.45–7.35 (m, 4H), 4.15–4.05 (m, 2H), 3.95–3.90 (m, 1H), 3.71–3.65 (m, 1H), 2.85 (m, 1H), 2.65 (m, 1H), 1.65 (s, 3H), 1.52 (s, 9H), 1.41 (s, 3H); MS m/z 450 (M^++H^+), 434, 376, 350, 334, 244, 105, 77, 57, 41; anal. calcd for $C_{27}H_{31}NO_5$: C, 72.14, H, 6.95, N, 3.12; found: C, 71.88; H, 7.00; N, 3.11.

*3.2.9. (1*R,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropanecarboxylic acid, morpholino amide* ***6e***

$[\alpha]_D^{20}=-12.3$ (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, $J=7.5$ Hz, 2H), 7.55 (t, $J=7.4$ Hz, 1H), 7.42 (t, $J=7.7$ Hz, 2H), 4.1 (m, 1H), 4.0 (m, 1H), 3.91–3.75 (m, 3H), 3.71–3.52 (m, 6H), 3.42 (t, $J=4.6$ Hz, 1H), 2.72–2.68 (dd, $J=9.1$, 4.4 Hz, 1H), 2.15 (dt, $J=9.2$, 5.2 Hz, 1H), 1.5 (s, 3H), 1.41 (s, 9H), 1.37 (s, 3H); MS m/z 459 (M^++H^+), 359, 343, 253, 105, 57; anal. calcd for $C_{25}H_{34}N_2O_6$: C, 65.48; H, 7.47; N, 6.11; found: C, 65.21; H, 7.46; N, 5.82.

*3.2.10. (1*S,*2*R,*3*R*)-2-Benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid, morpholino amide* ***7e*** *and (1*S,*2*S,*3*R*)-2-benzoyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropanecarboxylic acid, morpholino amide* ***8e***

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J=7.3$ Hz, 2H), 7.55 (m, 1H), 7.48 (t, $J=7.4$ Hz, 2H), 4.08 (m, 1H), 4.01–3.92 (m, 1H), 3.88 (m, 1H), 3.55–3.45 (m, 8H), 2.93–2.75 (m, 2H), 2.65–2.47 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.52 (s, 9H); MS m/z 459 (M^++H^+), 359, 345, 256, 105, 57; anal. calcd for $C_{25}H_{34}N_2O_6$: C, 65.48; H, 7.47; N, 6.11; found: C, 65.49; H, 7.73; N, 6.10.

*3.2.11. (1*R,*2*R,*3*R*)-2-Acetyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropanecarboxylic acid, ethyl ester* ***6f***

$[\alpha]_D^{20}=-30.7$ (c 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25–4.13 (m, 2H), 4.09–3.95 (m, 2H), 3.82 (m, 1H), 2.45 (m, 2H), 2.2 (s, 3H), 1.95 (dd, $J=13.4$, 8.2 Hz, 1H), 1.58 (s, 3H), 1.5 (s, 3H), 1.4 (s, 9H), 1.25 (t, $J=7.1$ Hz, 3H); MS m/z 356 (M^++H^+), 256, 254, 240, 194, 57, 43; anal. calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94; found: C, 61.25; H, 8.43; N, 3.90.

*3.2.12. (1*S,*2*R,*3*R*)-2-Acetyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropanecarboxylic acid, ethyl ester* ***7f*** *and (1*S,*2*R,*3*R*)-2-acetyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid, ethyl ester* ***8f***

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15–4.09 (m, 3H), 3.97 (m, 1H), 3.81 (m, 1H), 2.65–2.30 (m, 2H), 2.25 (s, 3H), 2.18 (m, 1H), 1.69–1.47 (m, 15H), 1.24 (m, 3H); MS m/z 340 (M^+–CH_3), 282, 240, 194, 57, 43; anal. calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94; found: C, 60.86; H, 8.35; N, 3.29.

*3.2.13. (1*R,*2*R,*3*R*)-2-Acetyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropanecarboxylic acid,* tert*-butyl ester* ***6g***

$[\alpha]_D^{20}=-60.6$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (m, 1H), 3.82–3.75 (m, 1H), 2.45–2.38 (m, 2H), 2.3 (s, 3H), 2.10 (m, 1H), 1.52–1.41 (m, 24H); MS m/z 384 (M^++H^+), 328,

284, 272, 212, 57, 43; anal. calcd for $C_{20}H_{33}NO_6$: C, 62.64; H, 8.67; N, 3.65; found: C, 62.58; H, 8.76; N, 3.56.

*3.2.14. (1*S,*2*R,*3*R*)-2-Acetyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropane-carboxylic acid*, tert-*butyl ester* ***7g*** *and (1*S,*2*R,*3*R*)-2-acetyl-3-[(*R*)-((3-((2,2-dimethyl-1-oxo)propyl)-2,2-dimethyl)-4-oxazolidinyl)]-cyclopropanecarboxylic acid*, tert-*butyl ester* ***8g***

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (m, 1H), 3.75 (m, 1H), 3.75–3.52 (m, 1H), 2.38–2.28 (m, 1H), 2.28–2.22 (m, 1H), 2.21 (s, 3H), 2.05–1.95 (m, 1H), 1.52–1.35 (m, 24H); MS m/z 384 (M^++H^+), 368, 328, 284, 272, 212, 57, 43; anal. calcd for $C_{20}H_{33}NO_6$: C, 62.64; H, 8.67; N, 3.65; found: C, 62.62; H, 8.43; N, 3.38.

3.3. Synthesis of ***9a*** *and* ***10a*** *from a mixture of* ***7a*** *and* ***8a***

To a mixture of **7a** and **8a** (61 mg, 0.15 mmol) in 0.5 mL of methanol was added 20 mg of Dowex-50W. The resultant mixture was stirred at room temperature for 24 h. After the resin was filtered off, the filtrate was concentrated in vacuo and the residue was chromatographed (1/3 ethyl acetate/petroleum ether as eluent) to afford 21 mg (38%) of **9a** and 19 mg (34%) of **10a**. **9a**: $[\alpha]_D^{20}$ = +26 (*c* 0.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 5.09 (m, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.79 (m, 2H), 3.54 (m, 1H), 2.78 (t, J = 7.3 Hz, 1H), 2.50 (dd, J = 8.9, 6.0 Hz, 1H), 2.38 (dd, J = 13.1, 7.5 Hz, 1H), 1.45 (s, 9H), 1.04 (t, J = 7.1 Hz, 3H); MS m/z 378 (M^++H^+), 346, 304, 290, 276, 105, 57; HRMS found m/z 346.1670 (M^+–CH_2OH), $C_{19}H_{24}NO_5$ requires 346.1654. **10a**: $[\alpha]_D^{20}$ = –32 (*c* 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 5.10 (m, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.85 (m, 2H), 3.49 (m, 1H), 3.08 (m, 1H), 2.52 (m, 1H), 2.31 (m, 1H), 1.44 (s, 9H), 1.09 (t, J = 7.1 Hz, 3H); MS m/z 378 (M^++H^+), 346, 304, 290, 276, 105, 57; HRMS found m/z 346.1639 (M^+–CH_2OH), $C_{19}H_{24}NO_5$ require 346.1654.

3.4. Hydrogenation of ***6a***

A mixture of **6a** (70 mg, 0.17 mmol), 10 mg of 10% Pd/C, 0.5 mL of 70% acetic acid in 2 mL of ethyl acetate was stirred under 20 atm of hydrogen at room temperature overnight. After the catalyst was filtered off, the filtrate was basified with saturated aqueous $NaHCO_3$ and then the solution was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford 58 mg (86%) of **11**. $[\alpha]_D^{20}$ = –0.5 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.23 (m, 3H), 4.28–4.01 (m, 3H), 3.84 (dd, J = 8.9, 6.0 Hz, 1H), 3.52 (m, 1H), 2.82 (dd, J = 14.3, 6.0 Hz, 1H), 2.80–2.49 (m, 2H), 1.80 (m, 2H), 1.61 (s, 6H), 1.46 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H); MS m/z 404 (M^++H^+), 304, 288, 212, 91, 57.

*3.5. (*R*)-*N*-tert-Butoxycarbonyl-2-((1′*R*,2′*R*,3′*S*)-(2′-benzyl-3′-ethoxycarbonylcyclopropyl))-glycine* ***12***

A mixture of **11** (146 mg, 0.36 mmol) and Dowex-50W (100 mg) in 1 mL of MeOH was stirred at room temperature for 24 h. The resin was filtered off and the filtrate was concentrated

in vacuo. The residue was purified by flash chromatography to give 105 mg of alcohol, which was dissolved in 0.5 mL of acetone. To this stirring solution was added 0.16 mL of Jone's reagent at 0°C before it was stirred for 8 h at the same temperature. After 1 mL of *i*-PrOH was added to quench the reaction, the mixture was partitioned between 10 mL of ethyl acetate and 5 mL of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography to give 74 mg (54%) of **12**. $[\alpha]_D^{20}=-11$ (*c* 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.23–7.15 (m, 3H), 5.24 (d, $J=7.6$ Hz, 1H), 4.38 (br s, 1H), 4.14 (q, $J=7.1$ Hz, 2H), 2.80 (dd, $J=14.6$, 5.8 Hz, 1H), 2.70 (dd, $J=14.6$, 6.7 Hz, 1H), 2.03 (dt, $J=11.5$, 6.1 Hz, 1H), 1.72 (dd, $J=8.7$, 5.4 Hz, 1H), 1.58 (m, 1H), 1.42 (s, 9H), 1.25 (t, $J=7.1$ Hz, 3H); EIMS *m*/*z* 332 (M^+-CO_2H), 276, 232, 203, 115, 91, 57; HRMS found *m*/*z* 332.1838 (M^+-CO_2H), $C_{19}H_{26}NO_4$ require 332.1862.

3.6. (2R,1′R,2′R,3′S)-2-(2′-Benzyl-3′-carboxycyclopropyl)glycine **13**

A solution of **12** (40 mg, 0.106 mmol) in 0.5 mL of 1N NaOH was stirred at room temperature for 24 h. After the solution was acidified with 10% citric acid, it was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography to give the corresponding dicarboxylic acid, which was dissolved in 2 mL of methylene chloride. To this stirring solution gaseous hydrochloride was introduced for a few minutes before the mixture was stirred at room temperature for 3 h. The suspension solution was extracted with water and the combined aqueous layers were washed with methylene chloride. The aqueous layer was concentrated to dryness in vacuo affording 16 mg (100%) of **13**. $[\alpha]_D^{20}=-24$ (*c* 0.14, 6N HCl); ^{1}H NMR (300 MHz, D_2O) δ 7.34 (m, 2H), 7.26 (m, 3H), 4.22 (d, $J=10.4$ Hz, 1H), 2.97 (dd, $J=14.4$, 6.3 Hz, 1H), 2.88 (dd, $J=14.4$, 7.1 Hz, 1H), 2.15 (dt, $J=12.8$, 6.4 Hz, 1H), 2.03 (dd, $J=7.8$, 5.5 Hz, 1H), 1.85 (m, 1H); ESIMS *m*/*z* 250 (M^++H^+).

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