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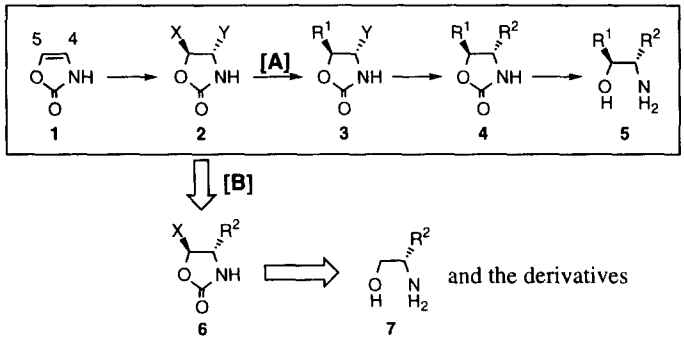
# Chiral Electrophilic "Glycinal" Equivalents. New Synthons for Optically Active α-Amino Acids and 4-Substituted 2-Oxazolidinones

**Hirofumi Matsunaga, Tadao Ishizuka and Takehisa Kunieda***

*Faculty of Pharmaceutical Sciences, Kumamoto University*
*5-1 Oe-honmachi, Kumamoto 862, Japan*

***Abstract:*** The thermal reaction of 3-[(*1S*)-2-alkoxy-1-apocamphanecarbonyl]-2-oxazolones (**21a-c**) with dialkyl azodicarboxylates (**9**) results in exclusive formation of [4 + 2] type cycloadducts (**22** and **23**) with moderate levels of diastereofacial selection (up to 72% d.e.). The diastereomers thus obtained were readily purified and subsequent treatment with acidic methanol followed by removal of the auxiliary with $LiBH_4$/MeOH (1:2) gave optically pure 4-methoxy-5-hydrazino-2-oxazolidinones (**26** and **27**), which serve as α-aminoaldehyde templates useful for the synthesis of a wide variety of optically active α-amino acids as well as 4-alkyl and 4-aryl-2-oxazolidinones.


Recently we have developed a promising methodology for the versatile synthesis of 2-amino alcohols which involves highly regio- and stereoselective introduction of easily replaceable groups (X and Y) at the 4,5-olefinic moiety of the 2-oxazolone (**1**) followed by stereospecific and stepwise substitution with appropriate groups as key steps (Scheme 1).[2]



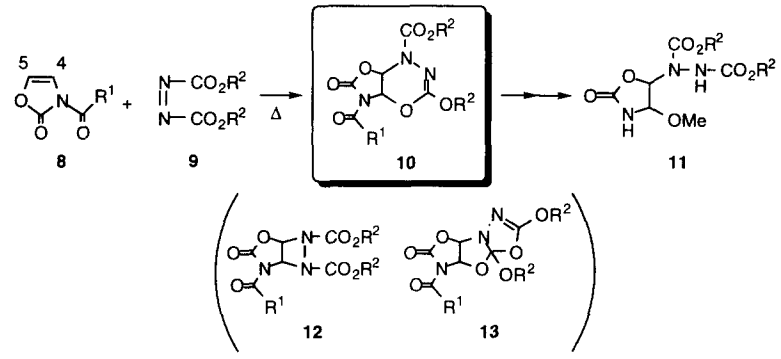

**Scheme 1**

Versatility of this method would be further improved by developing a new class of chiral synthons (**2**) which permit stereospecific substitution of Y-group prior to the replacement of X-substituents (route B).

This paper describes synthetic potential of such synthons obtainable from chiral *N*-acyl-2-oxazolones such as **21** and azodicarboxylates (**9**) with emphasis on chiral synthesis of α-amino acids[3] and 4-substituted 2-oxazolidinones.

## RESULTS AND DISCUSSION

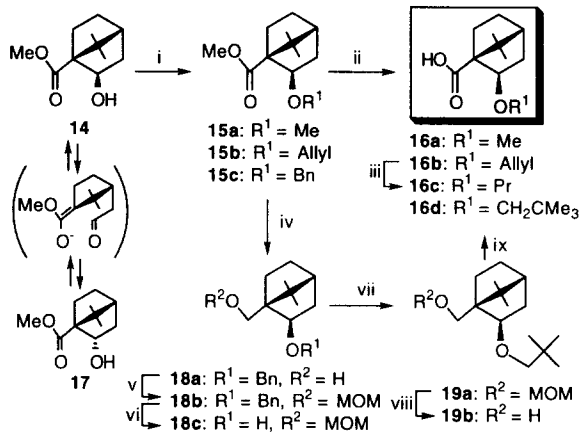
With our continuing interest in the synthetic potential of 2-oxazolone as a building block, we have explored its dienophilic ability[4,5] in cycloaddition reactions with dialkyl azodicarboxylates.[6-9] The thermal cycloadditions of *N*-acyl-2-oxazolones (**8**) to azodicarboxylates (**9**) were found to proceed smoothly under mild conditions (80 °C for 8h) to give the regio-controlled [4 + 2] cycloadducts (**10**) exclusively, though there exist two other possible addition modes:[6-8] neither diazetidine (**12**) (1,2-addition) nor isoxazolidines (**13**) (1,3-addition) were detected (Scheme 2). Thus, reaction of *N*-pivaloyl- and *N*-benzoyl-2-oxazolones with diethyl azodicarboxylate gave nearly 90% yield of the cycloadducts (**10**), which upon subsequent treatment with acidic methanol, followed by deacylation gave *trans*-4-methoxy-5-hydrazino-2-oxazolidinones (**11**) exclusively. The 2-oxazolidinone thus formed serves as an electrophilic glycinal equivalent which would be expected to smoothly undergo stereospecific substitution of the 4-methoxy groups by a variety of alkyl and aryl nucleophiles producing α-amino aldehyde derivatives.




**Scheme 2**

***Preparation of Chiral Carboxylic Acid Auxiliaries:*** A series of (1*S*,2*R*)-2-alkoxy-1-apocamphanecarboxylic acids (**16a,c,d**) having different alkoxy substituent in size were prepared as chiral auxiliaries by standard procedures. Thus, methyl (1*S*)-2-*exo*-hydroxy-1-apocamphanecarboxylate (**14**),[10] prepared by the reduction of methyl (1*S*)-ketopinate with L-Selectride®, was smoothly alkylated with methyl and allyl halides to give the 2-methoxy and 2-allyloxy derivatives (**15a** and **15b**), while *O*-alkylation with neopentyl iodide resulted in the mixture of 2-*exo* and 2-*endo*-alkoxy derivatives (**14** and **17**) as a result of partial *retro*-aldol type cleavage followed by reclosure.[10] The neopentyloxy derivative (**16d**) was cleanly prepared by a lengthy, alternative route involving hydroxyl protection *via* **18** and **19** (Scheme 3).

***Diastereoselective [4 + 2] Cycloaddition:***[1] Optically active 3-[(1*S*)-2-*exo*-alkoxy-1-apocamphanecarbonyl]-2-oxazolones (**21a-c**) were readily prepared by treatment of the lithium salts derived from the carboxylic acids with DPPOx[11] (**20**).




i) $R^1X$, NaH; ii) KOH, EtOH; iii) Pd-C, $H_2$; iv) $LiAlH_4$; v) MOMCl, NaH; vi) Pd-C, $H_2$; vii) $Me_3CCH_2I$, NaH; viii) HCl/MeOH; ix) 1) PCC, 2) $KMnO_4$.

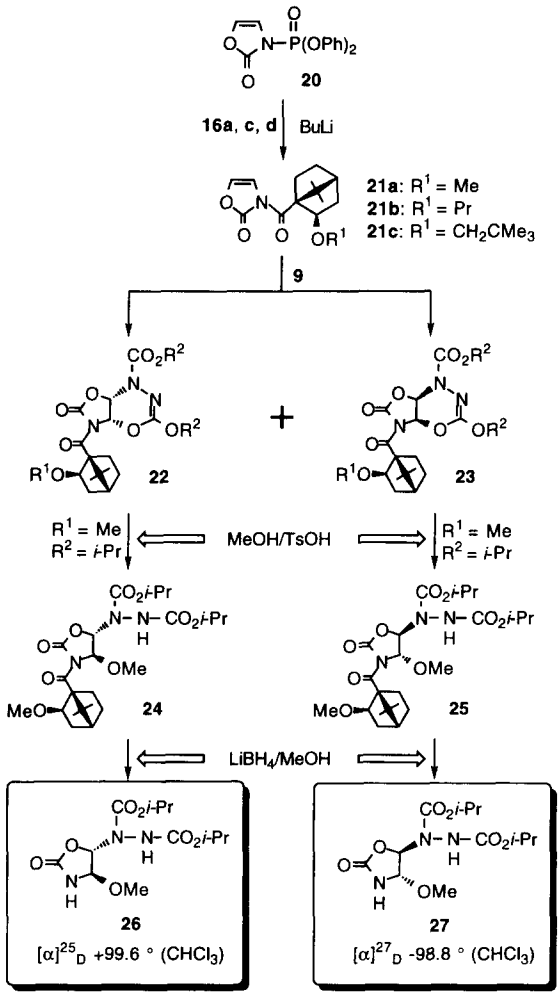
**Scheme 3**

Treatment of 3-[(1*S*)-2-*exo*-alkoxy-1-apocamphanecarbonyl]-2-oxazolones (**21**) with a series of azodicarboxylates (**9**) in benzene under reflux resulted in excellent yields of a diastereomeric mixture of cycloadducts (**22** and **23**), in which the former was the major isomer in moderate diastereoselectivity (Table 1).

**Table 1. Diastereomeric Ratios Obtained from [4 + 2] Cycloaddition of *N*-Acyl-2-oxazolones (21a-c) to Azodicarboxylates (9)[a]**

| $R^2$ | $R^3$ | Time (h) | Yield (%)[b] | **22** : **23**[c] |
|---|---|---|---|---|
| Me | Me | 6 | 83 | 1.9 : 1 |
| Pr | Me | 6 | 77 | 2.9 : 1 |
| $CH_2CMe_3$ | Me | 12 | 83 | 5.3 : 1 |
| Me | Et | 6 | 93 | 2.6 : 1 |
| Pr | Et | 9 | 76 | 3.4 : 1 |
| $CH_2CMe_3$ | Et | 17 | 92 | 5.3 : 1 |
| Me | *i*-Pr | 12 | 93 | 3.2 : 1<br>(4.9 : 1)[d] |
| Pr | *i*-Pr | 12.5 | 76 | 3.6 : 1 |
| $CH_2CMe_3$ | *i*-Pr | 19 | 85 | 5.7 : 1 |
| Pr | Bzl | 6 | 86 | 4.6 : 1 |
| $CH_2CMe_3$ | Bzl | 18 | 93 | 6.2 : 1 |

[a] The reaction was performed in refluxing benzene. [b] Isolated yields.
[c] Determined based on $^1$H-NMR (400 MHz) analysis. [d] Under UV-irradiation at room temperature.




**Scheme 4**

As was previously reported for *N*-apocamphanecarbonylated-2-oxazolidinones,[2a,12] the isomeric cycloadducts (**22** and **23**) were easily and efficiently separated by chromatography on silica gel. An $^1$H NMR analysis indicated that the isolated cycloadducts were 1,4-addition products. In addition, X-ray crystallographic analysis of the key adduct **23** ($R^1 = R^2 = Me$) provided unequivocal proof of the [4 + 2] addition structure.[1]

The use of bulky groups for $R^1$ and $R^2$ improved the diastereoselectivity. Thus, the highest selectivity of 72% d.e. was achieved when 2-neopentyloxy-1-apocamphanecarbonyl-oxazolone was reacted with dibenzyl azodicarboxylate. The UV-irradiation with a Hg-lamp (400W) at room temperature also promoted the cycloaddition[8c,9] and gave a slightly higher diastereoselectivity than that obtained in benzene under reflux. The transition state assembly as illustrated in Figure 1 might be responsible for this diastereofacial selectivity.

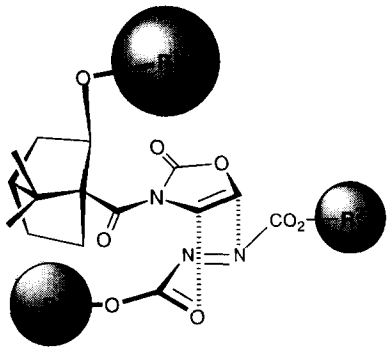
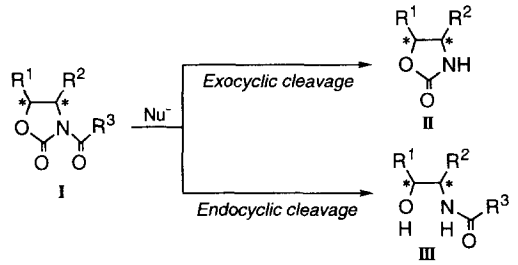


**Figure 1.** Favored orientation for cycloaddition of **21** to **9.**

***Exocyclic Deacylation:***[1] The cycloadduct **22** was ring-opened with a catalytic amount of *p*-toluenesulfonic acid in methanol within a few minutes to form *trans*-4-methoxy-2-oxazolidinone (**24**), but the removal of the sterically congested *N*-acyl auxiliaries was unsatisfactory due to low reactivity and accompanying endocyclic cleavage as far as conventional reagents[2a,13] including lithium benzylmercaptide[13g] and lithium hydroperoxide[13f] were concerned.




**Scheme 5**

The exocyclic selective cleavage of sterically hindered *N*-acyl-2-oxazolidinones was extensively explored because the nondestructive recovery of the 2-oxazolidinones from the *N*-acyl-derivatives would be an important requirement of this class of transformation (Scheme 5). As shown in Table 2, the reductive species derived from $LiBH_4$/MeOH (1:2) was found to be exceptionally effective for the exocyclic deacylation of **24**. This is in contrast to previous findings[13a,c,d] which reported that some reducing agents preferentially attacked the *endo*-carbonyl groups, resulting in the destruction of 2-oxazolidinone rings. Thus, treatment of *N*-acyl-2-oxazolidinones (**24**) with $LiBH_4$/MeOH gave a 70% yield of (4*R*, 5*S*)-*trans*-4-methoxy-5-hydrazino-2-oxazolidinone (**26**) in addition to 2-methoxy-1-apocamphane-methanol.[14] The addition of methanol is critical for the selective exocyclic cleavage and, otherwise, **26** was obtained only in poor yield (Table 2). The optimal ratio of $LiBH_4$:MeOH was 1 to 2, and a combination of $NaBH_4$, LiCl and MeOH in a molar ratio of 2:2:1 was also effective. Methoxyborane complexes generated *in situ* might serve as active species having the appropriate nucleophilicity to attack the exocyclic carbonyl groups.[15]

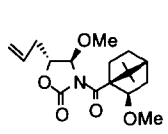
The generality of this procedure is demonstrated by highly selective *exo*-cleavage of other sterically congested examples such as **28**[2a], **29**[5a], **30**[5b] and **31**[16]. Among the reagents examined, the combination of $LiBH_4$ and MeOH was the reagent of choice to give the most selective results (Table 3).

**Table 2. Exocyclic Deacylation of *N*-Acyl-2-oxazolidinone (24) to 26**

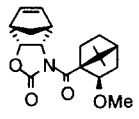
| Reagents (equiv.) | Temp/Time | Yield (%)[a] |
|---|---|---|
| **$LiBH_4$ (8), MeOH (16)** | **0 °C/2.5h** | **70** |
| $NaBH_4$ (20), LiCl (20), MeOH (10) | 0 °C/24h | 68 |
| $LiBH_4$ (8) [13d] | 0 °C → r.t./2h | 21 |
| $PhCH_2OLi$ (1.5) [13a] | 0 °C → r.t./2h | 11 |
| $PhCH_2SLi$ (1.5) [13g] | 0 °C/2h | 23 |
| $Bu_2CuLi$ (8) [2a] | -30 °C → 0 °C/1h | 16 |
| $H_2O_2$ (8), LiOH (2) [13f] | 0 °C/6h | 23 |

[a] Isolated yields after almost complete consumption of **24**.

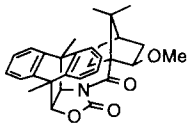
**Table 3. Exocyclic Deacylation of Sterically Congested *N*-Acyl-2-oxazolidinones (28-31)[a]**



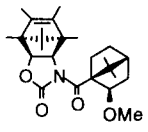

**28**




**29**




**30**




**31**

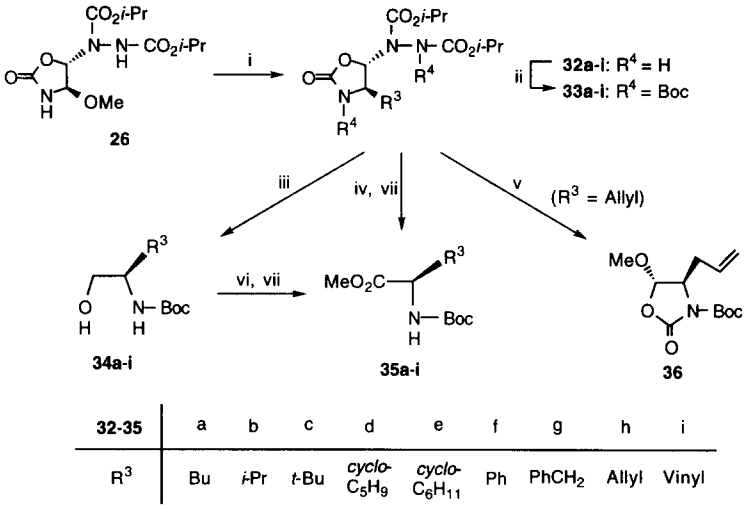
| | Yield (%) | | | |
|---|---|---|---|---|
| Reagents[b] | **28** | **29** | **30** | **31** |
| $LiBH_4$-MeOH (1:2) | 85 | 84 | 91 (9) | 82 |
| $PhCH_2SLi$ [13g] | 83 | 91 | 5 (90) | 0 (100) |
| $PhCH_2OLi$ [13a] | 28 | 13 (85) | | |
| LiOOH [13f] | 51 | 20 (68) | | |
| $LiBH_4$ [13d] | 62 | 20 (59) | | |

[a] Isolated yields. Yields recovered unchanged are given in parentheses. [b] Performed as given in Table 2.

The minor cycloadduct **23** was analogously treated to give (4*S*, 5*R*)-4-methoxy-5-hydrazino-2-oxazolidinone (**27**), enantiomer of **26** in 78% yield. Both enantiomers of the 2-oxazolidinones **26** and **27** have synthetic potential as chiral electrophilic "glycinal" equivalents, whose applications to α-amino acids and the derivatives are given below.

***Preparation of Optically Pure α-Amino Acids:*** The readily accessible isopropyl ester **26** was employed as chiral synthon for a variety of (*R*)-α-amino acids and β-amino alcohols (Scheme 4). The chiral "α-methoxyglycinal" equivalent **26** was treated with organocuprates in the presence of $BF_3$•$OEt_2$ to undergo a smooth replacement of the methoxy group with a wide variety of 1°-3° alkyl, aryl and alkenyl groups with full retention of configuration.[2b,17] Thus, *trans*-4-substituted-2-oxazolidinones (**32**) were formed exclusively with

no contamination with *cis*-isomers. Table 4 shows the results of typical $BF_3$-promoted substitution with organocuprates and allylsilane.[1]




| 32-35 | a | b | c | d | e | f | g | h | i |
|---|---|---|---|---|---|---|---|---|---|
| $R^3$ | Bu | *i*-Pr | *t*-Bu | *cyclo*-$C_5H_9$ | *cyclo*-$C_6H_{11}$ | Ph | $PhCH_2$ | Allyl | Vinyl |

i) See Table 4; ii) $(Boc)_2O$, $NEt_3$, DMAP/$CH_2Cl_2$; r.t., 4h; iii) $NaBH_4$ (4 eq.)-MeOH (4 eq.)/EtOH; r.t., 24h; iv) KOH (20 eq.), $KMnO_4$ (40 eq.)/*t*-BuOH-$H_2O$ (2:1); r.t., 17-23h; v) $Cs_2CO_3$ (0.1 eq.)/MeOH; r.t., 2h; vi) PDC (15 eq.)/DMF; r.t., 6h; vii) $CH_2N_2$

**Scheme 6**

**Table 4. $BF_3$-Promoted Substitution of 4-Methoxy-2-oxazolidinone (26) to 32[a]**

| Reagents (equiv.) | $R^3$ | Yield (%)[b] |
|---|---|---|
| $Bu_2CuLi$ (4) | Bu | 79 (81) |
| *i*-PrCuCNMgBr (4), LiCl (8.8) | *i*-Pr | 85 (100) |
| (*t*-Bu)$_2$CuCN(MgBr)$_2$ (4) | *t*-Bu | 75 (87) |
| *cyclo*-$C_5H_9$CuCNMgBr (4), LiCl (8.8) | *cyclo*-$C_5H_9$ | 80 (80) |
| *cyclo*-$C_6H_{11}$CuCNMgBr (4), LiCl (8.8) | *cyclo*-$C_6H_{11}$ | 84 (90) |
| PhCuCNMgBr (4), LiCl (8.8) | Ph | 85 (99) |
| $(PhCH_2)_2CuCN(MgCl)_2$ (4) | Bzl | 79 (92) |
| $CH_2$=$CHCH_2$-$SiMe_3$ (4) | Allyl | 90 (90)[c] |
| $(CH_2$=$CH)_2CuCN(MgBr)_2$ (4) | Vinyl | 72 (95) |

[a] Performed at -30 °C. [b] Yields and trans stereochemistry were determined by $^1$H-NMR (400MHz) analysis. The values in parentheses are corrected yields based on consumed starting material. [c] Performed at -78 °C → r.t..

A Boc group made the 2-oxazolidinone rings more susceptible to nucleophilic attack to lead to ring-opening under mild conditions.[18] Thus, 3-Boc-2-oxazolidinones (**33**) were readily cleaved by borohydride reduction in MeOH to give good yields of (*R*)-*N*-Boc-2-amioalcohols (**34**) with no racemization (Table 5). Subsequent treatment with pyridinium dichromate (PDC) resulted in the smooth formation of optically pure (*R*)-*N*-Boc-α-amino acid methyl esters (**35**) (Table 5).

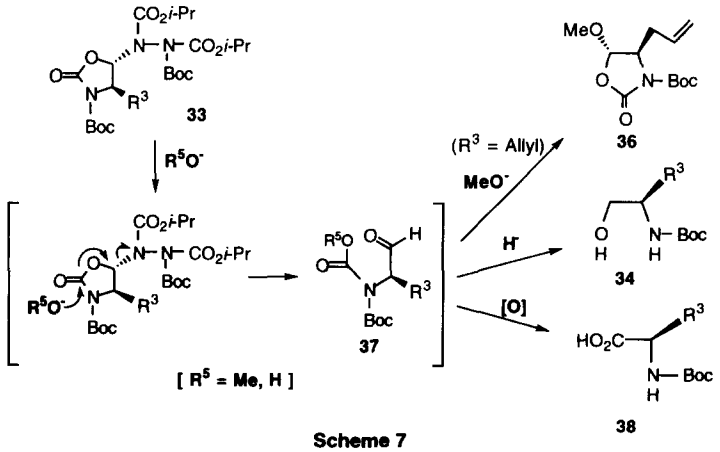
Direct conversion of **33** to optically active α-amino acid methyl esters (**35**) was readily achieved by treatment with $KMnO_4$ under basic conditions (Table 5).

**Table 5. Conversion of *N*-Boc-2-Oxazolidinones (33) to Optically Pure (*R*)-*N*-Boc-2-Aminoalcohols (34) and (*R*)-*N*-Boc-α-Amino Acid Methyl Esters (35)[a]**

| | $R^3$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compounds | Bu | *i*-Pr | *t*-Bu | *cyclo*-$C_5H_9$ | *cyclo*-$C_6H_{11}$ | Ph | $PhCH_2$ | Allyl | Vinyl |
| **34** | 80% | 74% | 78% | 74% | 74% | 76% | 75% | 71% | 75% |
| **35** | 81 | 92 | 82 | 82 | 81 | - | 54 | - | - |
| **35 (from 34)** | 86 | 89 | 92 | 66 | 66 | 60 | 88 | 82 | - |

[a] Isolated yields.

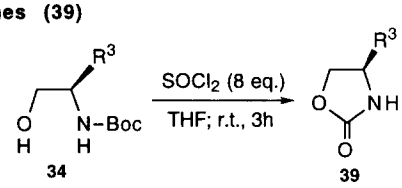
The ring-cleavage of **33** under basic conditions would be expected to proceed *via* nucleophilic attack at the C-2 carbonyl group on the oxazolidinone ring, followed by the elimination of the hydrazino group to give α-aminoaldehydes (**37**). As shown in Scheme 7, reductive and oxidative treatments of **33** give 2-aminoalcohols (**34**) and α-amino acids (**38**), respectively. The intervention of α-aminoaldehydes (**37**) as intermediates is suggested by the fact that *trans*-5-methoxy-2-oxazolidinone (**36**) is readily formed on treatment of **33** with $Cs_2CO_3$ in MeOH.




**Scheme 7**

***Preparation of 4-Substituted 2-Oxazolidinones:*** Treatment of (*R*)-*N*-Boc-2-aminoalcohols(**34**) with thionyl chloride in THF gave quantitative yields of (*R*)-4-substituted-2-oxazolidinones (**39**), which served as Evans' type chiral auxiliaries[19] (Table 6).

**Table 6. Conversion of (*R*)-*N*-Boc-2-Aminoalcohols (34) to (*R*)-4-Substituted-2-oxazolidinones (39)**




34 39

| $R^3$ | Yield (%)[a] | $[\alpha]_D$ | Lit. $[\alpha]_D$ |
|---|---|---|---|
| *i*-Pr | 100 | +17.5 ° (EtOH) | -16.6 ° (EtOH)[b] |
| *t*-Bu | 100 | +21.8 ° (MeOH) | +22.8 ° (MeOH)[c] |
| Ph | 100 | -56.7 ° ($CHCl_3$) | -57.1 ° ($CHCl_3$)[c] |
| $PhCH_2$ | 100 | +63.0 ° ($CHCl_3$) | +62.5 ° ($CHCl_3$)[c] |

[a] Isolated yields. [b] (4*S*)-Form. See ref. 20. [c] See ref. 12.

## CONCLUSION

This article has further demonstrated the synthetic potential of simple heterocycle 2-oxazolone as a building block. Both enantiomers of *trans*-4-methoxy-5-hydrazino-2-oxazolidinones (**26** and **27**), which are readily available from regio- and diastereoselective [4 + 2] cycloaddition of chiral *N*-(2-*exo*-alkoxy-1-apocamphanecarbonyl)-2-oxazolones with azodicarboxylates, serve well as new class of chiral synthons for a wide variety of α-amino acids and 4-substituted-2-oxazolidinones. The chiral 2-oxazolidinones of type **33** can serve as precursors for optically active "α-aminoaldehyde" useful in aldol condensations and Wittig reactions as well. This will be a subject of a separate paper.

## EXPERIMENTAL SECTION

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP 370 polarimeter. $^1H$ NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard on a JEOL ALPHA 500 (500 MHz), JEOL JNM-GX400 (400 MHz), Hitachi R-24B (60 MHz) and Hitachi R-1200 (60 MHz) spectrometers. Infrared spectra were measured with a JASCO IR Report-100 spectrometer. MS and HRMS (EI or CI) were obtained with a JEOL JMS-DX303HF mass spectrometer.

Column chromatography was performed using silica gel 60 (70-230 mesh, Merck). All the solvents were distilled before use; THF over Na/benzophenone, $Et_2O$ over $LiAlH_4$, $CH_2Cl_2$ over $CaH_2$, MeOH over NaOMe and benzene over $CaH_2$.

Azodicarboxylates were purchased from Tokyo Kasei and Aldrich and used without further purification.

**3-Pivaloyl-2-oxazolone (8; $R^1$ = $CMe_3$).** A mixture of 2-oxazolone (7.5 g, 88.1 mmol) and pivaloyl chloride (10.6 g, 88.1 mmol) in $CH_2Cl_2$ (200 mL) was stirred in the presence of $NEt_3$ (8.9 g, 88.1 mmol) at 0 °C for 10 h. The solution was passed through a silica gel-pad (EtOAc as eluent) and purified by chromatography on silica gel (hexane-$CH_2Cl_2$ (8:2) to $CH_2Cl_2$) to give *N*-pivaloyl-2-oxazolone (10.3 g, 69%) as a colorless oil; $^1H$ NMR (60 MHz, $CDCl_3$) δ 1.43 (9H, s), 6.78 (1H, d, *J* = 2.2 Hz), 7.23 (1H, d, *J* = 2.2 Hz).

**3-Benzoyl-2-oxazolone (8; $R^1$ = Ph).**[21] Analogously as above, this compound was obtained quantitatively as colorless crystals, mp 79-80 °C (from $CH_2Cl_2$-hexane); $^1H$ NMR (60 MHz, $CDCl_3$) δ 6.84 (1H, d, *J* = 2.2 Hz), 7.22 (1H, d, *J* = 2.2 Hz), 7.35-7.85 (5H, m).

**(*1S,2R*)-2-Methoxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid [(*1S,2R*)-2-methoxy-1-apocamphanecarboxylic acid; MAC acid] (16a).** Methyl (*1S,2R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate[10] **(14)** (4.3 g, 21.5 mmol) was methylated with MeI (12.2 g, 85.9 mmol) and NaH (60% in oil; 2.1 g, 51.5 mmol) in THF (47.5 mL) at room temperature for 2 h. The excess of NaH was quenched with $H_2O$ (10 mL) at 0 °C and EtOAc (200 mL) was added. The whole was washed (brine, 50 mL × 3), dried ($Na_2SO_4$) and evaporated *in vacuo* to give the methoxy ester **15a** as an oil, which was saponified with KOH (24.1 g, 0.4 mol) in refluxing EtOH (123 mL) and $H_2O$ (2 mL) for 1 h. The usual work-up, followed by column chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (8:2)) gave **16a** (3.4 g, 80%) as colorless crystals, mp 85-85.5 °C (from hexane); $[\alpha]^{26}_D$ -82.5 ° (*c* 1.10, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, s), 1.10-1.13 (1H, m), 1.17 (3H, s), 1.26-1.33 (1H, m), 1.75-1.93 (3H, m), 1.96-2.02 (1H, m), 2.34-2.41 (1H, m), 3.40 (3H, s), 3.67 (1H, dd, *J* = 3.3, 7.3 Hz), 11.1 (1H, br). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.42; H, 8.93.

**(*1S,2R*)-2-Allyloxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (16b).** Similarly, **14** (2.0 g, 10 mmol) with allyl bromide (24.2 g, 0.2 mol) gave methyl (*1S,2R*)-2-allyloxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate **(15b)** (2.2 g, 90%) as a colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.03-1.30 (1H, m), 1.31 (3H, s), 1.41-1.56 (1H, m), 1.64-1.82 (3H, m), 1.86-2.06 (2H, m), 3.68 (3H, s), 3.72 (1H, dd, *J* = 3.7, 7.7 Hz), 3.87 (1H, ddt, *J* = 1.5, 5.1, 13.6 Hz), 3.97 (1H, ddt, *J* = 1.5, 5.1, 13.6 Hz), 5.10 (1H, dq, *J* = 1.5, 3.3 Hz), 5.21 (1H, dq, *J* = 1.8, 3.7 Hz), 5.77-5.86 (1H, m).

The methyl ester **15b** (9.4 g, 39.3 mmol) was heated in EtOH (250 mL) and $H_2O$ (6.3 mL) under reflux for 1 h in the presence of KOH (44.1 g, 0.8 mol). The usual work-up, followed by chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (9:1)) afforded a quantitative yield of **16b** (8.8 g) as a colorless oil; $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.90-2.55 (7H, m), 1.05 (3H, s), 1.23 (3H, s), 3.65-3.92 (1H, m), 3.92-4.25 (2H, m), 5.03-5.47 (2H, m), 5.6-6.22 (1H, m), 11.2 (1H, br).

**(*1S,2R*)-2-Propoxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (16c).** A solution of **16b** (8.8 g, 39.3 mmol) in MeOH (100 mL) was stirred in the presence of 10% Pd-C (0.88 g) under a hydrogen atmosphere at room temperature for 12 h. Removal of the catalyst followed by concentration *in vacuo* gave a quantitative yield of **16c** (8.9 g) as a colorless oil; $[\alpha]^{24}_D$ -85.2 ° (*c* 1.08, $CHCl_3$); $^1H$ NMR

(400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.04 (3H, s), 1.06-1.15 (1H, m), 1.18 (3H, s), 1.23-1.28 (1H, m), 1.62-1.69 (2H, m), 1.77-1.81 (1H, m), 1.83-1.91 (2H, m), 1.97-2.02 (1H, m), 2.41-2.47 (1H, m), 3.42 (1H, dt, *J* = 6.1, 9.2 Hz), 3.59 (1H, dt, *J* = 6.1, 9.2 Hz), 3.76 (1H, dd, *J* = 3.1, 7.3 Hz), 11.20 (1H, br s).

**(*1R,2R*)-2-Benzyloxy-7,7-dimethylbicyclo[2.2.1]heptane-1-methanol (18a).** Similar procedure as **15a**, **14** (3.5 g, 17.7 mmol) with benzyl bromide (12.1 g, 70.8 mmol) and NaH (60% in oil; 1.7 g, 42.5 mmol) gave methyl (*1S,2R*)-2-benzyloxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate **(15c)** (5.6 g, quant.) as a colorless oil, which was treated with $LiAlH_4$ (1.3g, 35.4 mmol) in $Et_2O$ (52 mL) at 0 °C, quenched with $H_2O$ (10 mL) and acidificated with HCl. Product was extracted (EtOAc, 100 mL × 3), washed (brine, 50 mL × 3) and dried ($Na_2SO_4$). Evaporation *in vacuo* followed by column chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (9:1)) gave **18a** (3.6 g, 78%) as a colorless oil; $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.78-2.13 (7H, m), 0.92 (3H, s), 1.23 (3H, s), 2.29 (1H, br), 3.51-3.89 (3H, m), 4.38 (1H, d, *J* = 11.6 Hz), 4.50 (1H, d, *J* = 11.6 Hz), 7.23 (5H, s).

**(*1R,2R*)-2-Benzyloxy-1-methoxymethoxymethyl-7,7-dimethylbicyclo[2.2.1]heptane (18b).** The alcohol **18a** (3.6 g, 13.7 mmol) was treated with chloromethyl methyl ether (4.4 g, 54.9 mmol) and NaH (60% in oil; 1.3 g, 32.9 mmol) in DMF (41.4 mL) at room temperature for 2 h. The usual work-up, followed by chromatography on silica gel (hexane-$CH_2Cl_2$ (5:5 to 1:9) with 0.5% $NEt_3$) gave **18b** (3.4 g, 80%) as a colorless oil; $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.80-2.20 (7H, m), 0.89 (3H, s), 1.09 (3H, s), 3.28 (3H, s), 3.28-3.70 (1H, m), 3.48 (1H, d, *J* = 9.4 Hz), 3.79 (1H, d, *J* = 9.4 Hz), 4.56 (2H, s), 4.34-4.69 (2H, m), 7.21 (5H, s).

**(*1R, 2R*)-2-[(2,2-Dimethylpropyl)oxy]-1-methoxymethoxymethyl-7,7-dimethylbicyclo-[2.2.1]heptane (19a).** A solution of **18b** (3.0 g, 9.9 mmol) in MeOH (31.4 mL) was shaken in the presence of 10% Pd-C (0.946 g) in an atmosphere of hydrogen (1.7 kg/cm$^2$) at room temperature for 22 h. Purification of the product by chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (8:2) with 0.5% $NEt_3$) gave (*1R,2R*)-2-hydroxy-1-methoxymethoxymethyl-7,7-dimethylbicyclo[2.2.1]heptane **(18c)** (2.0 g, 96%) as a colorless oil; $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.80-1.90 (7H, m), 0.87 (3H, s), 1.14 (3H, s), 2.90 (1H, d, *J* = 2.4 Hz), 3.36 (3H, s), 3.64 (1H, d, *J* = 9.8 Hz), 3.70-4.06 (1H, m), 3.74 (1H, d, *J* = 9.8 Hz), 4.60 (2H, s).

The mixture of **18c** (2.0 g, 9.5 mmol) and NaH (0.7 g, 28.5 mmol) in *N*-methyl-2-pyrrolidinone (7 mL) was stirred at room temperature for 1 h. To this solution was added 1-iodo-2,2-dimethylpropane (9.4 g, 47.6 mmol), followed by heating at 100-110 °C for 3 h. The usual work-up, followed by chromatography on silica gel (hexane-$CH_2Cl_2$ (5:5 to 1:9) with 0.5% $NEt_3$) afforded **19a** (2.0 g, 75%) as a colorless oil; $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.88 (12H, s), 0.90-2.00 (7H, m), 1.04 (3H, s), 2.89 (1H, d, *J* = 8.2 Hz), 2.98 (1H, d, *J* = 8.2 Hz), 3.31 (3H, s), 3.35-3.58 (1H, m), 3.48 (1H, d, *J* = 9.4 Hz), 3.69 (1H, d, *J* = 9.4 Hz), 4.57 (2H, s).

**(*1R,2R*)-2-[(2,2-Dimethylpropyl)oxy]-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acid ((*1S,2R*)-2-neopentyloxy-1-apocamphanecarboxylic acid) (16d).** Compound **19a** (1.6 g, 5.7 mmol) was dissolved in MeOH (20 mL) saturated with anhydrous HCl and the mixture was stirred for 5 min at room temperature. Evaporation, followed by chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$:EtOAc (9:1)) yielded (*1R,2R*)-2-[(2,2-dimethylpropyl)oxy]-1-hydroxymethyl-7,7-dimethylbicyclo[2.2.1]heptane **(19b)** (1.3 g, 97%) as a colorless oil; $^1H$ NMR (60 MHz, $CDCl_3$) δ 0.89 (12H, s), 0.95-2.02 (7H, m), 1.20 (3H, s), 2.90 (1H, br s), 2.91 (1H, d, *J* = 8.0 Hz), 3.06 (1H, d, *J* = 8.0 Hz), 3.38-3.90 (3H, m).

The alcohol **(19b)** (1.3 g, 5.6 mmol) was oxidized with PCC (pyridinium chlorochromate; 2.4 g, 11.1 mmol) in $CH_2Cl_2$ (11.4 mL) at room temperature for 4 h. $Et_2O$ (11.4 mL) was added and the mixture was filtered through a short silica gel column (EtOAc as eluent). After concentration *in vacuo*, acetone (12.1 mL) and aqueous $KMnO_4$ solution (1.1 g, 6.7 mmol) were added and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched with 30% HCHO solution (8 mL) and then stirred at room temperature for 30 min. The precipitate was filtered off and the filtrate was acidified, extracted (EtOAc; 100 mL × 2), washed (brine, 45 mL × 3) and dried ($Na_2SO_4$). Evaporation *in vacuo* followed by chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (8:2)) yielded **16d** (1.1 g, 77%) as colorless crystals, mp 106.0 °C (from hexane); $[\alpha]^{25}_D$ -88.7 ° (*c* 0.59, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.95 (9H, s), 1.05 (3H, s), 1.13-1.17 (1H, m), 1.19 (3H, s), 1.23-1.29 (1H, m), 1.7 (1H, dd, *J* = 7.3, 13.2 Hz), 1.85-1.99 (3H, m), 2.41-2.47 (1H, m), 3.12 (1H, d, *J* = 8.4 Hz), 3.2 (1H, d, *J* = 8.4 Hz), 3.74 (1H, dd, *J* = 3.3, 7.3 Hz). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.08; H, 10.41.

**[(1*S*)-2-Alkoxy-1-apocamphanecarbonyl]-2-oxazolones (21a-c): General Procedure.** To a solution of (*1S,2R*)-2-alkoxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acids (**16**) in THF was added BuLi (1.0 eq. in hexane) at -78 °C. After stirring for 30 min, DPPOx[11] (**20**) (diphenyl 2-oxo-3-oxazolinylphosphonate; 1.0 eq.) in THF was added at -78 °C and the mixture was stirred at 0 °C for 5 h. The solution was passed through a silica gel-pad (EtOAc as eluent) and the products were purified by column chromatography on silica gel (hexane-$CH_2Cl_2$ (1:1) to $CH_2Cl_2$).

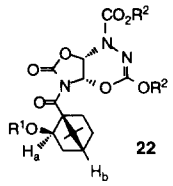
**[(*1R,2R*)-2-Methoxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carbonyl]-2-oxazolone (21a):** 91% yields as colorless crystals, mp 77.5-78 °C (from hexane); $[\alpha]^{30}_D$ -58.0 ° (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.14 (1H, s), 1.17-1.21 (1H, m), 1.32 (3H, s), 1.61-1.93 (5H, m), 2.39-2.43(1H, m), 3.18 (3H, s), 4.61 (1H, dd, *J* = 3.7, 7.7 Hz), 6.78 (1H, d, *J* = 2.2 Hz), 7.29 (1H, d, *J* = 2.2 Hz). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.32; H, 7.18; O, 5.39.

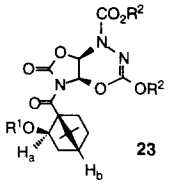
**[(*1R,2R*)-2-Propoxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carbonyl]-2-oxazolone (21b):** 70% yields as a colorless oil; $[\alpha]^{30}_D$ -55.5 ° (*c* 0.94, $CHCl_3$); $^1H$ NMR (400MHz, $CDCl_3$) δ 0.76 (3H, t, *J* = 7.3 Hz), 1.15 (3H, s), 1.16-1.20 (1H, m), 1.33 (3H, s), 1.37-1.45 (2H, m), 1.67-1.71 (2H, m), 1.79-1.92 (3H, m), 2.40-2.46 (1H, m), 3.11 (1H, dt, *J* = 6.7, 9.2 Hz), 3.38 (1H, dt, *J* = 6.7, 9.2 Hz), 4.63 (1H, q, *J* = 3.7 Hz), 6.77 (1H, d, *J* = 1.8 Hz), 7.28 (1H, d, *J* = 1.8 Hz); MS (EI): m/z 293 ($M^+$), 209 ([M-84]$^+$); HRMS (EI) Calcd for $C_{16}H_{23}NO_4$ ($M^+$): m/z 293.1627, found: m/z 293.1601.

**[(*1R,2R*)-2-[(2,2-Dimethylpropyl)oxy]-7,7-dimethylbicyclo[2.2.1]heptane-1-carbonyl]-2-oxazolone (21c):** 79% yields as colorless crystals, mp 51.0-51.5 °C (from hexane); $[\alpha]^{24}_D$ -55.0 ° (*c* 1.00, $CHCl_3$); $^1H$ NMR (400MHz, $CDCl_3$) δ 0.74 (9H, s), 1.17 (3H, s), 1.20-1.22 (1H, m), 1.31 (3H, s), 1.63-1.70 (2H, m), 1.82-1.87 (3H, m), 2.41-2.46 (1H, m), 2.76 (1H, d, *J* = 8.1 Hz), 3.07 (1H, d, *J* = 8.1 Hz), 4.62 (1H, dd, *J* = 3.7, 7.7 Hz), 6.75 (1H, d, *J* = 2.2 Hz), 7.28 (1H, d, *J* = 2.2 Hz). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 66.95; H, 8.50; N, 4.28.

**Cycloadducts of 3-Acyl-2-oxazolones with Azodicarboxylates: General Procedure.** A mixture of 3-acyl-2-oxazolone (1 mmol) and azodicarboxylate (3 mmol) in benzene (0.14 mL) was heated under reflux for 6-19 h. The cycloadducts were isolated by chromatography on silica gel with hexane-$CH_2Cl_2$ or hexane-EtOAc. The diastereomeric cycloadducts derived from 3-[(1*S*)-2-alkoxy-1-apocamphane-carbonyl]-2-oxazolone were readily separable by chromatography on silica gel and the isomeric ratio was determined by $^1H$ NMR-analysis based on peaks $H_a$ or $H_b$ and their chemical shifts (δ) are given in Table 7.

**Table 7. $^1$H NMR Spectral Data Characteristic of Cycloadducts 22 and 23**


22


23

| $R^1$ | $R^2$ | Chemical Shift (δ) 22 $H_a$ | 23 $H_a$ |
|---|---|---|---|
| Me | Me | 4.32 (dd) | 4.43 (dd) |
| Me | Et | [ 2.27 (m) | 2.21 (m) ][a] |
| Me | *i*-Pr | 4.33 (dd) | 4.46 (dd) |
| Pr | Me | 4.36 (dd) | 4.57 (dd) |
| Pr | Et | [ 2.30 (m) | 2.17 (m) ][a] |
| Pr | *i*-Pr | 4.35 (dd) | 4.59 (dd) |
| Pr | $CH_2Ph$ | 4.33 (dd) | 4.57 (dd) |
| $CH_2CMe_3$ | Me | 4.35 (dd) | 4.61 (dd) |
| $CH_2CMe_3$ | Et | [ 2.32 (m) | 2.07 (m) ][a] |
| $CH_2CMe_3$ | *i*-Pr | 4.35 (dd) | 4.62 (dd) |
| $CH_2CMe_3$ | $CH_2Ph$ | 4.33 (dd) | 4.60 (dd) |

[a] The peaks assignable to the proton $H_b$.

**Ethyl *cis*-4a,7a-Dihydro-3-ethoxy-6-oxo-5-pivaloyl-oxazolino[5,4-e][1,3,4]oxadiazine-1-carboxylate (10, $R^1$ = $CMe_3$, $R^2$ = Et).** From 3-pivaloyl-2-oxazolone (**8**, $R^1$ = $CMe_3$) (0.5 g, 3.0 mmol) and diethyl azodicarboxylate (1.6 g, 8.9 mmol) the cycloadduct **10** was obtained as a colorless amorphous solid (0.93 g, 92%); IR (nujol, $cm^{-1}$): 1806, 1752, 1720, 1675; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, *J* = 7.0 Hz), 1.36 (3H, t, *J* = 7.0 Hz), 1.39 (9H, s), 4.25-4.37 (4H, m), 6.51 (1H, d, *J* = 5.9 Hz), 6.59 (1H, br d, *J* = 5.9 Hz); MS (EI): m/z 343 ($M^+$), 259 (M+$COCMe_3$+H), 176 ($(NHCO_2Et)_2$), 57 ($CMe_3$); HRMS (EI) calcd for $C_{14}H_{21}N_3O_7$ ($M^+$): m/z 343.1379, found: m/z 343.1370.

**Ethyl 5-Benzoyl-*cis*-4a,7a-dihydro-3-ethoxy-6-oxo-oxazolino[5,4-e][1,3,4]oxadiazine-1-carboxylate (10, $R^1$ = Ph, $R^2$ = Et).** From 3-benzoyl-2-oxazolone (**8**, $R^1$ = Ph) (0.4 g, 2.1 mmol) and diethyl azodicarboxylate (1.1 g, 6.3 mmol) the cycloadduct **10** was obtained as colorless crystals (0.58 g, 76%), mp 147.2 °C (from hexane); IR (nujol, $cm^{-1}$): 1810, 1724, 1704, 1685; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, t, *J* = 7.0 Hz), 4.28-4.37 (4H, m), 6.61 (1H, d, *J* = 5.5 Hz), 6.70 (1H, br d, *J* = 5.5 Hz), 7.43-7.69 (5H, m). Anal. Calcd for $C_{16}H_{17}N_3O_7$: C, 52.89; H, 4.72; N, 11.57. Found: C, 53.08; H, 4.76; N, 11.77.

**(4a*S*,7a*S*)- and (4a*R*,7a*R*)-Isopropyl *cis*-4a,7a-Dihydro-3-isopropoxy-5-[(1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl]-6-oxo-oxazolino[5,4-*e*][1,3,4]oxadiazine-1-carboxylates (22 and 23; $R^1$ = Me, $R^2$ = *i*-Pr).**

**(4a*S*, 7a*S*)-Isomer (22):** 71% yield as a colorless amorphous solid. $[\alpha]^{25}_D$ +208.8 ° (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.12-1.20 (1H, m), 1.15 (3H, s), 1.25 (3H, s), 1.32 (3H, d, *J* = 6.2 Hz), 1.33 (3H, d, *J* = 6.2 Hz), 1.34 (6H, d, *J* = 6.2 Hz), 1.64-1.70 (2H, m), 1.78-1.94 (3H, m), 2.24-2.30 (1H, m), 3.18 (3H, s), 4.33 (1H, dd, *J* = 3.7, 7.7 Hz), 5.00 (1H, br septet, *J* = 6.2 Hz), 5.07 (1H, septet, *J* = 6.2 Hz), 6.48 (1H, d, *J* = 5.9 Hz), 6.53 (1H, br d, *J* = 5.9 Hz); MS (EI): m/z 467($M^+$), 181, 149, 121, 95; HRMS (EI) calcd for $C_{22}H_{33}N_3O_8$ ($M^+$): m/z 467.2268, found: m/z 467.2285.

**(4a*R*, 7a*R*)-Isomer (23):** 22% yield as colorless crystals. mp 155 °C (from hexane); $[\alpha]^{26}_D$ -255.4 ° (*c* 1.02, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, s), 1.13-1.17 (1H, m), 1.30 (3H, s), 1.30 (3H, d, *J* = 6.2 Hz), 1.32 (3H, s), 1.32 (3H, d, *J* = 6.2 Hz), 1.34 (6H, d, *J* = 6.2 Hz), 1.66-1.91 (5H, m), 2.17-2.22 (1H, m), 3.19 (3H, s), 4.46 (1H, dd, *J* = 3.7, 7.7 Hz), 4.96 (1H, br septet, *J* = 6.2 Hz), 5.08 (1H, septet, *J* = 6.2 Hz), 6.52 (1H, d, *J* = 5.9 Hz), 6.57 (1H, d, *J* = 5.9 Hz). Anal. Calcd for $C_{22}H_{33}N_3O_8$: C, 56.52; H, 7.11; N, 8.99. Found: C, 56.47; H, 7.07; N, 8.96.

**(4*R*,5*S*)-5-[1,2-Bis(isopropoxycarbonyl)hydrazino]-4-methoxy-3-[(1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl]-2-oxazolidinone (24).** A solution of the (4a*S*,7a*S*)-cycloadduct **22** ($R^1$ = Me, $R^2$ = *i*-Pr) (3.5 g, 7.6 mmol) in MeOH (80 mL) was treated with *p*-toluenesulfonic acid monohydrate (72 mg, 0.38 mmol) at room temperature for 3 min. After addition of $NEt_3$ (152 mg, 1.5 mmol), removal of the solvent, and purification by chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (9:1)), **24** was obtained (3.5 g, 94%) as colorless crystals, mp 140.7-141.4 °C (from hexane-$CH_2Cl_2$); $[\alpha]^{26}_D$ +65.2 ° (*c* 1.02, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, s), 1.12-1.17 (1H, m), 1.23-1.30 (12H, m), 1.30 (3H, s), 1.64-1.75 (4H, m), 1.88-1.92 (1H, m), 2.04-2.21 (1H, m), 3.22 (3H, s), 3.50 (3H, s), 4.53 (1H, dd, *J* = 3.7, 7.7 Hz), 4.92-5.02 (2H, m), 5.78 (1H, br s), 6.11 (1H, br), 6.47 (1H, br s). Anal. Calcd for $C_{23}H_{37}N_3O_9$: C, 55.30; H, 7.45; N, 8.41. Found: C, 55.29; H, 7.52; N, 8.53.

**(4*S*,5*R*)-5-[1,2-Bis(isopropoxycarbonyl)hydrazino]-4-methoxy-3-[(1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl]-2-oxazolidinone (25).** Treatment of **23** ($R^1$ = Me, $R^2$ = *i*-Pr) (0.8 g, 1.7 mmol) in MeOH (17 mL) with *p*-toluenesulfonic acid monohydrate (16 mg, 0.09 mmol) as described above, gave the (4*S*,5*R*)-form (**25**) (0.83 g, 97%) as a colorless amorphous solid, $[\alpha]^{26}_D$ -74.8 ° (*c* 0.88, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s), 1.15-1.19 (1H, m), 1.22-1.27 (12H, m), 1.25 (3H, s), 1.65-1.69 (2H, m), 1.79-1.90 (3H, m), 2.17-2.33 (1H, m), 3.18 (3H, s), 3.52 (3H, s), 4.40 (1H, br s), 4.94-5.02 (2H, m), 5.73 (1H, br s), 6.15 (1H, br), 6.50 (1H, br s); MS (EI): m/z 499 ($M^+$), 467, 181, 180, 43; HRMS (EI) calcd for $C_{23}H_{37}N_3O_9$ ($M^+$): m/z 499.2530, found: m/z 499.2488.

**(4*R*,5*S*)-5-[1,2-Bis(isopropoxycarbonyl)hydrazino]-4-methoxy-2-oxazolidinone (26).** A mixture of **24** (0.3 g, 0.6 mmol) in THF (10 mL) was treated with $LiBH_4$ (2.0 M in THF; 2.4 mL, 4.8 mmol) and MeOH (308 mg, 9.6 mmol) at 0 °C in an argon atmosphere for 2.5 h. The mixture was passed through a short column of silica gel with EtOAc as an eluent, which was evaporated *in vacuo*. Chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (8:2)) afforded, in addition to the oily 2-methoxy-1-apocamphanemethanol (**40**)[14] (56 mg, 76%), the deacylated 2-oxazolidinone (**26**) (134 mg, 70%) as a colorless amorphous solid; $[\alpha]^{25}_D$ +99.6 ° (*c* 1.02, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.28 (6H, d, *J* = 6.2 Hz), 1.29 (6H, d, *J* = 6.2 Hz), 3.39 (3H, s), 4.92-5.07 (2H, m), 5.07 (1H, br s), 6.20 (1H, br), 6.92 (2H, br s); MS (EI): m/z

320($MH^+$), 204, 162, 118, 76, 43; HRMS (EI) calcd for $C_{12}H_{22}N_3O_7$ ($MH^+$): m/z 320.1458, found: m/z 320.1423.

**(4*S*,5*R*)-5-[1,2-Bis(isopropoxycarbonyl)hydrazino]-4-methoxy-2-oxazolidinone (27)** Similar procedure as **26**, **25** (828 mg, 1.6 mmol) with $LiBH_4$ (2.0 M in THF; 3.3 mL, 6.6 mmol) and MeOH (423 mg, 13.2 mmol) in THF (30 mL) gave, in addition to the alcohol **40**[14] (256 mg, 84%), the deacylated 2-oxazolidinone (**27**) (419 mg, 80%) as a colorless amorphous solid; $[\alpha]^{27}_D$ -98.8 ° (*c* 1.60, $CHCl_3$). This compound was spectroscopically identical with the enantiomer **26** obtained above.

**Exocyclic Deacylation of 28.** Similar procedure as **26**, **28** (1.00 g, 3.0 mmol) with $LiBH_4$ (2.0 M in THF; 5.9 mL, 11.9 mmol) and MeOH (760 mg, 23.7 mmol) in THF (59 mL) gave, in addition to the alcohol **40**[14] (423 mg, 78%), the deacylated 2-oxazolidinone[2a] (396 mg, 85%) as colorless crystals, mp 49.5-50.5 °C (from hexane); $[\alpha]^{22}_D$ +114.5 ° (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 2.38-2.58 (2H, m), 3.33 (3H, s), 4.45 (1H, dt, *J* = 2.0, 6.0 Hz), 4.70 (1H, d, *J* = 2.0 Hz), 5.18-5.25 (2H, m), 5.70-5.84 (1H, m), 7.55 (1H, br s). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.15; N, 8.91. Found: C, 53.69; H, 7.00; N, 8.65.

**Exocyclic Deacylation of 29.** Similar procedure as **26**, **29** (3.08 g, 9.3 mmol) with $LiBH_4$ (2.0 M in THF; 37.2 mL, 74.4 mmol) and MeOH (4.77 g, 0.15 mol) in THF (158 mL) gave, in addition to the alcohol **40**[14] (1.53 g, 89%), the deacylated 2-oxazolidinone[5a] (1.18g, 84%) as colorless crystals, mp 189 °C (from EtOAc); $[\alpha]^{27}_D$ +85.5 ° (*c* 1.00, MeOH); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.20 (1H, d, *J* = 9.5 Hz), 1.47 (1H, dd, *J* = 1.8, 9.5 Hz), 2.92 (1H, s), 3.14 (1H, s), 3.99 (1H, dd, *J* = 3.3, 8.4 Hz), 4.91 (1H, dd, *J* = 4.0, 8.4 Hz), 6.07 (1H, dd, *J* = 2.9, 5.9 Hz), 6.12 (1H, dd, *J* = 2.9, 5.9 Hz), 7.57 (1H, br s). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.74; H, 6.26; N, 9.20.

**Exocyclic Deacylation of 30.** Similar procedure as **26**, **30** (1.40 g, 3.0 mmol) with $LiBH_4$ (2.0 M in THF; 11.9 mL, 23.8 mmol) and MeOH (1.52 g, 47.5 mmol) in THF (52 mL) gave, in addition to the alcohol **40**[14] (0.54 g, 98%), the deacylated 2-oxazolidinone[5b] (0.79g, 91%) as colorless crystals, mp 287 °C (from hexane-$CH_2Cl_2$); $[\alpha]^{28}_D$ -48.4 ° (*c* 1.00, MeOH); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.82 (3H, s), 2.05 (3H, s), 3.71 (1H, d, *J* = 8.8 Hz), 4.51 (1H, d, *J* = 9.2 Hz), 6.69 (1H, s), 7.18-7.29 (6H, m), 7.35-7.38 (2H, m). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.48; H, 5.84; N, 4.86.

**Exocyclic Deacylation of 31.** Similar procedure as **26**, **31** (1.51 g, 3.6 mmol) with $LiBH_4$ (2.0 M in THF; 14.6 mL, 29.1 mmol) and MeOH (1.86 g, 58.2 mmol) in THF (50 mL) gave, in addition to the alcohol **40**[14] (0.65 g, 98%), the deacylated 2-oxazolidinone[16] (0.70g, 82%) as colorless crystals, mp 190.5-191.5 °C (from EtOH); $[\alpha]^{26}_D$ -56.8 ° (*c* 0.50, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.65 (3H, s), 0.66 (3H, s), 1.00 (3H, s), 1.08 (3H, s), 1.58 (3H, d, *J* = 1.1 Hz), 1.62 (3H, d, *J* = 1.1 Hz), 3.86 (1H, d, *J* = 8.1 Hz), 4.71 (1H, d, *J* = 8.1 Hz), 6.68 (1H, br s). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.57; H, 9.04; N, 6.08.

**(4*R*,5*S*)-4-Butyl-5-[1,2-bis(isopropoxycarbonyl)hydrazino]-2-oxazolidinone (32a). Typical Procedure A:** A solution of **26** (200 mg, 0.63 mmol) in THF (2.9 mL) and $BF_3$•$OEt_2$ (89 mg, 0.63 mmol) were subsequently added to a suspension of CuI (525 mg, 2.8 mmol) and BuLi (1.59 M in hexane; 3.15 mL, 5.0 mmol) in THF (13.2 mL) which had been stirred at -30 °C under an argon atmosphere for 30 min. The mixture was then stirred at -30 °C for an additional 1 h. The reaction was quenched by the addition of saturated $NH_4Cl$ solution (1.4 mL) and EtOAc (100 mL) was added. The whole was washed (i) satd. $NH_4Cl$ aq (20 mL × 3), ii) brine (45 mL × 3)), dried ($Na_2SO_4$) and evaporated *in vacuo* followed by chromatography on silica gel (hexane:EtOAc (7:3 to 6:4)) to give **32a** (170 mg, 79%) as a colorless amorphous solid; $[\alpha]^{27}_D$ +73.3 ° (*c*

1.02, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, $J$ = 6.7 Hz), 1.26-1.29 (12H, m), 1.33-1.44 (4H, m), 1.61-1.73 (2H, m), 3.83 (1H, br s), 4.98 (2H, m), 5.73-6.30 (2H, br), 6.53-6.91 (1H, br); MS (EI): m/z 346($MH^+$), 302, 259, 204, 162, 118, 103, 76, 43; HRMS (EI) calcd for $C_{15}H_{28}N_3O_6$ ($MH^+$): m/z 346.1978, found: m/z 346.1970.

**(4*R*,5*S*)-5-[1,2-Bis(isopropoxycarbonyl)hydrazino]-4-isopropyl-2-oxazolidinone (32b). Typical Procedure B:** A solution of **26** (150 mg, 0.47 mmol) in THF (2.2 mL) and $BF_3$•$OEt_2$ (67 mg, 0.47 mmol) were subsequently added to a suspension of LiCl (175 mg, 4.13 mmol; dried at 150 °C for 1 h under reduced pressure), CuCN (185 mg, 2.07 mmol) and *i*-PrMgBr (0.40 M in THF; 4.70 mL, 1.88 mmol) in THF (9.9 mL) which had been stirred at -30 °C under an argon atmosphere for 30 min. The mixture was then stirred at -30 °C for an additional 1 h. The reaction was quenched by the addition of saturated $NH_4Cl$ aq (1.4 mL) and EtOAc (100 mL) was added. The whole was washed (i) satd. $NH_4Cl$ aq (20 mL × 3), ii) brine (45 mL × 3)), dried ($Na_2SO_4$) and evaporated *in vacuo* followed by chromatography on silica gel (hexane:EtOAc (7:3 to 6:4)) afforded **32b** (132 mg, 85%) as a colorless, amorphous solid; $[\alpha]^{28}_D$ +56.8 ° (*c* 1.06, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.98 (6H, d, $J$ = 6.7 Hz), 1.29 (12H, d, $J$ = 6.2 Hz), 1.83 (1H, septet, $J$ = 6.7 Hz), 3.61 (1H, br), 4.98 (2H, m), 5.82-6.38 (2H, br), 6.50-6.96 (1H, br s); MS (EI): m/z 332($MH^+$), 302, 288, 245, 204, 162, 118, 76, 43; HRMS (EI) calcd for $C_{14}H_{26}N_3O_6$ ($MH^+$): m/z 332.1822, found: m/z 332.1800.

**(4*R*,5*S*)-4-*tert*-Butyl-5-[1,2-bis(isopropoxycarbonyl)hydrazino]-2-oxazolidinone (32c).** According to procedure A, treatment of **26** (150 mg, 0.47 mmol) with the cuprates prepared from CuCN (185 mg, 2.07 mmol)/THF (9.9 mL) and *tert*-BuMgBr (1.12 M in THF; 3.36 mL, 3.76 mmol) in the presence of $BF_3$•$OEt_2$ (67 mg, 0.47 mmol) gave **32c** (121 mg, 75%) as a colorless, amorphous solid; $[\alpha]^{26}_D$ +50.0 ° (*c* 0.98, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.29 (12H, d, $J$ = 6.2 Hz), 3.57 (1H, br), 4.99 (2H, m), 6.29 (2H, br), 6.71 (1H, br s); MS (EI): m/z 346($MH^+$), 288, 204, 162, 118, 76, 57, 43; HRMS (EI) calcd for $C_{15}H_{28}N_3O_6$ ($MH^+$): m/z 346.1978, found: m/z 346.1974.

**(4*R*,5*S*)-4-Cyclopentyl-5-[1,2-bis(isopropoxycarbonyl)hydrazino]-2-oxazolidinone (32d).** According to procedure B, treatment of **26** (100 mg, 0.31 mmol) with the cuprates prepared from LiCl (117 mg, 2.76 mmol), CuCN (123 mg, 1.38 mmol)/THF (5.0 mL) and *cyclo*-$C_5H_9MgBr$ (0.44 M in THF; 2.82 mL, 1.25 mmol) in the presence of $BF_3$•$OEt_2$ (45 mg, 0.31 mmol) gave **32d** (90 mg, 80%) as a colorless, amorphous solid; $[\alpha]^{28}_D$ +67.5 ° (*c* 1.01, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.15-1.42 (3H, m), 1.28 (12H, d, $J$ = 6.2 Hz), 1.63 (4H, m), 1.82 (1H, m), 2.04-2.12 (1H, m), 3.71 (1H, br s), 4.98 (2H, m), 6.26 (2H, br), 6.70 (1H, br s); MS (EI): m/z 358($MH^+$), 314, 271, 204, 162, 118, 103, 76, 43; HRMS (EI) calcd for $C_{16}H_{28}N_3O_6$ ($MH^+$): m/z 358.1978, found: m/z 358.1988.

**(4*R*,5*S*)-4-Cyclohexyl-5-[1,2-bis(isopropoxycarbonyl)hydrazino]-2-oxazolidinone (32e).** According to procedure B, treatment of **26** (100 mg, 0.31 mmol) with the cuprates prepared from LiCl (117 mg, 2.76 mmol), CuCN (123 mg, 1.38 mmol)/THF (5.0 mL) and *cyclo*-$C_6H_{11}MgBr$ (0.31 M in THF; 4.04 mL, 1.25 mmol) in the presence of $BF_3$•$OEt_2$ (45 mg, 0.31 mmol) gave **32e** as a colorless, amorphous solid; $[\alpha]^{26}_D$ +53.9 ° (*c* 0.99, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.02 (2H, m), 1.09-1.36 (4H, m), 1.28 (12H, d, $J$ = 6.2 Hz), 1.50 (1H, m), 1.61-1.85 (4H, m), 3.58 (1H, br s), 4.98 (2H, m), 6.23 (2H, br), 6.67 (1H, br s); MS (EI): m/z 372($MH^+$), 328, 285, 204, 162, 118, 103, 76, 43; HRMS (EI) m/z calcd for $C_{17}H_{30}N_3O_6$ ($MH^+$): m/z 372.2135, found: m/z 372.2133.

**(4*R*,5*S*)-5-[1,2-Bis(isopropoxycarbonyl)hydrazino]-4-phenyl-2-oxazolidinone (32f).** According to procedure B, treatment of **26** (450 mg, 1.41 mmol) with the cuprates prepared from LiCl (526

mg, 12.40 mmol), CuCN (555 mg, 6.20 mmol)/THF (33.8 mL) and PhMgBr (0.63 M in THF; 8.90 mL, 5.64 mmol) in the presence of $BF_3$•$OEt_2$ (200 mg, 1.41 mmol) gave **32f** (440 mg, 85%) as colorless crystals, mp 148-149 °C (from hexane-$CH_2Cl_2$); $[\alpha]^{29}_D$ +97.0 ° (*c* 1.01, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.23-1.32 (12H, m), 4.98 (3H, m), 6.28 (1H, br s), 5.91-6.51 (1H, br), 6.90 (1H, br), 7.34-7.42 (5H, m). Anal. Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 55.68; H, 6.35; N, 11.28.

**(4*R*,5*S*)-4-Benzyl-5-[1,2-bis(isopropoxycarbonyl)hydrazino]-2-oxazolidinone (32g).** According to procedure A, treatment of **26** (150 mg, 0.47 mmol) with the cuprates prepared from CuCN (185 mg, 2.07 mmol)/THF (9.9 mL) and $PhCH_2MgCl$ (1.06 M in THF; 3.56 mL, 3.76 mmol) in the presence of $BF_3$•$OEt_2$ (67 mg, 0.47 mmol) gave **32g** (140 mg, 79%) as a colorless, amorphous solid; $[\alpha]^{26}_D$ +72.6 ° (*c* 1.01, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.26 (12H, d, *J* = 6.2 Hz), 2.84 (1H, br s), 3.06 (1H, br s), 4.11 (1H, br s), 4.96 (2H, septet, *J* = 6.2 Hz), 5.42-6.47 (2H, br), 6.86 (1H, br); MS (EI): m/z 379($MH^+$), 293, 288, 204, 162, 118, 91, 76, 43; HRMS (EI) calcd for $C_{18}H_{25}N_3O_6$ ($MH^+$): m/z 379.1743, found: m/z 379.1764.

**(4*R*,5*S*)-4-Allyl-5-[1,2-bis(isopropoxycarbonyl)hydrazino]-2-oxazolidinone (32h).** To a solution of **26** (100 mg, 0.31 mmol) and allyltrimethylsilane (143 mg, 1.25 mmol) in $CH_2Cl_2$ (2.5 mL) was added $BF_3$•$OEt_2$ (45 mg, 0.31 mmol) in $CH_2Cl_2$ (0.6 mL) at -50 °C under an argon atmosphere, followed by stirring at room temperature for 10 h. The mixture was passed through a short column of silicagel with EtOAc as an eluent. Concentration of the mixture *in vacuo* followed by chromatography on silica gel (hexane-EtOAc (7:3 to 6:4)) afforded **32h** (97 mg, 94%) as a colorless amorphous solid; $[\alpha]^{26}_D$ +75.4 ° (*c* 1.01, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.28 (12H, d, *J* = 5.9 Hz), 2.34-2.50 (2H, m), 3.95 (1H, br s), 4.97 (2H, m), 5.21 (1H, d, *J* = 10.3 Hz), 5.23 (1H, d, *J* = 18.3 Hz), 5.72-5.82 (1H, m), 6.14 (2H, br), 6.84 (1H, br s); MS (EI): m/z 330 ($MH^+$), 243, 204, 162, 118, 76, 43; HRMS (EI) calcd for $C_{14}H_{24}N_3O_6$ ($MH^+$): m/z 330.1665, found: m/z 330.1697.

**(4*R*,5*S*)-5-[1,2-Bis(isopropoxycarbonyl)hydrazino]-4-vinyl-2-oxazolidinone (32i).** According to procedure A, treatment of **26** (450 mg, 1.41 mmol) with the cuprates prepared from CuCN (555 mg, 6.20 mmol)/THF (33.8 mL) and $CH_2$=CH-MgBr (1.01 M in THF; 11.16 mL, 11.28 mmol) in the presence of $BF_3$•$OEt_2$ (200 mg, 1.41 mmol) gave **32i** (320 mg, 72%) as a colorless, amorphous solid; $[\alpha]^{26}_D$ +86.3 ° (*c* 0.98, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.28 (6H, d, *J* = 6.2 Hz), 1.29 (6H, d, *J* = 6.2 Hz), 4.39 (1H, br s), 4.98 (2H, m), 5.32 (1H, d, *J* = 10.3 Hz), 5.42 (1H, d, *J* = 16.9 Hz), 5.90 (1H, ddd, *J* = 6.6, 10.3, 16.9 Hz), 5.96 (1H, br), 6.21 (1H, br s), 6.92 (1H, br s); MS (EI): m/z 316($MH^+$), 288, 272, 204, 162, 118, 76, 43; HRMS (EI) calcd for $C_{13}H_{22}N_3O_6$ ($MH^+$): m/z 316.1508, found: m/z 316.1512.

***N*-*tert*-Butoxycarbonylation of Compound 33. General Procedure:** In a typical experiment, a solution of the 2-oxazolidinones (**32**) (1 mmol) in $CH_2Cl_2$ (20 mL) was treated with di-*t*-butyl dicarbonate (3 eq.) in the presence of $NEt_3$ (3.5 eq.) and DMAP (1 eq.) at room temperature for 9 h. The mixture was concentrated *in vacuo* and purified by chromatography on silica gel to give the di-Boc derivatives **33** in quantitative yield.

**2-Amino Alcohols (34). General Procedure:** A series of *N*-Boc-2-oxazolidinones (**33**) (1 mmol) were treated with $NaBH_4$ (4 mmol) and MeOH (4 mmol) at room temperature in EtOH (20 mL) for 24 h. The mixture was filtered through a short column of silica gel using EtOAc as an eluent. Concentration of the mixture *in vacuo* followed by column chromatography on silica gel ($CH_2Cl_2$-EtOAc (9:1 to 7:3)) afforded *N*-*tert*-butoxycarbonyl-2-amino alcohols **34** (71-80%). The optical purity of the 2-amino alcohols thus obtained was

found to exceed 99 %ee by HPLC analysis as the MTPA esters ((*R*)-(+)-2-methoxy-2-(trifluoromethyl) phenylacetates) (DAICEL CHIRALCEL OJ for **34a,b,h,i**, DAICEL CHIRALCEL OD for **34c-f**) or the 4-benzyl-2-oxazolidinone (DAICEL CHIRALCEL OD for **34g**) (Table 5).

***N*-Boc-α-Amino Acid Methyl Esters (35).**

**PDC Oxidation of 34. General Procedure:** To a solution of *N*-Boc-2-amino alcohol **34** (0.5 mmol) in DMF (1 mL/PDC 1 g) was added pyridinium dichromate (PDC) (7.5 mmol, 15 eq.) and the solution was stirred at room temperature for 6 h. After addition of $H_2O$ (5 mL), the product was extracted with EtOAc (50 mL × 4), washed (brine, 20 mL × 3) and dried ($Na_2SO_4$). The solution was evaporated *in vacuo* to give the α-amino acid which was converted into the methyl ester with diazomethane and purified by column chromatography on silica gel (hexane-$CH_2Cl_2$ (2:8) to $CH_2Cl_2$-EtOAc (95:5)) (Table 5).

**Oxidative Conversion of 33. General Procedure:** To a solution of **33** (0.2 mmol) in *t*-BuOH (4 mL)-$H_2O$ (2 mL) were added $KMnO_4$ (8 mmol, 40 eq.) and KOH (4 mmol, 20 eq.). After vigorous stirring at room temperature for 17-23 h, the reaction was quenched with aqueous formaldehyde (4 mL) at 0 °C, acidified with citric acid and extracted with EtOAc (35 mL × 4). The combined extracts were evaporated *in vacuo* to give the *N*-Boc-α-amino acid, which was treated with diazomethane. Column chromatography on silica gel (hexane-$CH_2Cl_2$ (2:8) to $CH_2Cl_2$-EtOAc (95:5)) afforded *N*-Boc-α-amino acid methyl ester (**35**), identical with the product derived from the PDC oxidation of **34**. The optical purity of the protected α-amino acids thus obtained was found to exceed 99 %e.e. by HPLC analysis (Merck LiChrospher Si60) as the MTPA amides except for **35f** directly analyzed.

***trans*-4-Allyl-5-methoxy-2-oxazolidinone (36).** Compound **33h** (3.1 g, 5.9 mmol) was treated with $Cs_2CO_3$ (0.58 mg, 1.8 mmol) in MeOH (59 mL) at room temperature for 2 h. The solution was filtered through a short column of silica gel with EtOAc as an eluent. Concentration of the mixture *in vacuo*, followed by column chromatography on silica gel ($CH_2Cl_2$ to $CH_2Cl_2$-EtOAc (95:5)) gave **36** (0.92 g, 60%) as a colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.55 (9H, s), 2.40 (1H, m), 2.59 (1H, m), 3.50 (3H, s), 4.07 (1H, dd, $J$ = 3.7, 8.8 Hz), 4.98 (1H, d, $J$ = 1.1 Hz), 5.17-5.24 (2H, m), 5.67-5.76 (1H, m).

**4-Substituted-2-oxazolidinones (39). General Procedure:** A solution of the *N*-Boc-2-amino alcohol **34** (1 mmol) in THF (20 mL) was treated with thionyl chloride (8 mmol) at 0 °C for 3 h. Evaporation *in vacuo* followed by column chromatography on silica gel ($CH_2Cl_2$-EtOAc (9:1 to 8:2)) afforded a quantitative yield of **39** as colorless crystals.

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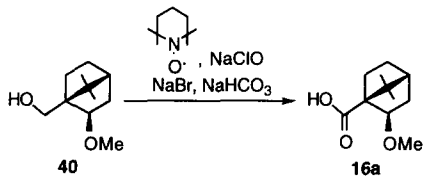
14. Combined reagents, TEMPO (2,2,6,6,-tetramethyl-1-piperidinyloxy free radical)/NaClO,[22] were found to be suitable for conversion of the recovered 2-methoxy-1-apocamphanemethanol (**40**) to the corresponding carboxylic acid (**16a**) for reuse.




**40** **16a**

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