# AN ACCESS TO OPTICALLY ACTIVE CARBACEPHEMS

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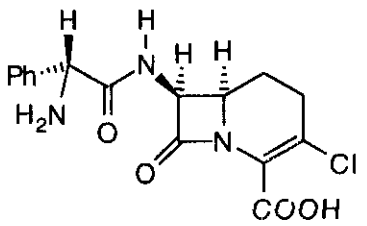
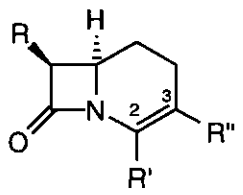
**Abstract** - Optically active 4-allyl-1-hydroxymethylazetidin-2-ones (**1**) (R = H, Ph, $CH_2CO_2Me$, $CH_2OAc$, $CH_2SPh$; R' = H: R = $CO_2Me$; R' = Me) have been obtained by enzymatic transesterification with vinyl acetate in the presence of the lipase from *Pseudomonas cepacia*. These compounds were either transformed into chiral carbacephems (R = Ph, $CH_2CO_2Me$) by reaction with Lewis acids or into *N*-methoxycarbonylhydroxymethyllactam (**11c**) (R = $CH_2CO_2Me$). Lactam (**11c**) was then transformed into the corresponding optically active carbacepham (**17**) or after chemical transformation into optically active carbacephem (**18**).

The recent preparation [1] and commercialisation of Lorabid,® an antibiotic of the carbacephem family, shows the interest in developing new methods allowing the preparation of such compounds. Indeed, in general this class of unnatural β-lactams show an enhanced of their stability by oral absorption, compared to structurally closed natural β-lactams. [2] Several methods have been developed for the preparation of racemic carbacephems,[3] with some allowing to obtain optically active compounds.



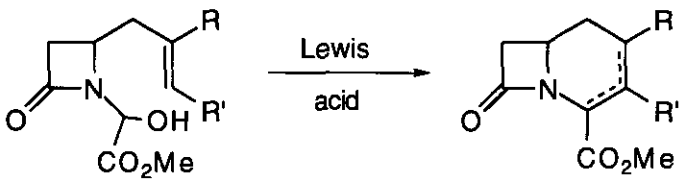

Lorabid ®




carbacephems

These compounds have been obtained by degradation of a penicillin derivatives,[4] transformation of chiral synthons,[5] diastereoselective reactions,[6] enzymatic resolution of β-lactam rings,[7] or an enantioselective reaction.[8]

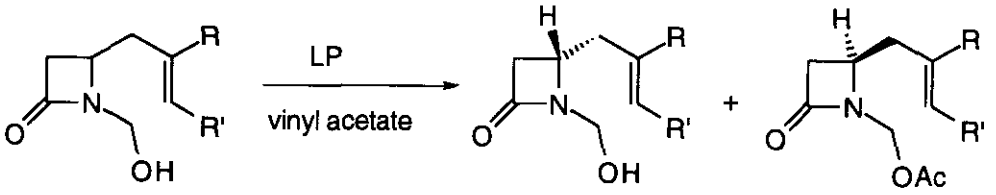
The aim of our work was to study the possibility to obtain optically active carbacephems from 4-allyl-1-alkoxycarbonylhydroxymethylazetidin-2-ones (Scheme 1), using the high reactivity of *N*-acyliminium ions.[9]




**Scheme 1**

Only few results have been reported about the enzymatic resolution of β-lactams.[7,10] We recently reported that the transesterification of *N*-hydromethyl-γ-butyrolactams in *tert*-butyl methyl ether using vinyl acetate in the presence of the lipase from *Pseudomonas cepacia* led to optically active γ-butyrolactams.[11] We decided to use the same approach for the preparation of optically active 4-allyl β-lactams.[12] The racemic 4-allyl-1-hydroxymethylazetidin-2-ones (**1a-1f**) were prepared in two steps from 4-acetoxyazetin-2-one by reaction first with the corresponding allylsilanes then formaldehyde (50-80 % overall yields).[12a] The results of the enzymatic resolution are resumed in Table 1.

**Table 1**: Enzymatic Transesterification of Alcohols (**1a-1f**)



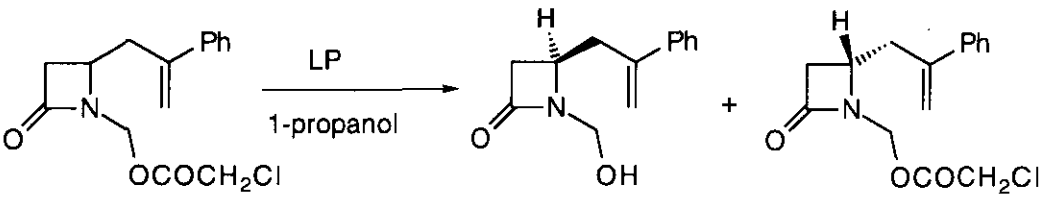

(*S*)-**1a-1f** (*R*)-**2a-2f**

| substate | | | conversion rate[a] | alcohol (**1**) | acetate (**2**) | E[a] |
|---|---|---|---|---|---|---|
| R, R' | No | reaction time (h) | | ee (%) | ee (%) | |
| H, H | **1a** | 0.83 | 0.45 | 73 | 88 | 36 |
| Ph, H | **1b** | 6.00 | 0.64 | 90 | 50 | 9 |
| $CH_2CO_2Me$, H | **1c** | 1.33 | 0.37 | 56 | >95 | 71 |
| $CO_2Me$, Me | **1d** | 2.00 | 0.49 | 77 | 80 | 21 |
| $CH_2OAc$, H | **1e** | 1.50 | 0.29 | 38 | >95 | 49 |
| $CH_2SPh$, H | **1f** | 1.66 | 0.42 | 65 | 90 | 37 |

[a]calculated as reported in ref. 13

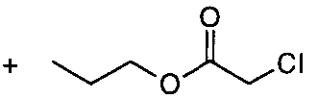
The absolute configurations of the alcohols (**1a-1f**) and the acetates (**2a-2f**) were determined as previously reported.[12a] In all cases, the *R*-alcohol was substrate of the enzyme, leading to the *R*-acetate

(**2a-2f**). Except with the β-lactam (**1b**), satisfactory results were observed. In this later case, the "inverse" transesterification was found to lead to improved results. Starting with the chloroacetate (**3b**), in *tert*-butyl methyl ether in the presence of 1-propanol the enantiomeric factor E was found to be 30, instead of 9 for the "normal" transesterification (Scheme 2) (for a conversion rate of 0.45; ee of **1b**: 87% , and ee of **3b**: 71%).

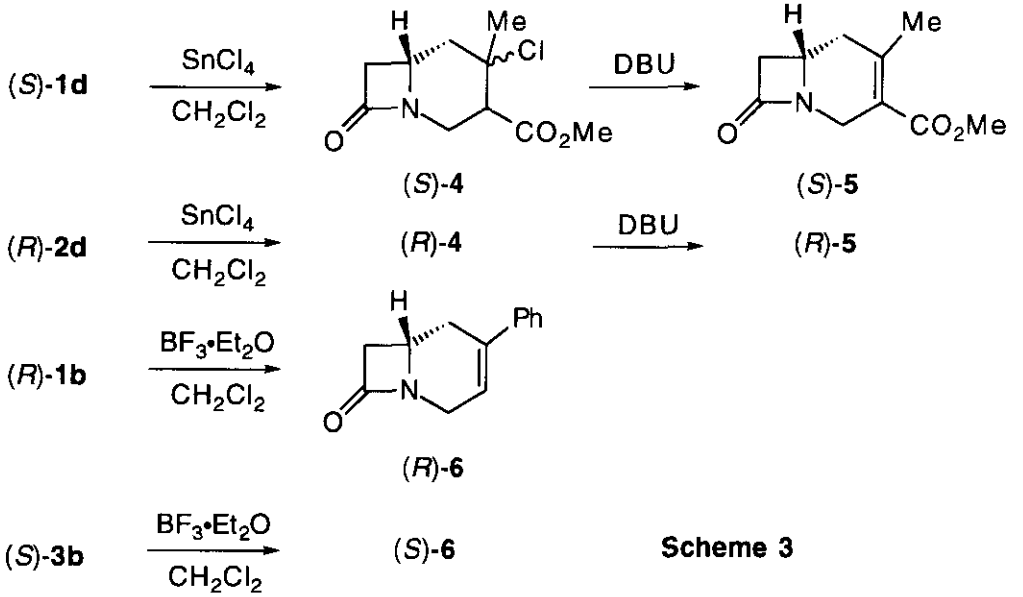



**3b** (*R*)-**1b** (*S*)-**3b**

**Scheme 2**



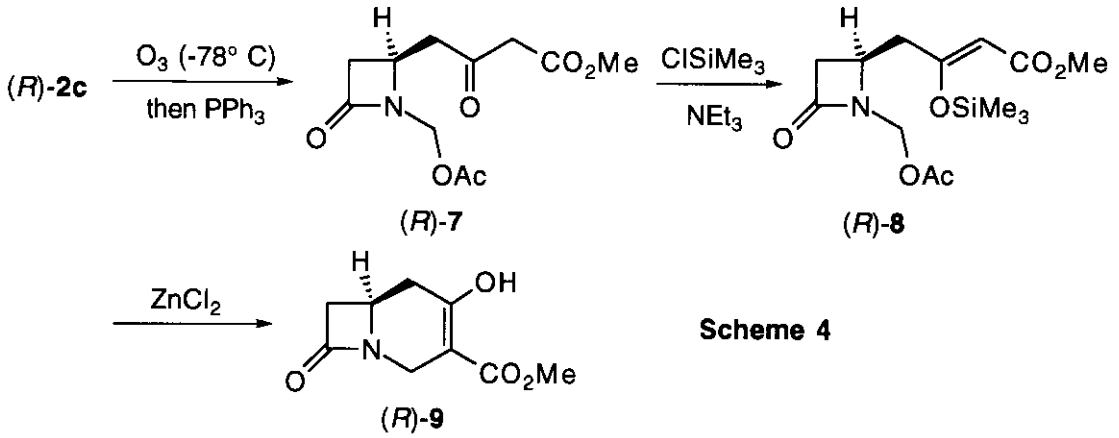

Reaction of the optically active alcohols (**1b, 1d**) and esters (**2d, 3b**) with $SnCl_4$ or $BF_3$•$Et_2O$ led as expected, *via* the intermediate *N*-acyl iminium ions,[9] to the bicyclic products (**4, 6**) (Scheme 3).




**Scheme 3**

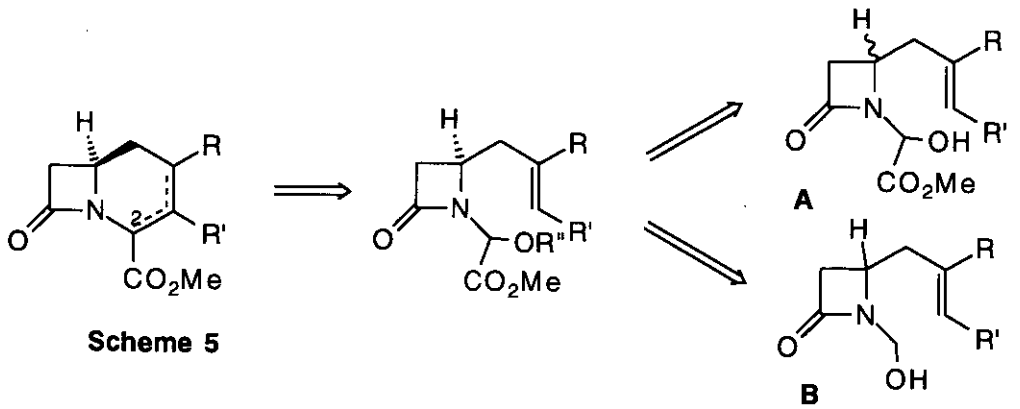
With the lactams ((*S*)-**1d**, (*S*)-**2d**), the bicyclic compounds (**4**) were obtained (mixture 50:50 of the two diastereoisomers) which after reaction with DBU led to the Δ-3-carbacephams (**5**) (88% overall yields). The enantiomeric excesses (determined by gas chromatography) of the bicyclic compound ((*S*)-**5**) and the starting lactam ((*S*)-**1d**) were the same. This result show that no racemization occurred during the cyclization. With $BF_3$•$Et_2O$ the results were less satisfactory. With the β-lactams ((*R*)-**1b**) and ((*S*)-**3b**), only $BF_3$•$Et_2O$ allowed the formation of the Δ–3-carbacephams (**6**). For an unknown reason the cyclization of the chloroacetate ((*S*)-**3b**) (or the chloroacetate obtained from ((*R*)-**1b**)) occurred in 77% yield while the cyclization of the alcohol ((*R*)-**1b**) (or its acetate) occurred in only 30% yield. Here also, no racemization was noticed.

In order to introduce a second function on the cyclohexane ring, the CC double bond of lactam ((*R*)-**2c**) (ee: 77%) was transformed into its enol ether. This transformation was accomplished in two steps (Scheme 4), by ozonolysis (70% yield in (*R*)-**7**) followed by reaction with chlorotrimethylsilane in the presence of triethylamine. Without purification the *Z* enol ether (**8**) was treated with zinc chloride (1 equiv.) to give the Δ-3-carbacepham ((*R*)-**9**) [$[\alpha]_D^{20}$ -53° (c = 0.7, $CH_2Cl_2$)] (60% yield from (R)-**7**). The structure of this product was easily established from its nmr, ir and mass spectra.



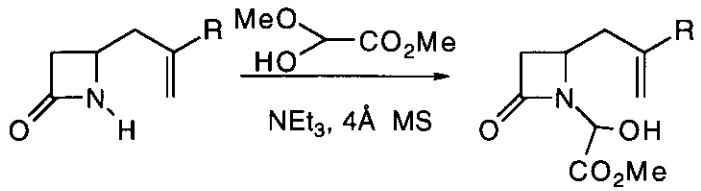

**Scheme 4**

The first study having established that it was possible to obtain optically active carbacephems by such an approach, our next step was to introduce an ester function at C2 onto the carbacephem skeleton. Two strategies were thought: 1) resolution of the racemic *N*-(methoxycarbonyl)hydroxymethyl-β-lactams (**A**) or 2) chemical transformation of optically active *N*-hydroxymethyl-β-lactams (**B**) (Scheme 5).




**Scheme 5**

To study the first approach different lactams (**11a-c**) were prepared by reaction of racemic 4-allyl-2-azetidinones (**10**) [12a] with the commercially available methyl 2-hydroxy-2-methoxyacetate in the presence of triethylamine in THF (95% yields) (Scheme 6). Only compound (**11c**) led to a cyclised product in the presence of with Lewis acids such as $SnCl_4$ or $BF_3$-$Et_2O$ (*vide infra*).



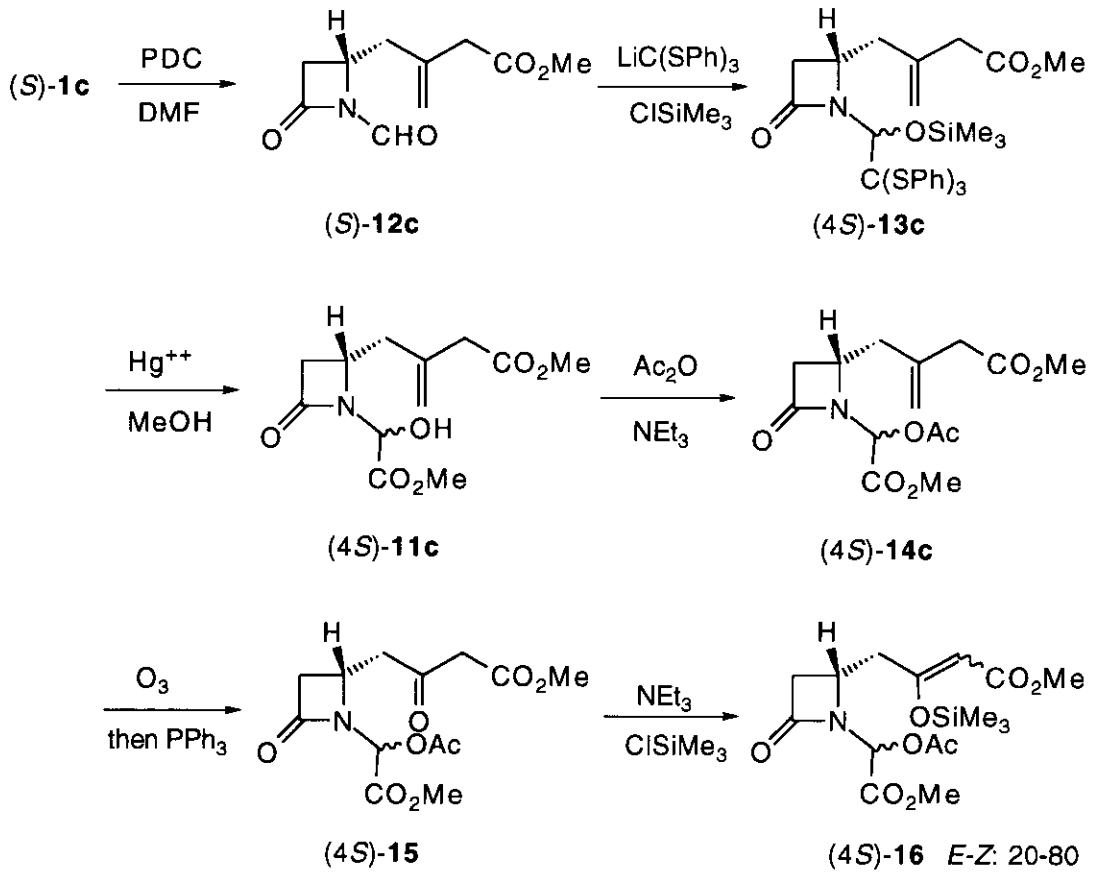

**10 a**: R = H
**b**: R = Ph
**c**: R = $CH_2CO_2Me$

**11a-c**

**Scheme 6**

The enzymatic resolution of these lactams, in the presence of vinyl acetate in *tert*-butyl methyl ether at room temperature was tested with lipases from *Candida cylindracea, Pseudomonas cepacia, Pseudomonas fluorescences, Antartica,* and *Mucor miehei* without success (no reaction). After formation of the chloroacetates, the inverse transesterifications in the presence of 1-propanol and these lipases occurred slowly (1-2 days) however without any enantioselectivity (E < 2).

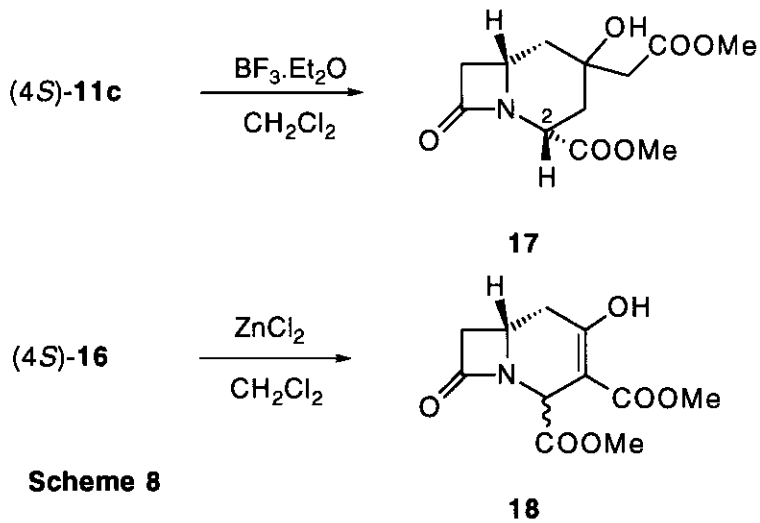
The second approach was studied starting with the β-lactam ((*S*)-**1c**) (ee = 56%), since the cyclization could be achieved only in this case. This lactam was oxidised with PDC in DMF [14] into *N*-formyl β-lactam ((*S*)-**12c**) [$[\alpha]_D^{20}$ -84° (c = 0.3, CH2Cl2), ee = 56%] (70% yield) (see Scheme 7).




**Scheme 7**

By reaction with tris(phenylthio)methyllithium [15] in the presence of chlorotrimethylsilane, the orthothioester ((4*S*)-**13c**) was isolated in 80% yield [$[\alpha]_D^{20}$ -57° (c = 1.3, $CH_2Cl_2$)] which was deprotected with mercuric salts [16] in a mixture of methanol-water to give the α-hydroxy ester ((4*S*)-**11c**) as a mixture of two diastereoisomers (50:50) (85% yield) [$[\alpha]_D^{20}$ 27 (c = 1, $CH_2Cl_2$)]. As previously reported (Scheme 4) for the transformation of (*R*)-**2c** into **8**, the lactam ((4*S*)-**11c**) was transformed into enol ether ((4*S*)-**16**) in three steps.

The cyclization of the lactams (**11a-c**) and (**16**) was then studied in the presence of Lewis acids. No reaction was observed with the racemic lactams (**11a**, **11b**). Lactam ((4*S*)-**11c**) led to the carbacepham (**17**) in the presence of $BF_3$•$Et_2O$ (33% yield). No cyclization product could be detected with Lewis acid such as $SnCl_4$, $AlCl_3$, $ZnCl_2$. Only one diastereoisomer was isolated, whose stereochemistry was in part deduced from its $^1H$ nmr spectra (Scheme 8). Indeed the stereochemistry of the carbon in 2 position was postulated to be *S* after comparison in $^1H$ nmr of the coupling constants of the hydrogen at this position with those calculated after determination of the more stable conformation of the different diastereoisomers by molecular modelisation (Pro Chemist Model 5 program) (see the ref 3 for a discussion). With the β-lactam ((4*S*)-**16**), $ZnCl_2$ was found to be the best Lewis acid. The Δ-3-carbacephams (**18**) was obtained in 50% yield as a mixture of two diastereoisomers.




**Scheme 8**

In conclusion, this study has shown that it was possible to obtain optically active carbacephams (and carbacephems) using a new method to build the 6-membered ring. Ester functions were introduced on the 6-membered ring onto C2 and (or) C3 positions.

## EXPERIMENTAL SECTION

All nmr spectra were measured in $CDCl_3$ and chemical shifts are expressed in ppm related to internal $CHCl_3$. Mass spectra were obtained at ionisation voltage of 70 eV. Solvents were purified by known standard procedures. $SnCl_4$ and $BF_3$•$Et_2O$ were distilled over $CaH_2$. Optical rotations were measured on a Perkin-Elmer 240 polarimeter. The proportions of the enantiomers were determinate on a 25 m length Cydex-B column. The racemic allylic β-lactams (**1a-f**) were prepared as previously reported.[3,12a]

**Enzymatic resolution of Lactams (1a-f).** *Preparation of the supported enzyme.* A mixture of 1 g of lipase from *Pseudomonas cepacia* (obtained from Amano), 3.4 g of Hyflo Super Cel and 5 ml of phosphate buffer pH 7 (0.1 $ML^{-1}$) was stirred for 15 min. The water is then removed under vacuum and the solid was dried under high vacuum (24 h at 0.1 mmHg, 25°C). This powder was used for the enzymatic transesterifications .

*Transesterifications.* Lactam (**1a**) (0.5 g, 3.54 mmol) was added to a mixture of supported lipase from *Pseudomonas cepacia* (0.2 g), vinyl acetate (0.65 ml, 7.10 mmol) and *tert*-butyl methyl ether (25 ml). After stirring 50 min at room temperature, the mixture was filtered and the filtrate was concentrated under vacuum. The acetate (**2a**) was then separated from the remaining alcohol (**1a**) by liquid chromatography over silica gel [elution: acetone-$CH_2Cl_2$ (3:97)]. The enantiomeric excesses of the alcohol (**1a**) and the acetate (**2a**) were measured by gas chromatography (Cydex-B column). The different results are reported in Table 1. The determination of the absolute configuration of optically active compounds (**1a-f**) and (**2a-f**) have been previously reported.[12a]

*Inverse transesterifications.* Lactam (**3b**) (0.5 g, 1.7 mmol) was added to a mixture of supported lipase from *Pseudomonas cepacia* (0.15 g), dry propanol (0.127 ml, 3.5 mmol) and *tert*-butyl methyl ether (20 ml). After stirring for 12 h at room temperature, the mixture was filtered, and the filtrate was concentrated under vacuum. The alcohol (**1b**) and the remaining chloroacetate were separated as above by liquid chromatography.

**(*S*)-4-Methyl-3-methoxycarbonyl-1-azabicyclo[4.2.0]-3-octen-8-one (5).** Under argon, to a solution of lactam (**1d**) (0.085 g, 0.4 mmol) in $CH_2Cl_2$ (5 ml) was added $SnCl_4$ (102 µl, 0.88 mmol). After 15 min at room temperature, a 10% aqueous solution of sodium bicarbonate (5 ml) was added and the organic phase was separated. After extraction of the aqueous phase with $CH_2Cl_2$ (3x5 ml), the combined organic phases were dried ($Na_2SO_4$) and concentrated. The residue was purified by liquid chromatography over silica gel [elution: $CH_2Cl_2$-MeOH (99:1)], then dissolved in MeOH (5 ml). Dry DBU (0.2 ml, 12 mmol) was added, and after 2 h at room temperature, the solvent was removed under vacuum. The residue was purified by liquid chromatography over silica gel to give an oil (0.068 g) (88 % yield) [elution: $CH_2Cl_2$-MeOH (99:1)]. $^1H$ Nmr (250 MHz) $\delta$ 2.10 (br s, 3H), 2.22 (m, 1H), 2.48 (m, 1H), 2.55 (dd, $J$ = 1.3, 14.7 Hz, 1H), 3.25 (ddd, $J$ = 1.8, 4.3, 14.7 Hz, 1H), 3.45 (m, 1H), 3.65 (m, 1H), 3.73 (s, 3H), 4.3 (br dt, $J$ = 3, 17 Hz, 1H). $^{13}C$ Nmr $\delta$ 166.5, 166.3, 145.1, 119.8, 51.5, 45.5, 42.3, 38.8, 37.2, 22.8. Ms CI *m/z* (rel. inten) 213 (100), 196 (60). 0.127 [$[\alpha]_D^{20}$ -148° (c 0.45, $CH_2Cl_2$), ee = 80%]. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found: C, 61.88; H, 6.81.

The (*R*) enantiomer was similarly obtained starting from (*R*)-**2d**. [$[\alpha]_D^{20}$ +143° (c 0.85, $CH_2Cl_2$), ee: 77%].

**(*R*)-4-Phenyl-1-azabicyclo[4.2.0]-3-octen-8-one (6).** The experimental protocol reported for the preparation of **5** was used using $BF_3$•$Et_2O$ as Lewis acid (0.102 ml, 0.88 mmol). $^1H$ Nmr (250 MHz) $\delta$ 2.38 (m, 1H), 2.60 (dd, $J$ = 1.3, 13.1 Hz, 1H), 2.80 (ddd, $J$ = 1.1, 5.3, 15.9 Hz, 1H), 3.22 (ddd, $J$ = 2.3, 4.7, 14.6 Hz, 1H), 3.49 (m, 1H), 3.60 (m, 1H), 4.20 (dt, $J$ = 2.4, 18.6 Hz, 1H), 5.90 (m, 1H), 7.40 (m, 5H). $^{13}C$ Nmr $\delta$ 167.0, 141.4, 134.5, 128.4, 127.6, 125.3, 119.6, 45.5, 43.8, 39.2, 32.5. Ms EI *m/z* (rel. inten) 199 (77), 170 (41), 156 (100), 141 (12), 129 (46), 115 (46). [$[\alpha]_D^{20}$ -110° (c 0.1,

$CH_2Cl_2$), ee: 92%]. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58. Found: C, 78.40; H, 6.63. The (*S*) enantiomer was similarly obtained starting from (*S*)-**3b** [$[\alpha]_D^{20}$ +88° ( c 0.6, $CH_2Cl_2$), ee = 71%].

**(*R*)-1-Acetoxymethyl-4-(2-oxo-3-methoxycarbonylpropyl)azetidin-2-one (7).** To a solution of lactam ((*R*)-**2c**) (0.255g, 1 mmol) in methylene chloride (20 ml) cooled at -78°C was bubbled a mixture oxygen-ozone until a persistent blue color appeared. After 30 min at -78°C, argon was bubbled into the solution to remove the excess of ozone and $PPh_3$ (0.395 g, 1.5 mmol) was added. The flask was warmed to room temperature and the solvent removed under vacuum. The residue was then purified by liquid chromatography over silica gel (elution: $CH_2Cl_2$) to give the β-keto ester (**7**) as an oil (0.179 g, 70% yield). [$[\alpha]_D^{20}$ - 3° (c 1, $CH_2Cl_2$), ee = 80 %]. $^1$H Nmr (200 MHz) $\delta$ 2.00 (s, 3H), 2.60 (dd, $J$ = 2.7, 15.3 Hz, 1H), 2.85 (dd, $J$ = 6.9, 18.1 Hz, 1H), 3.10 (dd, $J$ = 3.0, 5.7 Hz, 1H), 3.20 (d, $J$ = 6.5 Hz, 1H), 3.45 (s, 2H), 3.70 (s, 3H), 4.05 (m, 1H), 4.90 (d, $J$ = 11.3 Hz, A part of AB system, 1H), 5.09 (d, $J$ = 11.3 Hz, B part of a AB system, 1H). $^{13}$C Nmr $\delta$ 200.0, 170.0, 166.9, 166.6, 63.5, 52.2, 48.7, 47.4, 46.0, 43.2, 20.5. Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88. Found: C, 51.51; H, 5.71.

**(*R*)-(*Z*)-1-Acetoxymethyl-4-(3-methoxycarbonyl-2-trimethylsilyloxy-2-propenyl)-azetidin-2-one (8).** To a solution of lactam (**7**) (0.257 g, 1 mmol) in THF (5 ml) was added triethylamine (0.3 g, 3 mmol) and chlorotrimethylsilane (0.265 ml, 2 mmol). The mixture was stirred 2 h at room temperature, then filtered over dry Celite under argon. The filtrate was carefully concentrated under vacuum to give a residue (0.269 g, 85% yield in crude product) which was immediately used for the cyclization. $^1$H Nmr (200 MHz) $\delta$ 0.25 (s, 9H), 2.00 (s, 3H), 2.60 - 3.20 (m, 3H), 3.40 (dd, $J$ = 4.0, 9.5 Hz, 1H), 3.60 (s, 3H), 3.90 (m, 1H), 4.50 - 5.00 (m, 2H), 5.20 (s, 1H).

**(*R*)-4-Hydroxy-3-methoxycarbonyl-1-azabicyclo[4.2.0]-3-octen-8-one (9).** To a solution of lactam (**8**) (0.317 g, 1 mmol) in $CH_2Cl_2$ (5 ml) at room temperature was added dry $ZnCl_2$ (0.137 g, 1 mmol). After 12 h at room temperature, brine was added (5 ml). After separation, the aqueous phase was extracted with $CH_2Cl_2$ (3x10 ml). The combined organic phases were dried ($MgSO_4$), concentrated and purified by liquid chromatography over silica gel ($CH_2Cl_2$) to give lactam (**9**) as an oil (0.118 g, 60% yield from **7**). [$[\alpha]_D^{20}$ -53° (c 0.7, $CH_2Cl_2$), ee = 80%]. $^1$H Nmr (250 MHz) $\delta$ 2.43 (dd, $J$ = 7.8, 15.6 Hz, 1H, A part of a ABX system), 2.68 (dd, $J$ = 3.9, 15.6 Hz, 1H, B part of a ABX system), 2.66 (d, $J$ = 14.0 Hz, 1H), 3.33 (dd, $J$ = 14.0, 15.0 Hz, 1H), 3.60 (m, 1H), 3.68 (d, $J$ = 15.6 Hz, 1H), 3.78 (s, 3H), 4.30 (dd, $J$ = 1.6, 15.6 Hz, 1H), 11.10 (br s, 1H). $^{13}$C Nmr $\delta$ 170.0, 168.0, 166.0, 94.0, 51.7, 45.4, 43.2, 33.2, 20.2. Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62. Found: C, 54.80; H, 5.59.

**General procedure for the preparation of lactams (11a-c).** To a solution of lactam (**10**) [12a] (0.111 g, 1 mmol) in THF (5 ml) was added methyl 2-hydroxy-2-methoxyacetate (0.24 g, 2 mmol) triethylamine (0.2 g, 1 mmol) and 4Å molecular sieves (300 mg in powder). The mixture was stirred for 1 h at room temperature, filtered and concentrated under vacuum. The residue was heated at 60°C for 3 h under high vacuum (0.1 mmHg), and then purified by liquid chromatography over silica gel [elution: methanol-$CH_2Cl_2$ (2: 98)]. Lactams (**11a-c**) were obtained as a 50:50 mixture of diastereoisomers. They did not give satisfactory elemental analysis, so these latter where conducted on their corresponding chloroacetates.

**1-(1-Hydroxy-1-methoxycarbonylmethyl)-4-(2-propenyl)azetidin-2-one (11a).** $^1$H Nmr (200 MHz) $\delta$ 2.25 (m, 1H), 2.50 (m, 2H), 2.68 (dd, $J$ = 2.1, 14.8 Hz, 1H), 3.05 (dt, $J$ = 4.2, 14.8 Hz,

1H), 3.80 (s, 1.5H, (1st dia)), 3.90 (s, 1.5H, (2nd dia)), 4.00 (m, 1H), 5.10 (m, 2H), 5.38 (d, $J$ = 5 Hz, 0.5H, (1st dia)), 5.42 (d, $J$ = 5 Hz, 0.5H, (2nd dia)), 5.70 (m, 1H). $^{13}$C Nmr $\delta$ (mixture of diastereoisomers) 169.2, 168.3, 167.0, 166.5, 132.5, 132.0, 117.9, 72.1, 71.0, 52.5, 50.6, 49.1, 41.4, 41.3, 37.3, 36.3. Ms CI *m/z* (rel. inten) 217 (9), 129 (100).

**1-(1-Hydroxy-1-methoxycarbonylmethyl)-4-(2-phenyl-2-propenyl)azetidin-1-one (11b).** $^1$H Nmr (250 MHz) $\delta$ 2.65 (m, 1H), 2.72 (m, 1H), 2.80 (2d, $J$ = 8 Hz, 1H (2 diastereoisomers), 2.96 to 3.20 (m, 2H), 3.80 (s, 3H), 3.95 (m, 1H), 5.13 (br s, 1H), 5.18 (br s, 1H), 5.37 (d, $J$ = 8 Hz, 0.5H (1st dia)), 5.39 (d, $J$ = 8 Hz, 0.5 Hz (2nd dia), 7.40 (m, 5H). $^{13}$C Nmr $\delta$ (mixture of diastereoisomers) 169.9, 168.7, 157.3, 166.9, 144.1, 139.8, 128.4, 127.7, 125.8, 125.7, 71.8, 71.4, 53.2, 53.1, 50.9, 50.5, 49.3, 42.9, 39.8, 39.7. $^1$H Nmr of the chloroacetate (250 MHz) $\delta$ 2.70 (m, 2H), 3.05 (m, 2H), 3.78 (s, 1.5H, (1 dia)), 3.81 (s, 1.5H (2nd dia)), 3.90 (m, 1H), 4.12 (s, 2H), 5.13 (d, $J$ = 7.0 Hz, 1H), 5.38 (d, $J$ = 7.0 Hz, 1H), 6.19 (s, 0.5H (1st dia)), 6.40 (s, 0.5H, (2nd dia)), 7.40 (m, 5H). Anal. Calcd for $C_{17}H_{16}NO_5Cl$ (chloroacetates): C, 58.38; H, 4.61. Found: C, 58.59; H, 4.78.

**1-(1-Hydroxy-1-methoxycarbonylmethyl)-4-(3-methoxycarbonyl-2-methylenepropyl)-azetidin-1-one (11c).** $^1$H Nmr (200 MHz) $\delta$ 2.20 - 2.62 (m, 2H), 2.71 (dd, $J$ = 1.0, 14.8 Hz, 1H), 3.10 (s, 1H (1st dia)), 3.13 (s, 1H (2nd dia)), 3.20 (dd, $J$ = 6.3, 14.8 Hz, 1H), 3.70 (s, 3H), 3.88 (s, 1.5H, 1st dia)), 3.91 (s, 1.5H (2nd dia)), 4.99 (d, $J$ = 7.0 Hz, 1H), 5.06 (d, $J$ = 7.0 Hz, 1H), 5.34 (d, $J$ = 6.4 Hz, 0.5H (1st dia)), 5.36 (d, $J$ = 6.4 Hz, 0.5 H (2nd dia)). Anal. Calcd for $C_{14}H_{17}NO_7Cl$ (chloroacetates): C, 48.50; H, 4.94. Found: C, 48.81; H, 5.13.

The enzymatic resolution of lactams (**11a-c**) were conducted in the conditions reported for lactams (**1a-f**).

**(*S*)-1-Formyl-4-(3-methoxycarbonyl-2-methylenepropyl)azetidin-2-one (12c).** To a solution of 1-hydroxymethyl-4-(2-methylene-3-methoxycarbonylpropyl)azetidin-2-one ((*S*)-**1c**) (0.08 g, 0.38 mmol) in DMF (2 ml) was added pyridinium dichromate (0.206 g, 0.76 mmol). After 3 h at room temperature, water (15 ml) was added and the aqueous phase was extracted with a mixture of ether-pentane (50:50, 5x10 ml). The combined organic phases were dried ($MgSO_4$), and concentrated. The residue was purified by liquid chromatography over silica gel ($CH_2Cl_2$) to give lactam (**12c**) as an oil (0.056 g, 70% yield). $^1$H Nmr (200 MHz) $\delta$ 2.28 (dd, $J$ = 8.5, 12.7 Hz, 1H), 2.90 (dd, $J$ = 2.1, 12.7 Hz, 1H), 3.00 - 3.20 (m, 3H), 3.28 (dd, $J$ = 4.2, 12.7 Hz, 1H), 3.70 (s, 3H), 4.30 (m, 1H), 4.88 (s, 1H), 5.05 (s, 1H), 8.8 (s, 1H). $^{13}$C Nmr $\delta$ 171.2, 165.3, 156.2, 137.4, 116.6, 51.9, 49.3, 43.3, 41.8, 38.6. [$[\alpha]_D^{20}$ -102° (c 0.3, $CH_2Cl_2$), ee: 68%]. Anal. Calcd for $C_{10}H_{13}NO_4Cl$: C, 56.87; H, 6.20. Found: C, 56.98; H, 6.50.

**(4*S*)-1-[1-Trimethylsilyloxy-1-tris(phenylthio)methyl]-4-(3-methoxycarbonyl-2-methylenepropyl)azetidin-2-one (13c).** Under argon a solution of tris(phenylthio)methane (0.45 g, 1.33 mmol) in THF (5 ml) was cooled at -78°C and BuLi (0.83 ml of 1.6M sol in hexane, 1.33 mmol) was added. After 30 min at -78°C, lactam (**12c**) (0.140 g, 0.66 mmol) in solution in THF (1 ml) was added. The mixture was stirred at -78°C for 1 h, then $ClSiMe_3$ (0.245 ml, 1.99 mmol) was dropped in 5 min. After 1 h at this temperature, aqueous saturated solution of $NH_4Cl$ was added, and the cooling bath was removed. After separation, the aqueous phase was extracted with $CH_2Cl_2$ (3x10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by liquid chromatography over silica gel [elution: $CH_3OH$-$CH_2Cl_2$ (1:99)] to give 0.23 g of lactam (**13c**) as an oil

(59% yield). A 70:30 ratio of the two 1'-diastereoisomers was obtained. [$[\alpha]_D^{20}$ (mixture) -69° (c 1.3, $CH_2Cl_2$), ee: 68%]. $^1H$ Nmr (200 MHz) $\delta$ (mixture of diastereoisomers) -0.20 (s, minor diastereoisomer, 2.7H), -0.05 (s, 6.3H, major dia), 2.40 (m, 2H), 2.60 (dd, $J$ = 1.3, 13.6 Hz, 0.7H), 2.70 (dd, $J$ = 1.3, 13.6 Hz, 0.7H), 3.00 - 3.20 (m, 1H), 3.55 (s, 21H), 3.60 (s, 0.9H), 4.20 (m, 0.3H), 4.50 (m, 0.7H), 5.01 (s, 0.7H), 5.03 (s, 0.7H), 5.05 (s, 0.7H), 5.07 (s, 0.3H), 5.92 (s, 0.7H), 6.01 (s, 0.3H), 7.30 (m, 9H), 7.70 (m, 6H). $^{13}C$ Nmr (mixture) $\delta$ 171.2, 169.4, 166.2, 139.1, 138.8, 134.9, 132.7, 132.09, 128.5, 128.2, 115.6, 115.4, 80.6, 78.7, 78.2, 53.3, 52.8, 51.8, 51.7, 43.1, 42.9, 42.2, 41.9, 40.2, -0.2, -0.6.

**(4*S*)-1-[1-Hydroxy-1-methoxycarbonylmethyl)-4-(3-methoxycarbonyl-2-methylene-propyl)azetidin-2-one (11c).** Lactam (**13c**) (0.27 g, 0.43 mmol) was added to a mixture of methanol (6 ml), water (0.5 ml), HgO (0.153 g, 0.72 mmol) and $HgCl_2$ (0.478 g, 1.74 mmol) and was refluxed for 1 h. The reaction mixture was cooled and filtered. The solid was washed with $CH_2Cl_2$ (2x10 ml). Combined organic phases were diluted with water (15 ml) and extracted with $CH_2Cl_2$ (2x10 ml).The organic phase was washed with 75% aqueous ammonium acetate (2x10 ml), saturated ammonium chloride (2x10 ml) and dried ($MgSO_4$). After concentration under vacuum, the residue (0.127 g) was used for the next step without purification. For the spectra description see above.

**(4*S*)-1-(1-Acetoxy-1-methoxycarbonylmethyl)-4-(3-methoxycarbonyl-2-methylene-propyl)azetidin-2-one (14c).** To crude lactam (**11c**) in solution in $CH_2Cl_2$ (5 ml) was added triethylamine (0.06 ml, 0.4 mmol), acetic anhydride (0.05 ml, 0.5 mmol) and 4-dimethylaminopyridine (0.01 g, 0.08 mmol) and the mixture was stirred overnight at room temperature. The solution was concentrated under vacuum and the residue was purified by liquid chromatography over silica gel to give lactam (**14c**) (0.095 g, 70% yield from lactam (**13c**)) as a 50:50 mixture of the two 1'-diastereoisomers. [$[\alpha]_D^{20}$-33 (c 1, $CH_2Cl_2$), ee = 68%]. $^1H$ Nmr (200 MHz) $\delta$ 2.15 (s, 3H), 2.30 (m, 1H), 2.70 (m, 2H), 3.05 (s, 1H (1st dia)), 3,10 (s, 1H (2nd dia)), 3.25 (m, 1H), 3.70 (s, 3H), 3.78 (s, 1.5H (1st dia)), 3.80 (s, 1.5H, (2nd dia)), 4.00 (m, 1H), 4.91 (d, $J$ = 5.0 Hz, 1H), 4.99 (d, $J$ = 5.0 Hz, 1H), 6.20 (s, 0.5H (1st dia)), 6.30 (s, 0.5H, (2nd dia)). $^{13}C$ Nmr (mixture of diastereoisomers) $\delta$ 171.1, 171.0, 169.3, 169.2, 165.4, 164.8, 137.7, 137.6, 116.3, 116.1, 71.7, 71.6, 53.1, 52.9, 50.4, 50.1, 43.4, 43.3, 41.8, 41.7, 39.7, 38.9, 20.4, 20.2. Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11. Found: C, 53.81; H, 6.29.

**(4*S*)-1-(1-Acetoxy-1-methoxycarbonylmethyl)-4-(2-oxo-3-methoxycarbonylpropyl)-azetidin-2-one (15).** To a solution of lactam (**14c**) (0.313g, 1 mmol) in $CH_2Cl_2$ (20 ml) cooled at -78°C, was bubbled a mixture oxygen-ozone until a persistent blue color appeared. After 30 min at -78°C, argon was bubbled into the solution to remove the excess of ozone and then $PPh_3$ (0.395 g, 1.5 mmol) was added. The flask was warmed to room temperature and the solvent removed under vacuum. The residue was purified by liquid chromatography over silica gel (elution: $CH_2Cl_2$) to give lactam (**15**) (0.188 g, 60% yield) as an oily mixture of the two 1'-diastereoisomers. [$[\alpha]_D^{20}$-11.4° (c 1.1, $CH_2Cl_2$), ee = 67%]. $^1H$ Nmr (200 MHz) $\delta$ 2.15 (s, 3H), 2.70 (dd, $J$ = 2.1, 14.8 Hz, 1H), 2.95 (dd, $J$ = 8.6, 17.0 Hz, 1H), 3.25 ((m, 2H), 3.45 (d, $J$ = 12.3 Hz, 1H (A part of a AB system)), 3.54 (d, $J$ = 12.3 Hz, 1H (B part of a AB system)), 3.75 (s, 3H), 3.90 (s, 3H), 4.20 (m, 1H), 6.20 (s, 0.5H (1st dia)), 6.40 (s, 0.5H (2nd dia)). $^{13}C$ Nmr (mixture of diastereoisomers) $\delta$ 200.2, 199.8, 169.4, 169.2, 167.0, 165.8, 165.5, 164.8, 71.9,

system)), 3.75 (s, 3H), 3.90 (s, 3H), 4.20 (m, 1H), 6.20 (s, 0.5H (1st dia)), 6.40 (s, 0.5H (2nd dia)). $^{13}$C Nmr (mixture of diastereoisomers) $\delta$ 200.2, 199.8, 169.4, 169.2, 167.0, 165.8, 165.5, 164.8, 71.9, 71.6, 53.3, 52.8, 49.5, 47.4, 47.2, 46.4, 46.2, 43.4, 43.2, 20.3, 20.2. Anal. Calcd for $C_{13}H_{17}NO_8$: C, 49.53; H, 5.43. Found: C, 49.66; H, 5.81.

**(4*S*)-1-(1-Acetoxy-1-methoxycarbonylmethyl)-4-(3-methoxycarbonyl-2-trimethylsilyl-oxy-2-propenyl)azetidin-2-one (16).** To a solution of lactam (**15**) (0.315 g, 1 mmol) in THF (5 ml) was added triethylamine (3 mmol, 0.3 g) and chlorotrimethylsilane (2 mmol, 0.265 ml), and the mixture was stirred for 2 h at room temperature. After filtration over dry Celite under argon, the filtrate was carefully concentrated under vacuum to give a residue (85% yield in crude product) which was immediately used for the subsequent cyclization. $^1$H Nmr (200 MHz) $\delta$ 0.20 (s, 1.8H (*E* isomer)), 0.28 (s, 7.2H (*Z* isomer)), 2.15 (s, 3H), 2.70 - 3.20 (m, 9H), 3.70 (s, 3H), 3.80 (s, 0.6H (*E* isomer)), 3.88 (s, 2.4H (*Z* isomer)), 4.00 (m, 1H), 5.12 (s, 0.2H (*E* isomer)), 5.20 (s, 0.8H (*Z* isomer)), 6.40 - 6.42 (2s, 1H).

**(2*R*,6*S*)-4-Hydroxy-4-methoxycarbonylmethyl-2-methoxycarbonyl-1-azabicyclo[4.2.0]-octan-8-one (17).** The cyclization of (4*S*)-**11c** (0.108 g, 0.4mmol) was conducted in the conditions reported for the preparation of lactam (**4**) using $BF_3$•$Et_2O$ as Lewis acid (0.102 ml, 0.88 mmol) with a reaction time of 6 h. Lactam (**17**) was obtained as an oil (0.036 g, 33% yield). $[[\alpha]_D^{20}$ +31° (*c* 0.7, $CH_2Cl_2$), ee: 68%]. $^1$H Nmr (250 MHz, $C_6D_6$) $\delta$ 0.45 (dd, *J* = 10.7, 11.6 Hz, 1H), 0.97 (dd, *J* = 7.2, 13.6 Hz, 1H), 1.55 (ddd, *J* = 1.4, 4.4, 11.6 Hz, 1H), 1.88 (d, *J* = 15.9 Hz, 1H (A Part of a AB system)), 1.95 (d, *J* = 15.9 Hz, 1H (B Part of a AB system)), 2.08 (dd, *J* = 1.9, 14.4 Hz, 1H), 2.20 (dt, *J* = 1.5, 13.6 Hz, 1H), 2.70 (dd, *J* = 4.7, 14.4 Hz, 1H), 3.19 (s, 3H), 3.35 (s, 3H), 3.68 (m, 1H), 3.73 (s, 1H), 4.48 (d, *J* = 7.2 Hz, 1H). $^{13}$C Nmr ($CDCl_3$) $\delta$ 172.1, 171.3, 165.4, 69.0, 51.9, 51.2, 48.1, 45.2, 44.7, 43.1, 40.3, 36.6. Ms CI *m/z* (rel. inten) 289 (45), 272 (94), 256 (100), 212 (12). Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32. Found: C, 53.18; H, 6.51.

**(6*S*)-2,3-Dimethoxycarbonyl-4-hydroxy-1-azabicyclo[4.2.0]-3-octen-8-one (18).** The cyclization of (4*S*)-**16** (0.359 g, 1 mmol) was carried out as reported for the preparation of lactam (**4**) using dry $ZnCl_2$ as Lewis acid (0.137 g, 1 mmol). Lactam (**18**) was obtained as an oil (0.128 g, 50% yield). $^1$H Nmr (250 MHz) $\delta$ 2.45 (ddd, *J* = 1.3, 8.7, 18 Hz, 1H), 2.70 (m, 2H), 3.37 (dd, *J* = 4.7, 14.8 Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3.78 (m, 1H), 5.10 (d, *J* = 1.3 Hz, 1H), 11.8 (bs, 1H). $^{13}$C Nmr $\delta$ 171.3, 170.8, 169.9, 164.2, 95.08, 52.0, 51.4, 49.9, 46.4, 42.4, 32.5. Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13. Found: C, 51.91; H, 5.15.

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