ENVIRONMENTALLY BENIGN CHEMISTRY: MICROWAVE-INDUCED STEREOCONTROLLED SYNTHESIS OF β-LACTAM SYNTHONS[1] 祝喜寿

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祝喜寿 *dedicated to Dr. Shigeru Oae on the occasion of his 77th birthday*

Abstract - Microwave irradiation in open glass vessels in unmodified commercial microwave ovens has permitted stereocontrolled synthesis of useful β-lactam synthons not withstanding the fact that the nature of specific activation (if any) of organic reactions by microwaves is not yet completely understood.

The application of microwave energy to organic compounds for conducting synthetic reactions at highly accelerated rates is an emerging technology area. A recent international symposium[2] on "Microwaves and Chemical Synthesis" served in effect as the l0th anniversary of the initiation of this new field. The trail-blazing publications were two independent reports[3,4] in 1986 describing a variety of synthetic reactions completed in minutes after irradiation of reactants in sealed tubes in domestic microwave ovens. Since then a number of laboratories including our own have undertaken the study of microwave assisted organic reactions.[5]

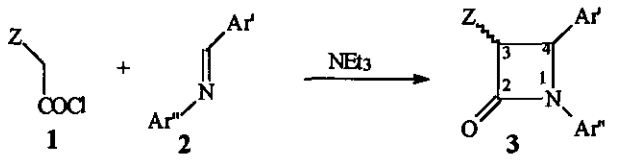
Sealed tube reactions in a microwave oven generate high pressure as the reaction temperature rises rapidly. Some explosions have been reported. We[6] have developed safe, convenient and inexpensive ways of using unaltered domestic microwave ovens by adopting untraditional experimental arrangements. In our laboratories a wide variety of organic reactions have been conducted in open vessels without the need for stirrers, reflux condensers, water-traps, etc. We have shown that by carefully selecting a polar, high boiling solvent as the reaction medium and controlling the energy input to prevent boiling, many reactions can be completed on several hundred grams scale in about 10 minutes. A domestic microwave oven with 600-800 Watts maximum power output is satisfactory for most reactions.

We wish to report here a variety of microwave-assisted synthetic reaction steps involving the formation of substituted β-1actams and their transformation to useful synthons for diverse natural products.[7a] Special attention will be paid to the stereochemical aspects of the reactions as we have had success in controlling the steric course (*cis/trans* ratio) of β-1actam ring formation in some cases.[7]

A. Synthesis of 4,4-Dialkoxycarbonyl-2-azetidinones

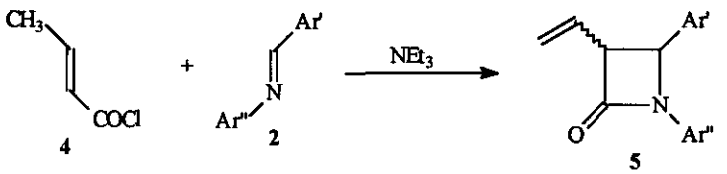
One of the most widely used methods[8] for the synthesis of β-lactams is the reaction between a Schiff base (**2**), an acid chloride (**1**) (or an equivalent) and a tertiary amine. The steric course of formation of the β-lactam (**3**) appears to depend on several factors - including the sequence of addition of the three reagents. Thus, the formation of the *cis* isomer of 3-azido-2-azetidinones (**3**, Z = N_3) was favored (*cis*/*trans* = 3) when the acid chloride (**1**) (Z = N_3) was added to a mixture of the Schiff base (**2**) and triethylamine.[9] Mostly the *trans* isomer was formed (*trans*/*cis* = 3), however, when triethylamine was added to a mixture of **1** and **2** (**Scheme 1**).

Scheme 1

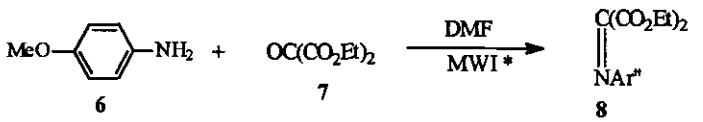


In 1971 we[10] discovered that the reaction of an α,β-unsaturated acid chloride (**4**) with a Schiff base (**2**) in refluxing benzene produces α-vinyl-β-lactams. Several hours of reaction led only to a modest yield; also a mixture of *trans* and *cis* β-lactams (**5**) was obtained in most cases (**Scheme 2**). We have reported[11] previously that the yield of **5** was much improved when the reaction was conducted in a microwave oven with chlorobenzene as the solvent/energy transfer agent. In most cases, however, the β-lactam was a mixture of *cis* and *trans* isomers. To circumvent this stereochemical feature we decided to replace the Schiff base (**2**) with the imino compound (**8**) obtained by the reaction of an amine (**6**) with diethyl ketomalonate (**7**)[12] (**Scheme 3**).

Scheme 2



Scheme 3



MWI * = Microwave irradiation Ar" = *p*-anisyl

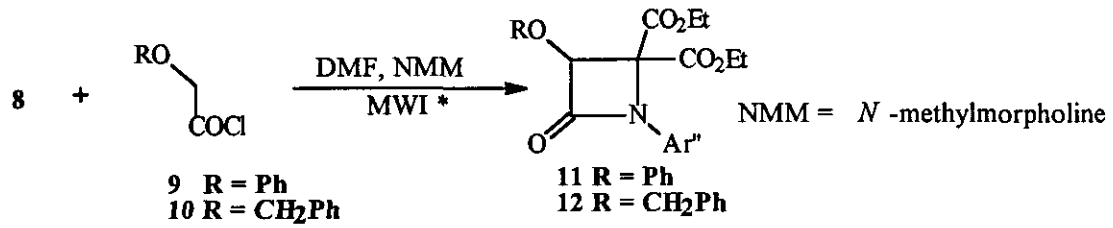
The strategy at this point was to combine the imino compound formation step and the β-lactam formation step into a one pot reaction. We wished to test the utility of our Microwave-induced

Organic Reaction Enhancement (M.O.R.E.) chemistry techniques for conducting this sequence of reactions. We had observed earlier that one of the "eco-friendly" aspects of M.O.R.E. chemistry technique is that we require only limited amounts of solvents - just enough to dissolve only a part of the reactants at the higher temperature of the reaction in the microwave oven.

Our solvent of choice was *N,N*-dimethylformamide (DMF) which has a boiling point of 154 °C - thereby allowing reactions to be conducted in open vessels at 120-140 °C without causing much vaporization of the solvent. Also, DMF appears to bind most of the water formed in the reaction - most probably through hydrogen bonding.

Our previous experience had been that β-lactam formation proceeds readily in DMF solution.[6] This solvent system was therefore used as the energy transfer medium for the synthesis of α-hydroxy-β-lactam derivatives. Using a domestic microwave oven, **11** and **12** were prepared in a few minutes from phenoxyacetyl chloride (**9**) and benzyloxyacetyl chloride (**10**). The yields of these β-lactams were comparable to that by classical methods which require 2-3 hour of reaction time (**Scheme 4**).

Scheme 4

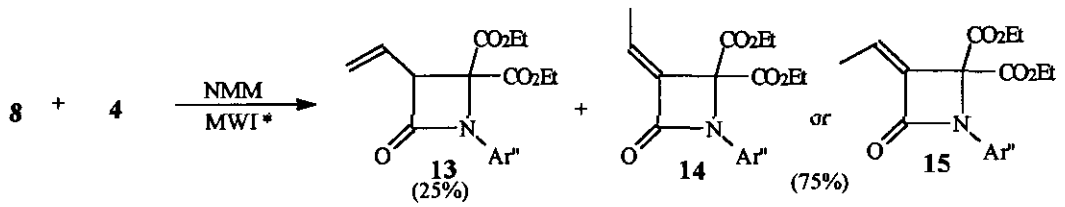


9 R = Ph
***10* R = CH_2Ph**

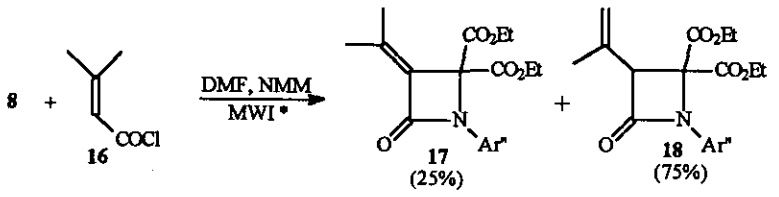
11 R = Ph
12 R = CH_2Ph

The same approach was applied to the synthesis of the α-vinyl-β-lactam (**5**). The reaction of crotonyl chloride (**4**) with **8** led to the formation of β-lactams in 65% yield. Analysis by ^1H NMR spectroscopy showed that the two β-lactams (**13**) and (**15**) were present in the proportion of 1:3 (**Scheme 5**). Similar results were obtained when **8** was heated under reflux with **4** and triethylamine in dichloromethane solution (outside the microwave oven) for 2 hours. For reasons not clear, when β,β-dimethylacryloyl chloride (**16**) was treated with (**8**), β-lactam (**18**) with the rearranged double bond was the major product under the same reaction conditions (**Scheme 6**).

Scheme 5



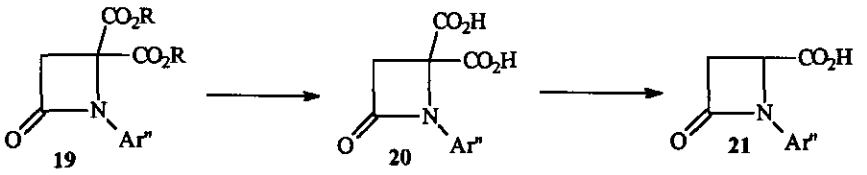
Scheme 6



B. Dealkoxycarbonylation

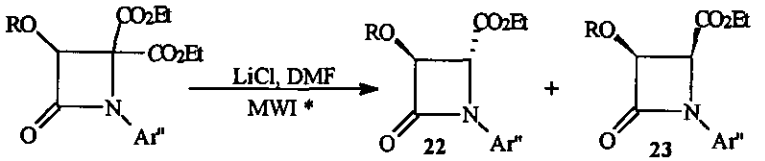
A carboxy group at C-4 of azetidine-2-ones has been shown to be useful for the elaboration of the second ring of fused bicyclic β-lactams. It is possible to saponify the two ester groups of a 4,4-dialkoxycarbonyl-2-azetidinone (e.g., **19**) without the scission of the β-lactam ring. Decarboxylation of the malonic acid system in **20** under mild heating with a base leads to a 4-carboxy-2-azetidinone (**21**) (**Scheme 7**).

Scheme 7



An alternative decarboxylation method suitable for a microwave oven is the scission of one ester group under the influence of lithium chloride in DMSO or DMF. As model experiments, this Krapcho reaction[13] was attempted on the β-lactams (**11**) and (**12**) with DMF as the reaction medium. Loss of an ester group was observed in each case, but, the reaction was not stereocontrolled (see **Scheme 8**). Both β-lactams (**11**) and (**12**) provided a mixture of *trans* and *cis* compounds (**22**) and (**23**).

Scheme 8



The same reaction conditions were utilized for the mixture of **13** and **15** (**Scheme 9**). The decarbethoxylation product (**24**) was a mixture of *E*- and *Z*- isomers (in about 1:1 proportion). The double bond in the side chain was in conjugation with the β-lactam carbonyl. The stereochemistry of these "*E*" and "*Z*" isomers was deduced from their ^{1}H nmr spectra.[14] The signal for the methyl group in the *E*-isomer (**24E**) appeared at 1.85 ppm while that for the *Z*-isomer (**24Z**) resonated at 2.22 ppm.

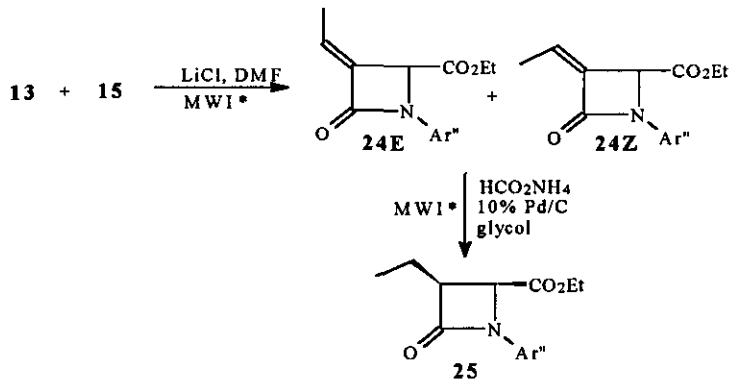
Decarboethoxylation of the mixture of **17** and **18** gave 80% yield of a single product (**26**) which was an isopropylidene compound (**Scheme 10**).

C. Stereospecific Hydrogenation

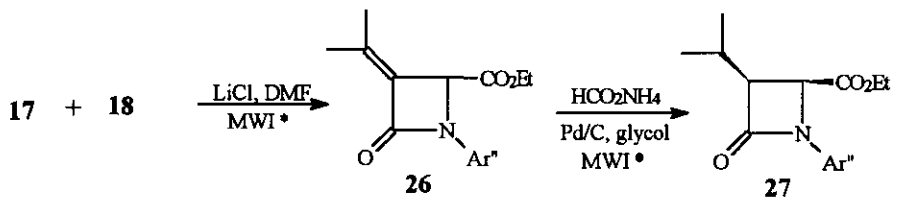
We have developed[15] a simplified technique for high temperature (about 130 °C) catalytic transfer hydrogenation that is rapid, easy to conduct in an open beaker and requires no special equipment other than a domestic microwave oven. Ammonium formate in presence of 10% Pd/C catalyst is the source of hydrogen. Ethylene glycol (bp 198 °C) is a readily available reaction medium that is a good solvent for many organic compounds at higher temperatures.

The product (**24**) (a mixture of *E* and *Z* isomers) was subjected to microwave-assisted catalytic transfer hydrogenation. The product, obtained in quantitative yield after about 90 sec of hydrogenation at about 130 °C, was the *cis* β-lactam **25** (**Scheme 9**).

Scheme 9



Scheme 10



Similar catalytic reduction of the isopropylidene compound (**26**) led in quantitative yield to the *cis* β-lactam (**27**) (**Scheme 10**).

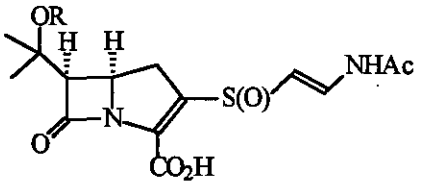
Compounds (**25**) and (**27**) were identical with samples prepared earlier by different routes.[10]

D. Useful Synthons

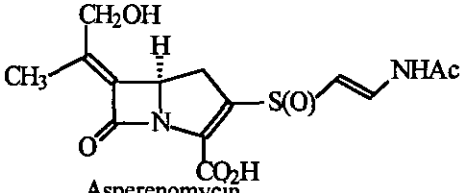
The synthetic approaches described here lead to α-vinyl- and α-alkyl-β-lactams; the former can be transformed into a variety of other functions. For example, we have converted the vinyl substituent at C-3 to the thienamycin side chain.[16]

We have described here stereocontrolled access to *cis*-β-lactams with an ester group at C-4. It is known that such an ester group can be reduced by lithium borohydride to a primary alcohol group without cleavage of the β-lactam ring and without altering the *cis* stereochemistry of the β-lactam starting material. On the other hand, the free carboxy group at C-4 has been utilized by various laboratories for easy access to *trans* β-lactam derivatives (including carbapenem antibiotics).[17]

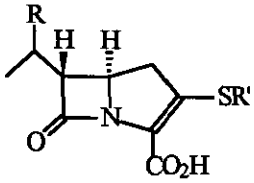
In a formal sense, *cis* carbapenems of the type of carpetimycin can be the end products from the *cis* β-lactam synthons **(25)** and **(27)**. The β-lactam **(25)** provides access to compounds of the type of asparenomycin. Access to the *trans* carbapenem derivatives PS-5 and PS-6 is also provided by **25** and **27** in light of previous work.[18]



Carpetimycin A: R = H
Carpetimycin B: R = SO_3H



Asperenomycin



PS-5: R = H, R' = CH_2CH_2NHAc
PS-6: R = Me, R' = CH=CHNHAc

E. Reducing Pollution at the Source

Pollution caused during the manufacture of chemicals has become a major concern now. As a result, "environmentally benign chemical syntheses and processes" are attracting serious attention. In this context our M.O.R.E. chemistry techniques provide an advantage over traditional synthetic methods since only limited amounts of solvents - just enough to dissolve most of the reagents at higher temperatures - are required.

For several of the reactions described here, we have chosen DMF as the reaction medium wherever possible. This has permitted one pot reaction for the formation of the Schiff base followed by β-lactam formation. It should be possible to combine the next step (decarboxylation with lithium chloride) also to these two reactions and conduct all three reaction in one pot. For the catalytic hydrogenation, however, the solvent has to be changed from DMF to ethylene glycol.

In some instances we have completed a sequence of several reactions (20 - 30 g scale) in one day taking advantage of the highly accelerated reaction rate under microwave irradiation.

ACKNOWLEDGEMENT

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thank Raza Naqvi, Keiko Tabei and Gregori Morriello (an undergraduate student) for technical assistance.

EXPERIMENTAL

Melting points were determined with a Mel-temp apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 1310 instrument. Nmr spectra were recorded on a Bruker AC-200 spectrometer using TMS as an internal standard. Chemical Ionization mass spectra were recorded on a Biospect instrument using CH_4 as the reagent gas. Thin layer chromatography was performed with Whatmann plates, and the spots were detected under UV light. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, NY. Compounds described here are all racemates.

Synthesis of the Schiff base (8):

In an Erlenmeyer flask (capacity 125 ml) was placed *p*-anisidine (**6**) (2 g, 16.2 mmol), DMF (5 ml) and diethyl ketomalonate (**7**) (2.82 g, 16.2 mmol). The mixture was shaken well. A beaker (500 ml capacity) containing water (100 ml) was kept in a microwave oven as a "heat sink". The solution containing the reaction mixture was irradiated for 6 min at low power setting. The temperature of the reaction mixture was kept below 130 °C by adjusting the "on and off" control for the power level. The Schiff base (**8**) was obtained in about 90% yield, ir (Neat) 1720,1700, 1620 cm^{-1}. This was used directly for the next step without any purification.

General Procedure for β-lactams (11, 12, 13, 15, 17 and 18)

To the solution of the Schiff base (**8**) obtained above in DMF (10 ml) were added *N*-methylmorpholine (5 g, 50 mmol) and an acid chloride (25 mmol). The mixture was irradiated in a microwave oven for 4-5 min. EtOAc (50 ml) was added and the organic phase was washed successively with dilute HCl (5%, 3 × 10 ml), saturated $NaHCO_3$ solution (3 × 10 ml), brine (2 × 10 ml) , dried and evaporated. The crude product showed the presence of β-lactams (60-65%).

11: Ir (neat) 1760, 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.53-6.85 (m, 9H), 5.90 (s, 1H), 4.59-4.14 (m, 4H), 3.80 (s, 3H), 1.31 (t = 7.27 Hz, 3H), 1.05 (t = 7.28 Hz, 3H); ^{13}C nmr: 165.66, 164.65, 161.71, 157.47, 157.16, 129.50, 128.97, 122.85, 121,51, 115.79, 114.05, 84.95, 72.20, 63.06, 62.06, 62.69, 55.40, 13.87, 13.69; CIms (CH_4) m/z 414 $(M+H)^+$; Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.60; N, 3.38. Found: C, 64.39; H, 5.67; N, 3.32.

12: mp 55 °C (EtOAc-Hexanes); ir (neat) 1760, 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.46-7.25 (m, 7H), 6.87 (d, *J* = 9 Hz, 2H), 5.27 (s, 1H), 4.87 (d, *J* = 11.65 Hz, 1H), 4.74 (d, *J* = 11.65 Hz, 1H); 4.42-4.14 (m, 4H), 3.76 (s, 3H), 1.31-1.10 (M, 6H); ^{13}C nmr: δ 165.17, 162.73, 157.03, 135.99, 129.23, 129.19, 128.62, 120.78, 113.85, 86.88, 73.62, 72.19, 62.71, 62.65, 55.33, 13.84, 13.62; CIms (CH_4) m/z 428 $(M+H)^+$; Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.89; N, 3.27. Found : C, 64.79; H, 5.73; N, 3.18.

The reaction between crotonyl chloride and **8** gave **13** and **15** in the ration of 1:3. Only **15** was isolated in pure form.

15: mp 74 °C, ir ($CHCl_3$) : 1750, 1735, 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.51 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.13 (q, J = 7.31 Hz, 1H), 4.37-4.15 (br q, 4H), 3.80 (s, 3H), 2.16 (d, J = 7.33 Hz, 3H), 1.23 (t, J = 7.25 Hz, 6H); ^{13}C nmr: 166.20, 160.51, 156.51, 137.01, 130.48, 129.10, 119.43, 119.39, 113.98, 113.95, 71.30, 62.53, 62.47, 55.33, 14.89, 13.82; CIMS (CH_4) *m/z* 348 $(M+H)^+$. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.23; H, 6.09; N, 4.03. Found : C, 62.55; H, 5.84; N, 3.58.

The reaction between β,β-dimethylacryloyl chloride and **8** afforded **17** and **18** in the ratio of 1:3 . From this mixture (**18**) was isolated in pure form.

18: oil, ir (Neat) 1750, 1725cm^{-1}; ^1H nmr ($CDCl_3$) δ : 7.46 (d, 2H), 6.86 (d, 2H), 5.14 (brs, 2H), 4.55 (s, 3H), 4.32-4.12 (m, 4H), 3.80 (s, 3H), 1.82 (s, 3H), 1.22-1.10 (m, 6H); ^{13}C nmr: 166.43, 165.80, 164.02, 156.77, 135.36, 129.69, 121.66, 117.50, 113.79, 70.22, 64.17, 62.59, 62.27, 55.15, 23.66, 13.71,13.64. Anal Calcd for $C_{19}H_{23}NO_6$: C, 63.14; H, 6.41; N, 3.87. Found C, 63.25; H, 6.33; N, 3.70; CIms (CH_4): m/z 362 $(M+H)^+$.

General Procedure for the Decarbethoxylation Reaction:

A mixture of the β-lactam (2 mmol), LiCl (0.168 g, 4 mmol) and DMF (10 ml) was heated in a microwave oven for 7-8 min (140 °C) by keeping water in a beaker as a heat sink. The heat sink was changed 4 times at the intervals of 2 min for better temperature control. The reaction mixture was diluted with dichloromethane (100 ml), washed with water (2 x 25 ml), dried (Na_2SO_4) and evaporated. The pure product was obtained after column chromatography (ethyl acetate-hexane mixtures).

22 (R = Ph): oil, ir (neat): 1750, 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.40-6.80 (m, 9H), 5.40 (d, J = 1.62 Hz, 1H) 4.60 (d, J = 1.76 Hz, 1H), 3.80 (s, 3H), 1.31 (t, J = 7.27 Hz, 3H); ^{13}C nmr: 168.43, 160.90, 156.97, 130.20, 129.74,1 2.85, 118.49, 115.70, 114.53, 114.49, 83.23, 62.27, 60.15, 55.43, 14.06; CIms (CH_4): *m/z* 342 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N,4.10. Found : C, 66.81; H, 5.54; N, 4.06.

23 (R = Ph): mp 90 °C (EtOAc-Hexanes), ir (nujol) 1745, 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.40-6.85 (m, 9H), 5.55 (d, J=5.1 Hz, 1H), 4.80 (d, J = 5.1 Hz, 1H), 4.15 (q, J = 7.08 Hz, 2H), 3.70 (s, 3H), 1.10 (t, J = 6.88 Hz, 3H); ^{13}C nmr: 166.75, 161.21, 157.16, 156.93, 130.18, 129.56, 122.78, 118.51, 115.91, 114.50, 80.59, 61.99, 59.0, 55.47, 13.94, CIms (CH_4): m/z 342 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10, Found C, 66.89; H, 5.49; N, 4.05.

23 (R = CH_2Ph) : mp 122 °C (EtOAc-Hexanes), ir (nujol) 1745, 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.40-6.81 (m, 9H), 5.05 (d, J = 5.31 Hz, 1H), 4.8 (s, 2H), 4.70 (d, J = 5.4 Hz, 1H), 4.25 (q, J = 7.2 Hz,

2H), 3.80 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H): ^{13}C nmr: 167.46, 162.67, 156.71, 136.40, 130.39, 128.42, 128.06, 127.77, 118.39, 114.43, 81.71, 73.22, 61.85, 59.13, 55.44, 14.09; CIms (CH_4) : m/z 356 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.95; N, 3.94. Found : C, 67.42; H, 5.63; N, 3.49.

22 (R = CH_2Ph): oil, ir (neat): 1750, 1745 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ :7.40-6.80 (m, 9H), 4.91-4.70 (m, 3H), 4.40 (d, J = 1.59 Hz, 1H), 4.22 (m, 2H) 3.75 (s, 3H) 1.25 (t, J = 7.2 Hz, 3H): ^{13}C nmr: 168.43, 161.95, 156.53, 135.94, 130.15, 128.51, 128.39, 128.32, 118.13, 114.17, 84.70, 72.66, 61.65, 59.67, 55.12, 13.78; CIms (CH_4) : m/z 356 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.95; N, 3.94 Found : C, 67.58; H, 6.04; N, 4.16.

24E : ir (nujol) 1735 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.31 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 6.41-6.29 (m, 1H), 4.94 (s, 1H), 4.37-4.12 (m, 2H), 3.77 (s, 3H), 1.85 (d, J = 6.2 Hz, 3H), 1.24 (t, J = 7.25 Hz, 3H), ^{13}C nmr: 168.55, 159.47, 156.18, 136.64, 131.04,124.54, 117.57, 114.34, 61.74, 59.18, 55.32, 13.93, 13.58; CIms (CH_4) : m/z 276 $(M+H)^+$ From the mixture (**24z**) isomer could not be separated in pure form.

26: mp 94 °C (EtOAc-Hexanes), ir (nujol) 1745, 1660 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.28 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H) , 4.86 (s, 1H), 4.38-4.14 (m, 2H), 3.78 (s, 3H), 2.14 (s, 3H), 1.86 (s, 3H), 1.24 (t, J =7.13 Hz, 3H); ^{13}C nmr: 169.28, 160.42, 156.04, 139.26, 131.47, 130.23, 117.37, 114.43, 61.70, 59.29, 55.44, 27.46, 27.43, 14.06; CIms (CH_4): m/z 290 $(M+H)^+$; This compound was identical with a previouly prepared sample in all respects.[10]

General Procedure for the Hydrogenation Reaction:

Caution must be exercised in conducting the catalytic hydrogenation because Pd-C is a fine powder that is flammable. It is standard practice in our laboratory to place the microwave oven in a hood. Unsaturated β-lactam (0.5 mmol) and Pd-C (10%, 50 mg) were placed in an Erlenmeyer flask (125 ml capacity) as a slurry in ethylene glycol (5ml). Ammonium formate (5.79 g, 92 mmol) was added next and the mixture was irradiated in a microwave oven for about 2 min. The power level of the oven is controlled to raise the temperature of the mixture to 120 - 130 °C. The approximate temperature of the reaction mixture is most easily measured by a thermometer after taking the flask out of the oven. The catalyst was removed after filtration and EtOAc (50 ml) was added to the filtrate. The organic layer was washed with water (2 X 25 ml), dried (Na_2SO_4) and evaporated. The crude product on crystallization gave the pure *cis*-β-lactam in almost quantitative yield.

25: mp 39 °C (EtOAc-Hexanes), ir (nujol) 1760, 1730 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ : 7.25-6.80 (AA-BB', J = 9 Hz, 4H), 4.60 (d, J = 6.12 Hz, 1H), 4.25 (q, J = 7.22 Hz, 2H), 3.80 (s, 3H), 3.50 (m, 1H), 1.91-1.62 (m, 2H), 1.30 (t, J = 7.48 Hz, 3H), 1.1 (t, J = 7.44 Hz, 3H); CIms (CH_4) : m/z 278 $(M+H)^+$. This

was found to be identical with a the previous sample of the compound prepared by a different method.[10]

27: mp 77-78 °C (EtOAc-Hexanes), ir (nujol) 1765, 1740 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ : 7.30-6.80 (AA'-BB', J = 9 Hz, 4H), 4.55 (d, J = 5.96 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 3.25 (dd, J = 5.89, 10.74 Hz, 1H), 2.15 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H), 1.20 (d, J = 6.58 Hz, 3H), 0.95 (d, J = 6.58 Hz, 3H): ^{13}C nmr: 169.29, 164.16, 156.24, 131.06, 117.74, 114.37, 61.65, 60.55, 55.44, 26.15, 21.55, 14.07; CIms (CH_4) : m/z 292 $(M+H)^+$.

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