A New Approach to the Asymmetric Synthesis of Carbacephams

Jean-François Berrien, Marie-Annick Billion, Henri-Philippe Husson, and Jacques Royer*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

Received December 12, 1994

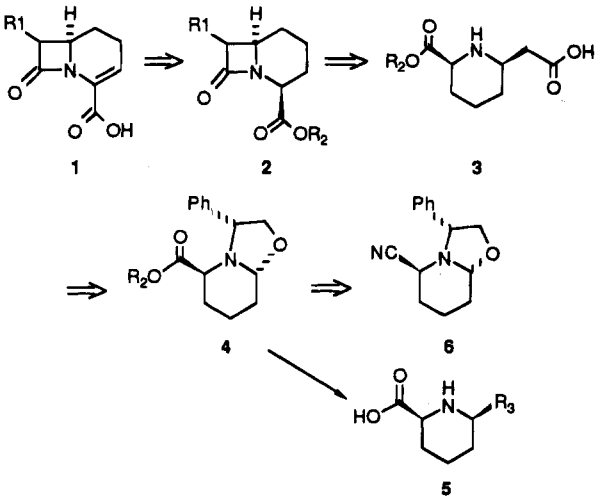
Carbacephems (**1**) are known to exhibit antibiotic activity[1–3] and have increased chemical stability compared to cephalosporins.[3] They are generally synthesized by first building the β-lactam ring (according to the Staudinger reaction[4,5]) followed by the formation of the six-membered ring.[6]

We describe herein a new approach to asymmetric synthesis of the carbacepham skeleton **2** (which can be conveniently used to prepare carbacephems **1** through known procedures in the field of carbapenem chemistry).[7]

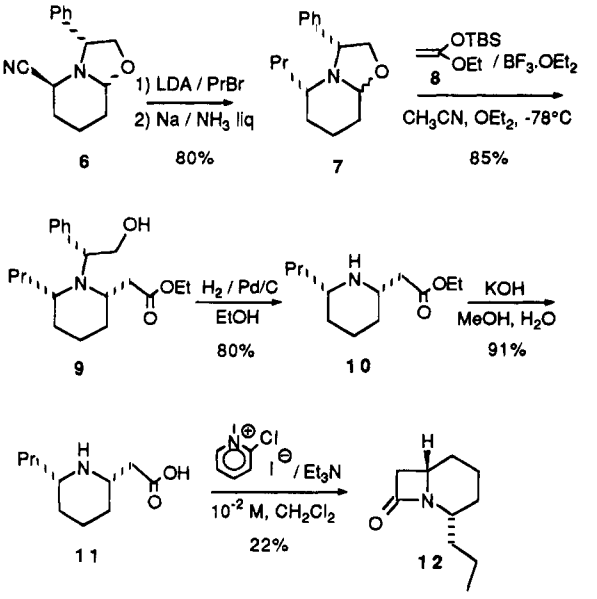
In a recent paper,[8] we described a novel access to enantiomerically pure 6-alkylated pipecolic acids **5** from the chiral synthon **6** (Scheme 1). The key step for this preparation was the diastereoselective alkylation of oxazolopipecolic ester **4** by a Grignard reagent to give the pipecolic acid **5**. We envisaged that this reaction could be extended to the addition of enolates in place of Grignard reagents to give the β-amino acid **3** which could then be cyclized to carbacepham **2**.

This route was first tested on a simple oxazolidine, namely 6-propyl-2-oxazolopiperidine **7** (Scheme 2), obtained in good yield in a two-step sequence from **6**.[9]

Scheme 1



Scheme 2



When **7** was reacted with silyl enol ether **8**[10] in acetonitrile at −78 °C, and in the presence of $BF_3{\cdot}Et_2O$, the β-amino ester **9** was obtained in 85% yield. Analysis of the crude mixture by GC–MS showed the formation of two epimers in a 9:1 ratio; the *cis* isomer was formed preferentially due to $A^{[1,2]}$ strain in the intermediate iminium.[11] This major *cis* isomer was readily separated from the *trans* isomer by chromatography, and enantiomerically pure β-amino acid **11** was obtained after hydrogenolysis of the chiral appendage of **9** followed by hydrolysis of the ester function of **10**.

Cyclization of **11** to β-lactam **12** was achieved using Mukaiyama's reagent.[12] The low yield (22%) of isolated

(1) For Loracarbef, see: Gao, C.; Chin, N. X.; Neu, H. C. *J. Antimicrob. Chemother.* **1988**, *22*, 155.

(2) (a) Blaszczak, L. C.; Brown, R. F.; Cook, G. K.; Hornback, W. J.; Hoying, R. C.; Indelicato, J. M.; Jordan, C. L.; Katner, A. S.; Kinnick, M. D.; McDonald, J. H., III; Morin, J. M.; Munroe, J. E.; Pasini, C. E. *J. Med. Chem.* **1990**, *33*, 1656. (b) Crowell, T. A.; Halliday, B. D.; McDonald, J. H., III; Indelicato, J. M.; Pasini, C. E.; Wu, E. C. Y. *J. Med. Chem.* **1989**, *32*, 2436. (c) Cook, G. K.; McDonald, J. H., III; Alborn, W.; Boyd, B. D.; Eudaly, J. A.; Indelicato, J. M.; Johnson, R.; Kasher, J. S.; Pasini, C. E.; Preston, D. A.; Wu, E. C. Y. *J. Med. Chem.* **1989**, *32*, 2442. (d) Ogasa, T.; Saito, H.; Hashimoto, Y.; Sato, K.; Hirata, T. *Chem. Pharm. Bull.* **1 989**, *37*, 315. (e) Uyeo, S.; Ona, H. *Chem. Pharm. Bull.* **1980**, *28*, 1563. (f) Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Patel, G. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551. (g) Guthikonda, R. N.; Cama, J. L.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584.

(3) (a) Matsukuma, I.; Yoshiiye, S.; Mochida, K.; Hashimoto, Y.; Sato, K.; Okachi, R.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 1239. (b) Mochida, K.; Ogasa, T.; Shimada, J.; Hirata,T.; Sato, K.; Okachi, R. *J. Antibiot.* **1989**, *42*, 283.

(4) For a review see: Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103.

(5) For the asymmetric Staudinger reaction, see, for example: Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. See also refs 6b and 2e.

(6) For a recent review see: Cooper, R. D. G. In *The Chemistry of Beta-Lactams*; Page, M. I., Ed.; Blackie and Son: London, 1992; pp 272–305. Cyclization reactions can be effected: (a) By carbenoid insertion: Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fischer, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M.; Nist, R. L.; Prather, D. E.; Sparks, D. L.; Vladuchick, W. C. *Tetrahedron Lett.* **1989**, *30*, 2321. (b) By Wittig reaction: Saito, S.; Ishikawa, T.; Moriwake, T. *Synlett* **1993**, 139. (c) By Horner-Emmons reaction: see ref 2g. (d) By Knoevenagel reaction: Mochida, K.; Hirata, T. *Chem. Pharm. Bull.* **1988**, *36*, 3642. (e) By Dieckmann reaction: Jackson, B. G.; Gardner, J. P.; Heath, P. C. *Tetrahedron Lett.* **1990**, *31*, 6317.

(7) (a) Asada, S.; Kato, M.; Asai, K.; Ineyama, T.; Nishi, S.; Izawa, K.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1989**, 486. (b) Ohta, T.; Shiokawa, S.; Iwashita, E.; Sato, N.; Sakurai, K.; Inayama, T.; Izawa, H.; Izawa, K.; Nozoe, S. *Heterocycles* **1992**, *33*, 143.

(8) Berrien, J.-F.; Husson, H.-P.; Royer, J. *J. Org. Chem.* **1994**, *59*, 3769.

(9) Oxazolopiperidine **7** was obtained as a mixture of diastereomers epimeric at the *N,O*-acetal center; see: Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.

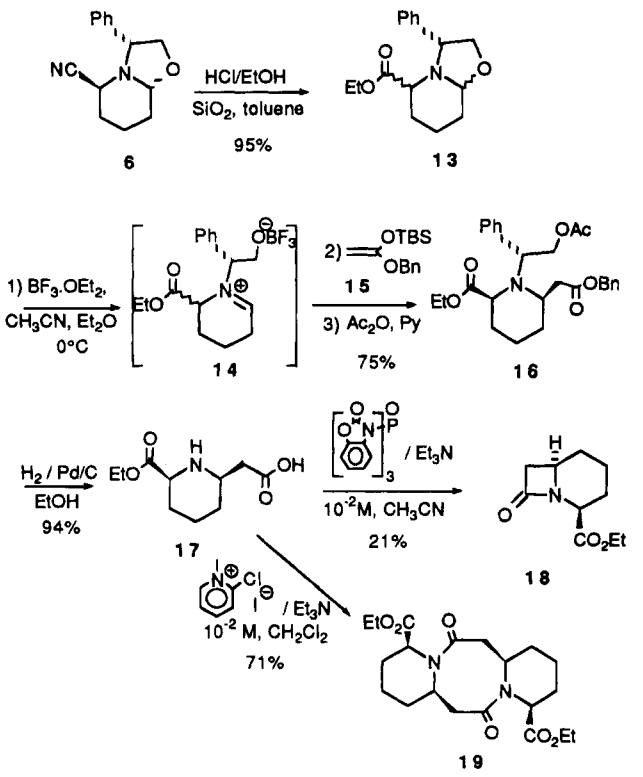
(10) Silyl enol ether **15** was prepared by the procedure described for **8**; see: Colvin, E. W. In *Best Synthetic Methods, Silicon in Organic Synthesis*; Katritsky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1988; p 122.

(11) Hwang, Y. C.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885.

(12) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465.

0022-3263/95/1960-2922$09.00/0

Scheme 3



product is due to the instability[13] of this simple 7-unsubstituted 1-azabicyclo[4.2.0]octan-8-one possessing an unfavored relative configuration. The use of other reagents[14] did not improve this result. As far as we know, similar products have never been prepared.

Despite the rather low yield of the cyclization step, this approach was extended to the synthesis of carbacephams bearing a carboxylic group at the C-2 position. Such derivatives have already been prepared by formation of the 6-membered ring,[13b,c] giving in most cases the natural, more stable relative configuration. The acidic ethanolysis of **6** gave **13** in high yield but as a mixture of epimers at the α position of the ester group in a 7:3 ratio (Scheme 3).[8] The silyl enol ether **15**[10] added as expected to the iminium **14** formed *in situ* from ester **13** by action of BF_3·Et_2O. The crude mixture was acetylated (Ac_2O, pyridine) to avoid lactonization and to obtain better separation of the four diastereomers (82:10:7:1 diastereomeric ratio as determined by GC–MS).[15] The major isomer *cis*-**16** was isolated in 75% yield after flash chromatography on silica gel. Hydrogenolysis of **16** gave the enantiomerically pure β-amino acid **17** in excellent yield. Cyclization of **17** to the β-lactam **18** was performed using Kunieda's reagent[16] in acetonitrile at 10^{-2} M. The yield of carbacepham **18** was estimated at 65% from the ^{1}H NMR spectrum of the crude product, but fell to 21% after purification by chromatography on silica gel. In this case, Mukaiyama's reagent in CH_2Cl_2 gave the dimer **19** (71%) as sole product.

It is noteworthy that **18** retains the expected relative configuration of the starting amino acid **17** without epimerization.[17] Barrett[13c] has reported the facile, complete epimerization of the corresponding thioester to the epimer having the more stable relative configuration under mild basic conditions. As in the case of β-lactam **12**, the lack of substituent at C-7 together with the unstable relative stereochemistry probably explains the modest yield of isolated product **18**. Better yields are thus expected for the preparation of bioactive compounds bearing subtituents at C-7. Nevertheless, β-lactam **18** was obtained in 14% overall yield from commercially available **6**.

Experimental Section[18]

[1′-(2″-Hydroxy-1″-phenylethyl)-6′-propylpiperidin-2′-yl]-acetic Acid Ethyl Ester (9). A dry solution of (5*S*)-3-phenyl-5-propylhexahydrooxazolo[3,2-*a*]pyridine (**7**)[9] (316 mg, 1.28 mmol) in a 1:1 mixture of CH_3CN and ether (12 mL) was treated at −10 °C under argon with 160 mL of BF_3·OEt_2 (1.30 mmol). After 5 min, the solution was cooled to −78 °C and silyl enol ether **8**[10] (1.95 mmol) was added. After 15 min of additional stirring, the reaction mixture was treated with a saturated solution of $NaHCO_3$ (12 mL) and H_2O_2 30% (1 mL) for 1 h. Organic solvents were then evaporated, and the resulting suspension was extracted with CH_2Cl_2 (3 × 15 mL). Organic layers were washed with water (10 mL), dried with $MgSO_4$, and evaporated. The resulting crude oil was purified by chromatography on silica gel (heptane/ether 1/1) to give 365 mg (85%) of *cis-(2S,6S)*-**9** as a colorless oil: $[\alpha]_D$ = +19.9 (*c* = 1.4, MeOH); IR (film, cm^{-1}) 3500, 1730; MS (CI) *m/z* 334 (MH^+, 100), 316 (17), 302 (15), 246 (32); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.5–7.3 (m, 5 H), 4.15–3.95 (m, 2 H), 3.90–3.75 (m, 2 H), 3.60 (dd, *J* = 3.1, 9.0 Hz), 2.9–2.8 (m, 1 H), 2.63 (dd, *J* = 6.9, 15.1 Hz), 2.28 (dd, *J* = 7.4, 15.1 Hz), 1.6–1.1 (m, 10 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 0.85 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.5, 140.5, 128.0, 127.1, 68.8, 62.1, 59.8, 53.0, 51.5, 39.1, 36.9, 27.8, 25.6, 20.9, 14.5, 13.9, 13.8. Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.04; H, 9.37; N, 4.20. Found: C,72.03; H, 9.20; N, 3.98.

***(2S,6S)*-1-(6′-propylpiperidin-2′-yl)acetic Acid Ethyl Ester (10).** A 163 mg portion of *(2S,6S)*-**9** (0.49 mmol) was subjected to hydrogenation at atmospheric pressure and room temperature in the presence of Pd/C (40 mg) in EtOH (10 mL). The suspension was then filtered and the solvent evaporated. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOH 97/3) to give 83 mg (80%) of *(2S,6S)*-**10** as a colorless oil: IR (film, cm^{-1}) 3400, 1735; MS (IC) *m/z* 214 (MH^+, 100); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.3 Hz, 2 H), 2.94 (dtd, *J* = 2.4, 6.5, 10.7 Hz, 1 H), 2.6–2.5 (m, 1 H), 2.41 (d, *J* = 6.6 Hz, 2 H), 1.78 (d quint, *J* = 3.2, 12.9 Hz, 1 H), 1.62 (td, *J* = 1.9, 12.5 Hz, 1 H), 1.5–0.85 (m, 14 H), 1.25 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (62,5 MHz, $CDCl_3$): δ 172.2 , 60.1, 56.4, 53.4, 41.3, 39.2, 32.2, 32.0, 24.4, 18.8, 14.0.

***(2S,6S)*-1-(6′-Propylpiperidin-2′-yl)acetic Acid (11).** To a solution of *(2S,6S)*-**10** (90 mg, 0.48 mmol) in MeOH was added 5 mL of a 0.15 M aqueous solution of KOH. The resulting solution was refluxed for 3 h, the pH adjusted to 5 with a 1 N HCl solution, and then the solvent evaporated. The residue was purified by chromatography on HP 20SS resin (H_2O/MeOH/AcOH 94/5/1) to give, after recrystallization (Et_2O/MeOH 5/1), 73 mg (91%) of *(2S,6S)*-**11**: mp 189 °C; $[\alpha]_D$ = +46.2 (*c* = 1.5, H_2O); $[\alpha]_D$ = +49.0 (*c* = 0.8, MeOH); IR (KBr, cm^{-1}) 3400, 1620; MS (IC) *m/z* 186 (MH^+, 100), 184 (6), 140 (4); ^{1}H NMR (250 MHz,

(13) (a) Busson, R.; Vanderhaeghe, H. *J. Org. Chem.* **1978**, *43*, 4438. (b) Kametani, T.; Chu, S.-D.; Itoh, A.; Maeda, S.; Honda, T. *J. Org. Chem.* **1988**, *53*, 2683. (c) Barrett, A. G. M.; Graboski, G. G.; Sabat, M.; Taylor, S. J. *J. Org. Chem.* **1987**, *52*, 4693.

(14) (a) The Mukaiyama–Ohno reagent gave 6% yield after tedious purification. For this reagent see: Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406. Bycroft, B. W.; Chhabra, S. R. *J. Chem. Soc., Chem. Comm.* **1989**, 423. (b) Mesyl chloride in phase transfer catalysis gave a 3% yield. For this reagent see: Loewe, M. F.; Cvetovich, R. J.; Hazen, G. G. *Tetrahedron Lett.* **1991**, *32*, 21, 2299. Bakasse, M.; Reliquet, A.; Reliquet, F.; Duguay, G.; Quiniou, H. *J. Org. Chem.* **1989**, *54*, 2889. (c) Thionyl chloride gave less than 2% yield. For this reagent see ref 13a.

(15) Epimerization α to the ethyl ester also occurred during this procedure.

(16) Nagamatsu, T.; Kunieda, T. *Chem. Pharm. Bull.* **1988**, *36*, 1249.

(17) This was shown in the ^{1}H NMR spectrum by the chemical shift of the proton based on C-2 (3.71 ppm compared to 4.5–4.6 values reported for epimeric ester analogues[13b,c]) and its long range coupling constant J^5 = 1.4 Hz with one proton at C-6 (1-azabicyclo[4.2.0] numbering).

(18) For a general experimental procedure see ref 8.

DMSO-d_6) δ 5.2 (bs, 2 H), 3.2–2.8 (m, 2 H), 2.32 (dd, J = 4.3, 16.5 Hz, 1 H), 2.19 (dd, J = 9.1, 16.5 Hz, 1 H), 1.9–1.2 (m, 10 H), 1.02 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (62.5 MHz, CD_3OD) δ 177.0, 58.1, 56.6, 40.1 36.9, 29.7, 29.5, 23.5, 19.4, 14.1. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.33; N, 7.56. Found: C, 64.45; H, 10.06; N, 7.55.

(2*S*, 6*S*)-2-Propyl-1-azabicyclo[4.2.0]octan-8-one (12). To a solution of 2-chloro-1-methylpyridinium iodide (335 mg, 1.3 mmol) and Et_3N (365 mL, 2.6 mmol) in dry CH_2Cl_2 (120 mL) was added β-aminoacid (2*S*,6*S*)-**11** (280 mg, 1.12 mmol) over a period of 2 h. After 2 h more, the solvent was evaporated and the residue purified by chromatography on silica gel (CH_2Cl_2/Et_2O 80/20) to give 57 mg (22%) of (2*S*,6*S*)-**12** as a colorless oil: $[\alpha]_D$ = −75.4 (c = 1.1, CH_2Cl_2); IR (film, cm^{-1}) 2920, 2850, 1742, 1395; MS (CI) m/z 168 (MH^+, 100), 73 (37), 71 (15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (dtd, J = 1.7, 4.3, 10.8 Hz, 1 H), 3.05–2.9 (m, 1 H), 2.98 (ddd, J = 1.4, 4.7, 14.3 Hz, 1 H), 2.48 (dd, J = 1.7, 14.1 Hz, 1 H), 2.3–2.15 (m, 1 H), 1.97 (dqd, J = 0.9, 3.5, 12.6 Hz, 1 H), 1.89 (dquint, J = 3.4, 13.8 Hz, 1 H), 1.71 (dqd, J = 0.4, 3.3, 12.8 Hz, 1 H), 1.6–1.0 (m, 6 H), 0.95 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (62,5 MHz, $CDCl_3$) δ 164.7, 56.7, 47.9, 43.9, 34.8, 31.8, 30.9, 22.8, 20.0, 13.9; HRMS (CI) 168.1384 (calcd for $C_{10}H_{18}NO$ 168.1388).

***(2S,6R)*-1-(2′-acetoxy-1′-phenylethyl)-6-[(benzyloxycarbonyl)methyl]piperidine-2-carboxylic Acid Ethyl Ester (16).** A dry solution of **13**[8] (1.95 g, 7.08 mmol) in a 1:1 mixture of CH_3CN and ether (50 mL) was treated at −10 °C under argon with 0.87 mL of BF_3-OEt_2 (7.08 mmol). After 5 min, the solution was cooled to −78 °C and silyl enol ether **15**[10] (11 mmol) was added. After 15 min of additional stirring, the reaction mixture was treated with a saturated solution of $NaHCO_3$ (25 mL) and H_2O_2 30% (5 mL) for 1 h. Organic solvents were then evaporated, and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were washed with water (50 mL), dried over $MgSO_4$, and evaporated. The resulting crude oil was dissolved in pyridine (15 mL), and acetic anhydride (5 mL) was added. The mixture was stirred at room temperature overnight. The solvent was then evaporated, and the residue treated with a saturated solution of $NaHCO_3$ (25 mL) and then extracted with CH_2Cl_2 (3 × 25 mL). Organic layers were washed with H_2O (20 mL) and dried over $MgSO_4$ and the solvent evaporated. The oily residue was analysed by GC–MS (dr 82: 10:7:1) and purified by chromatography on silica gel (heptane/ether 2/1) to give 2.48 g (75%) of the major diastereomer *(2S,6R)*-**16** as a colorless oil: $[\alpha]_D$: = −66.9 (c = 2.0, $CHCl_3$); IR (film, cm^{-1}) 1735; MS (CI) m/z 468 (MH^+, 100), 318 (12), 306 (11), 246 (8); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 10 H), 5.12 (s, 2 H), 4.57 (t, J = 5.5 Hz, 1 H), 4.41 (dd, J = 6.2, 11.6 Hz, 1 H), 4.30 (dd, J = 5.0, 11.6 Hz, 1 H), 4.03 (q, J = 7.0 Hz, 2 H), 3.9-3.75 (m, 1 H), 3.35–3.25 (m, 1 H), 2.95 (dd, J = 2.7, 15.2 Hz, 1 H), 2.58 (dd, J = 10.8, 15.2 Hz, 1 H), 1.91 (s, 3 H), 1.8–1.4 (m, 5 H), 1.20 (t, J = 7.1 Hz, 3 H), 0.95–0.75 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 172.8, 170.8, 140.2, 136.1, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 66.5, 66.1, 63.8, 60.3, 55.5, 51.0, 35.0, 29.1, 27.5, 20.8, 16.1, 14.2. Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 2.99. Found: C, 69.56; H, 7.05; N, 3.08.

(2*S*,6*R*)-6-(Carboxymethyl)piperidine-2-carboxylic Acid Ethyl ester (17). *(2S,6R)*-**16** (1.18 g) was subjected to hydrogenation (3 h) at atmospheric pressure and room temperature in the presence of Pd/C (85 mg) in EtOH (20 mL). The suspension was then filtered and the solvent evaporated. The residue was purified by chromatography on HP 20SS resin (H_2O/AcOH 99/1) to give 512 mg (94%) of (2*S*,6*R*)-**17** which was recrystallized from toluene: $[\alpha]_D$ = −35.4 (c = 0.9, $CHCl_3$); MS (CI) m/z 216 (MH^+, 100); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.1–6.9 (bs, 2 H), 4.22 (q, J = 7.1 Hz, 2 H, 3.66 (dd, J = 2.5, 1.7 Hz, 1 H), 3.3–3.15 (m, 1 H), 2.57 (d, J = 5.2 Hz, 2 H), 2.16 (bd, J = 11.5 Hz, 1 H), 1.95 (bd, J = 11.5 Hz, 1 H), 1.8–1.5 (m, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.95–0.8 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.4, 169.9, 61.9, 57.6, 54.1, 39.3, 28.7, 26.9, 23.1, 14.2. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.50. Found: C,55.35; H, 8.11; N, 6.60.

(2*S*,6*R*)-8-Oxo-1-azabicyclo[4.2.0]octane-2-carboxylic Acid Ethyl Ester (18). To a dry solution of (2*S*,6*R*)-**17** (105 mg, 0.48 mmol) and tris(2-oxo-3-benzoxazolinyl)phosphine oxide[19] (215 mg, 0.48 mmol) in CH_3CN (50 mL) under argon was added 220 mL of triethylamine (1.58 mmol). After being refluxed for 8 h, the reaction mixture was cooled, poured into 250 mL of ether, and washed with a 0.1 N solution of HCl in brine (20 mL) and then with a 0.1 N solution of $NaHCO_3$ in brine (20 mL) and finally with 30 mL of brine. The organic layer was dried over $MgSO_4$, and the solvents were evaporated. The residue was resuspended in 100 mL of ether and centrifuged. Evaporation of the etheral supernatant gave 210 mg of an oil composed of benzoxazolidinone and carbacepham **18** (small amount of dimer **19** was also detected by ^{1}H NMR). This crude oil was purified by chromatography on silica gel (heptane/acetone 4/6) to give 20 mg of (2*S*,6*R*)-**18** (21%) as a colorless oil. This sample did not give a satisfactory microanalysis, and extensive purification and chromatography resulted in an important lost of material: IR (KBr, cm^{-1}) 1755, 1737; MS (IC) m/z 198 (MH^+, 100); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.27 (q, J = 7.2 Hz, 2 H), 3.71 (ddd, J = 1.4, 4.6, 10.8 Hz, 1 H), 3.39 (dtd, J = 1.9, 4.4, 10.6 Hz, 1 H), 3.09 (ddd, J = 1.5, 4.6, 14.5 Hz, 1 H), 2.62 (dd, J = 1.9, 14.5 Hz, 1 H), 2.1–1.2 (m, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.5, 165.0, 61.7, 55.7, 48.3, 44.5, 29.8, 27.0, 21.1, 14.0; HRMS (CI) 198.1132 (calcd for $C_{10}H_{16}NO_3$ 198.1130).

***(4S,7aR,11S,14aR)*-6,13-Dioxododecahydrodipyrido[1,2-*a*:1′-*e*] [1,5]diazocine-4,11-dicarboxylic Acid Diethyl Ester (19).** The procedure for the obtention of **12** was applied to (2*S*,6*R*)-**17** (115 mg) and gave 35 mg of (4*S*,7a*R*,11*S*,14a*R*)-**19** (71%), recrystallized from heptane. Carbacepham **18** was not detected in the chromatographic fractions: IR (KBr, cm^{-1}) 1750, 1730, 1637; MS (IC) m/z 395 (MH^+, 50), 170 (15), 156 (20), 117 (17), 115 (12), 73 (100); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.32 (dd, J = 1.7, 6.5 Hz, 2 H), 4.66 (dtd, J = 2.7, 5.9, 12.7 Hz, 2 H), 4.3–4.0 (m, 4 H), 3.10 (dd, J = 12.7, 16.5 Hz, 2 H), 2.77 (dd, J = 5.8, 16.5 Hz, 2 H), 2.35–2.2 (m, 2 H), 1.9–1.5 (m, 10 H), 1.22 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.9, 170.3, 61.3, 50.5, 49.8, 44.5, 29.4, 25.9, 15.8, 14.2. Anal. Calcd for $C_{20}H_{30}NO_6$: C, 60.90; H, 7.66; N, 7.10. Found: C, 60.96; H, 7.61; N, 7.15.

JO9421079

(19) Tris(2-oxo-3-benzoxazolinyl)phosphine oxide was prepared according to: Nagamatsu, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 2375.