Ethoxycarbonylation of 3-keto-4-methyl-5-oxacephams

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Dedicated to Professor Mieczysław Mąkosza on his 70th birthday

(received 11 Nov 03; accepted 13 Apr 04; published on the web 16 Apr 04)

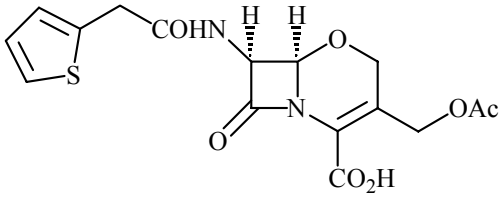
Abstract

Due to their multifunctional character, the ethoxycarbonylation of 3-keto-5-oxa-cephams (**10**, **27** and **28**) using ethyl cyanoformate in THF/HMPA solution led to expected products **14**, **27** and **29** in a low yield only. Apart from the desired compounds, the *O*-acylation, *C*-alkylation at C-7, and the addition of CN^- anion to the keto group were also observed.

Keywords: 5-Oxacephams, alkoxycarbonylation

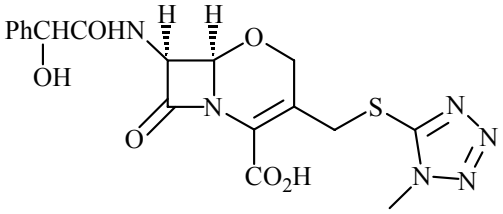
Introduction

Synthesis of the racemic 5-oxacephalotin (**1**) and 5-oxacephamandol (**2**) by Merck scientists[1,2] has shown that the substitution of cephalosporin sulfur atom by the oxygen atom resulted in the same or higher antibiotic activity in comparison to the parent drug. A thorough investigation undertaken during late seventies by Shionogi Co.[3] led to the introduction to the market of two novel oxacephamycins: latamoxef (**3**) and flomoxef (**4**) that represent third and fourth generation of this class of antibiotics. At the end of the eighties the Merck and Meiji groups[4] reported on a new 4-methyl-cephalosporin **5** which offers the stability toward β-lactamases together with a significant antibacterial activity. The later contribution had prompted us to demonstrate that the 4-methyl-5-oxacephem **6** related to cephalosporin **5** could be obtained starting from L-rhamnal **7**.[5] The formation of the six-membered oxazine ring proceeded *via* an intramolecular ester condensation in **8**.



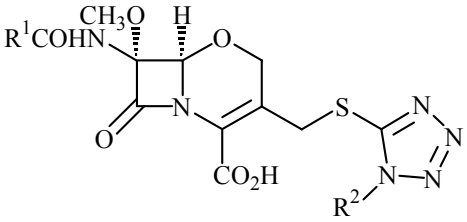
(±) 5-oxacephalotin

1



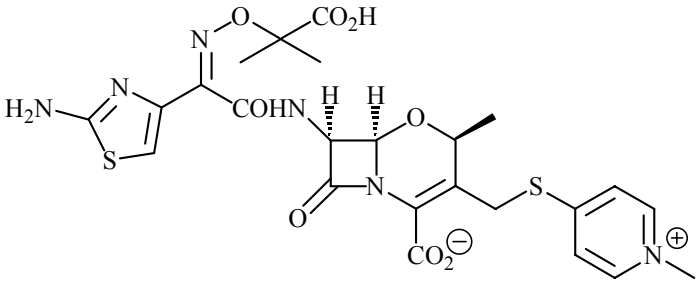
(±) 5-oxacephamandol

2

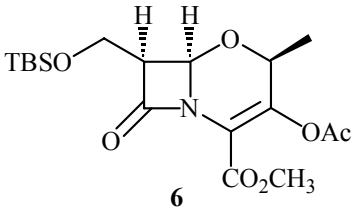


3: $R^1 = p\text{-}HOC_6H_4(CO_2H)CH$, $R^2 = CH_3$

4: $R^1 = CHF_2SCH_2$, $R^2 = HOCH_2CH_2$



OCP-9-176 **5**



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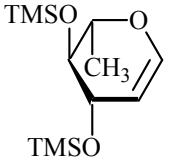

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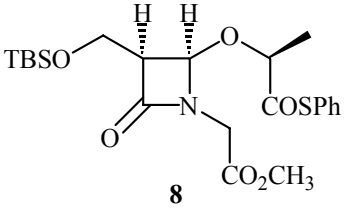
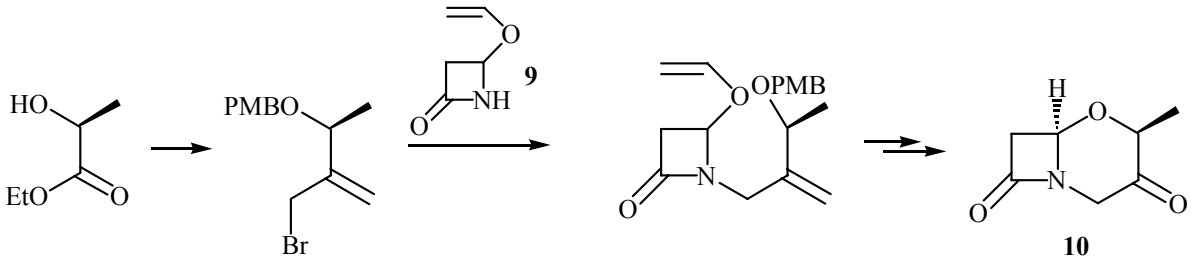


8

Very recently we have shown[6] that our new methodology, that utilizes the 4-vinyloxy-azetidin-2-one (**9**)[7] as a starting synthon, opens an entry to a range of compounds possessing the 4-methyl-5-oxacepham skeleton, providing that the ethyl lactate is used as a chiral starting material (Scheme 1).[6]

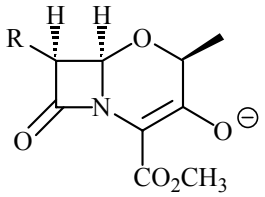


10

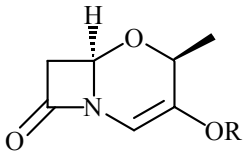
Scheme 1

The present paper describes the introduction of the alkoxycarbonyl function at C-2 of (4*S*,6*R*) 3-keto-4-methyl-5-oxacepham **10**. The alkoxycarbonylation of the enolate of **10** should proceed *via* the intermediate **11** (R=H), related to the product of the ester condensation performed on **8** [**11** (R=CH_2OTBS)].[5] Hence, we were able to expect a positive outcome of the reaction.

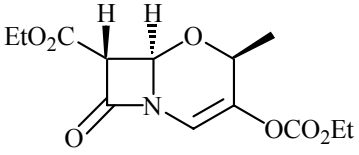
Results and Discussion



11: R = H, CH_2OTBS



12: R = COOEt
21: R = TMS

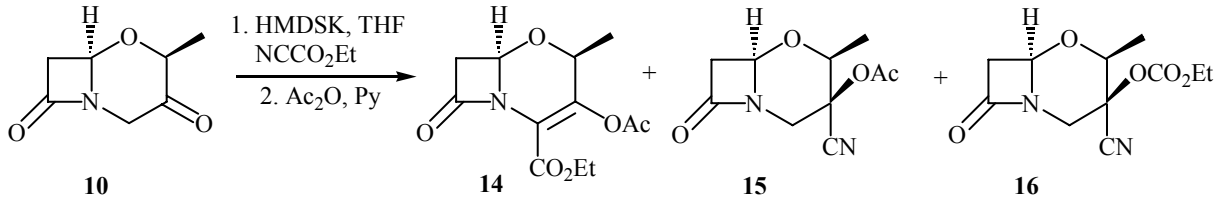


13

A multifunction character of **10** required generation of the enolate while under the kinetic control of the reaction, which, in turn, anticipated an addition of ketone to the excess of the strong base in order to avoid a self-condensation of the substrate.[8]

Reaction of **10** with 1.1 equiv. of HMDSLi at –78°C followed by the addition of ethyl chloroformate provided only the product of *O*-acylation (**12**). The same reaction carried out with 2.5 equiv. of the base led to a mixture of **12** and **13**.

Softer base, the ethyl cyanoformate and HMDSK gave after acetylation a mixture of three products **14**, **15** and **16** in a ratio 1:3.3:1.2, respectively (Scheme 2). Acetylation of a post reaction mixture was necessary since expected β-ketoesters have been found to be unstable.[5]

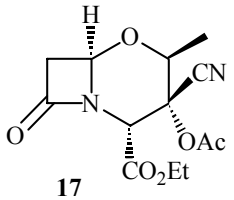


Scheme 2

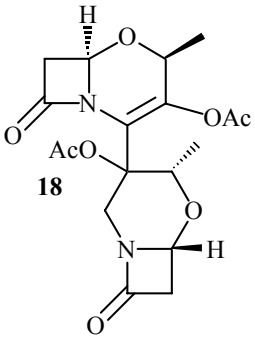
Configuration of **15** and **16** was assigned under the assumption of the *anti*-addition of a cyano group to the 4-methyl substituent of the substrate.

Addition of HMPA to the reaction mixture[9] resulted, after acetylation, of formation of two products: **14** (10%) and **17** (34%). Configuration of **17** was assigned by analogy to the related compound **22**.

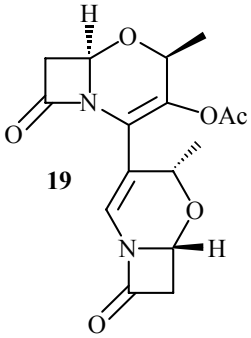
It was found that the ketone **10** undergoes the self-condensation easily to provide, after acetylation, the diacetate **18** which, upon heating, eliminates elements of acetic acid to give a dimeric compound **19** in a 50% overall yield.



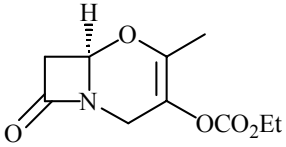
17



18



19

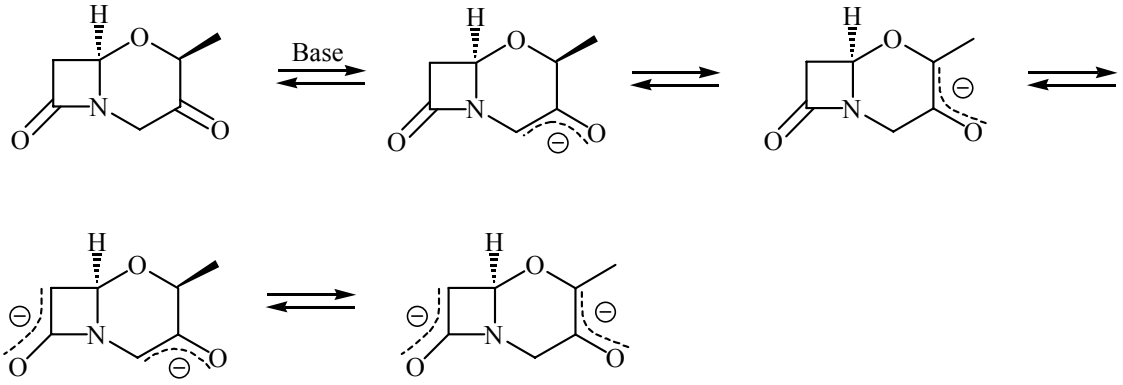


20

Attempts to introduce the alkoxycarbonyl function by treatment of the enolate of **10** with ethyl imidazoformate,[10] diethyl carbonate or the more reactive di-*p*-nitrobenzyl carbonate[11] were unsuccessful. As the result compound **18** was obtained as the only isolated product.

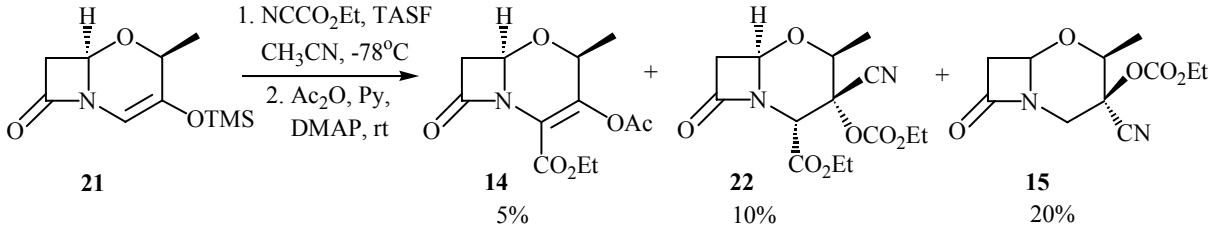
An interesting result was noticed when **10** has been treated with *S*-phenyl *O*-ethyl thiocarbonate[12] in the presence of HMDSLi and Bu_4NHSO_4. The enol carbonate **20**, obtained in 11% yield, was the only isolated product.

It was found that the order of addition of reactants during alkoxycarboylation of the enol of **10** did not influence significantly the final result of the reaction. The ketone **10** has three acidic centers at C-2, C-4 and C-7 carbon atoms. Bearing in mind the results of the alkoxycarboylation reactions, one can assume that deprotonation of **10** leads to a mixture of mono-anions, di-anions and the neutral compound (Scheme 3). The constituents of such a mixture may equilibrate leading, upon reaction with the electrophile, to a variety of alkoxycarbonyl compounds **12**-**15**, **17**, **20** and the dimer **18**. Moreover the 3-keto group may add cyano group to form corresponding cyanohydrins **15**-**17**. Consequently, complicated mixtures of products are formed.



Scheme 3

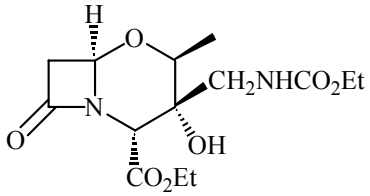
Similar results of alkoxycarbonylation were obtained when the silyl vinyl ether **21** (Scheme 4) was subjected to the reaction with ethyl cyanoformate in the presence of tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF). Desired products **14** and **22** were obtained in low yield only accompanied by undesired nitrile **15**.



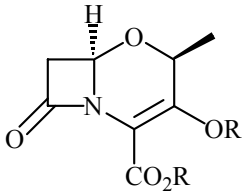
Scheme 4

The configuration of **22** was proved by analyzing the $^3J_{CH}$ coupling constants of the nitrile carbon atom. It has been found by Kingsbury and Wang[13] that the value of vicinal coupling constants in a six-membered ring depends on the relative location of nitrile substituent and the neighboring protons. For the axial-axial array, the $^3J_{CH}$ amounts to 9.2±0.5 Hz whereas for the respective axial-equatorial array its value is about 1.7 Hz (in a conformationally labile systems the value of such a coupling constant may increase to 3.5-4.6 Hz).[13] In the case of compound **22** the $^3J_{C,H\text{-}4}$ = 7.8 Hz whereas the $^3J_{C,H\text{-}2}$ = 4.8 Hz. These results suggest the pseudoaxial orientation of the nitrile *cis* to the methyl and *trans* to the ethoxycarbonyl group. The relative location of substituents at C-2, -3 and -4 of carbon atoms can be a consequence of the fast equilibration before the final product is quenched by acetylation.

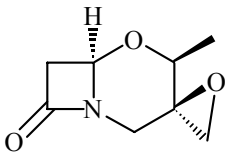
Hydrogenation of the nitrile group in **22** afforded **23** which is the result of migration of the acyl from oxygen to the nitrogen atom. The existence of NOE's between both protons of the methylene group at C-3 and vicinal H-2 and CH_3-4 supports the assignment made by the analysis of $^3J_{CH}$ coupling constants for the nitrile **22**.



23



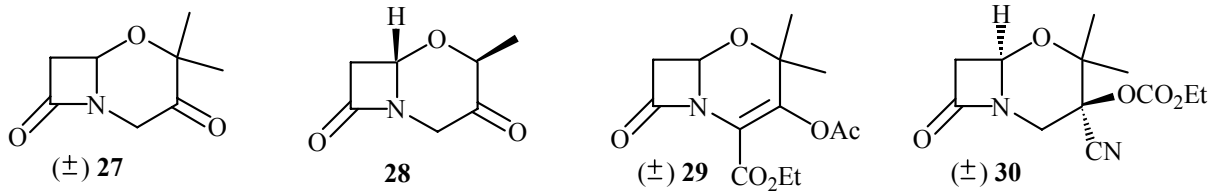
24: R = H
25: R = Me



26

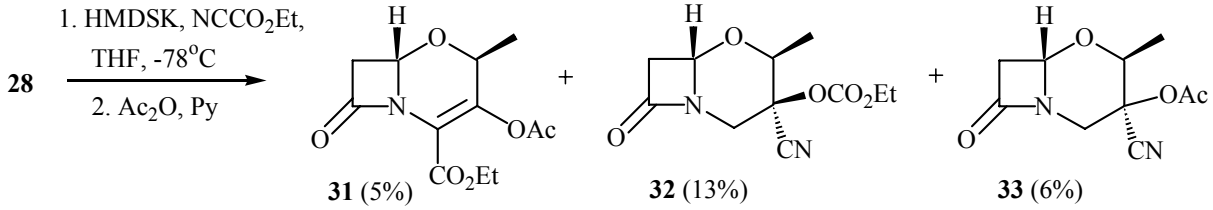
Direct carboxylation of the anion **10** with the carbon dioxide, following closely the known procedure[14] failed due to the low stability of the acid which underwent fast decarboxylation. As a result, instead of expected methylation of **24** with diazomethane, which should provide the ester **25**, the epoxide **26** was obtained which likely is a product of addition of diazomethane to the carbonyl group of **10**. The configuration of **26** was assigned by anticipation of the approach of diazomethane *anti* to the methyl substituent. Due to the presumed conformational flexibility of the spiroepoxide, the NOE's did not provide an unequivocal assignment.

For comparison we also performed the ethoxycarbonylation of racemic 4,4-dimethyl-5-oxacepham **27** as well as compound **28** which is the C-6-epimer of **10**.[6]



In the case of **27** under the same conditions as used for the ethoxycarbonylation of **10** (THF/HMPA), we obtained **29** (10%) accompanied by **30** (25%).

The ethoxycarbonylation of **28**, under the same conditions yielded three products **31**-**33** (Scheme 5). In neither case we did notice the presence of even a trace of products related to **17**.



Scheme 5

Configuration of **30**, **32** and **33** was assigned assuming the *exo*-approach to **27** *anti* to the 4-methyl group in **28**, respectively.

Conclusions

3-Keto-5-oxacephams **10**, **27** and **28** have several acidic centers. Deprotonation of these compounds leads to a number of mono- and di-anions which may also equilibrate. In addition, the free keto group may add CN^- anion derived from ethyl cyanoformate to form corresponding cyanohydrin or its ester. As a consequence of that, a mixture of products is formed, in which desired compounds **14**, **29** and **31** are obtained in low yield only.

Experimental Section

General Procedures. Melting points were determined on a Koefler hot-stage apparatus. NMR spectra were recorded using Brucker Avance 500 instrument. IR spectra were recorded on a Perkin-Elmer FTIR Spectrum 200 spectrophotometer. UV spectra were measured on a Cary 100 spectrophotometer in acetonitrile. CD spectra were recorded between 180-400 nm at room temperature with a JASCO J-715 spectropolarimeter using acetonitrile solutions. Mass spectra were recorded using AMD-604 Inectra GmbH and HPLC-MS with Mariner and API 356

detectors. Optical rotations were measured using a JASCO P 3010 polarimeter at 22±3°C. Column chromatography was performed using E. Merck Kiesel Gel (230-400 mesh).

(4*S*, 6*R*) 3-Ethoxycarbonyloxy-4-methyl-5-oxa-2-cephem (12). To a solution of **10** (23 mg, 0.15 mmol) in THF (4 mL), cooled to –78°C, HMDSLi (165 μL, 1 M solution in THF, 0.17 mmol) was added dropwise. Subsequently, ethyl chloroformate (16 μL, 0.17 mmol) was added and the mixture was left for 1 h at –78°C. The temperature was allowed to rise to 0°C and the mixture was poured into cold water and extracted with *t*–BuOMe (3 x 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography using AcOEt/hexane 20:80 v/v as an eluant to afford of **12** (4 mg, 20%). Syrup; $[\alpha]_D$ +4.30 (c 1.30, CH_2Cl_2); IR (CH_2Cl_2) 1780, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) 1.34 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.34 (d, 3H, J 6.6 Hz, Me), 2.96 (dd, 1H, *J* 15.8, 1.3 Hz, H_a–7), 3.26 (br dd, 1H, *J* 15.8, 3.8 Hz, H_b–7), 4.26 (q, 2H, *J* 7.1 Hz, CH_2CH_3), 4.74 (qd, 1H, *J* 6.6, 1.5 Hz, H–4), 5.13 (dd, 1H, *J* 3.7, 1.2 Hz, H–6), 6.63 (d, 1H, *J* 1.3 Hz, H–2); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.8, 44.6, 65.3, 70.1, 76.0, 112.3, 140.2, 152.9, 166.0; MS (EI–HR) m/z: M^+ calcd for $C_{10}H_{13}NO_5$: 227.07937. Found: 227.07986; Anal. Calcd for $C_{10}H_{13}NO_5$ (227.22): C, 52.86; H, 5.77; N, 6.16. Found: C, 53.15; H, 6.06; N, 5.92.

(4*S*, 6*R*, 7*R*) 7-Ethoxycarbonyl-3-ethoxycarbonyloxy-4-methyl-5-oxa-2-cephem (13). Compound **10** (47 mg, 0.3 mmol) in THF (5 mL) cooled to –78°C was treated dropwise with HMDSLi (750 μL, 1 M solution in THF, 0.75 mmol). After 5 min. ethyl chloroformate (72 μL, 0.75 mmol) was added. The mixture was left for 0.5 h at –78°C. Subsequently the temperature was allowed to rise to 0°C, the mixture was poured into cold water and extracted with ethyl acetate (3 x 5 mL). Combine extracts were dried over $MgSO_4$ and concentrated. The crude product was separated by chromatography using AcOEt/hexane 20:80 v/v as an eluant to yield: **13** (15 mg, 10%) and **12** (14 mg, 21%).

13. syrup; $[\alpha]_D$ +98.68 (c 0.47, CH_2Cl_2); IR (CH_2Cl_2) 1789, 1764, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): 1.35, 1.31 (2t, 6H, *J* 7.1 Hz, 2 CH_2CH_3), 1.36 (d, 3H, *J* 6.7 Hz, Me), 4.01 (d, 1H, *J* 1.8 Hz, H–7), 4.27, 4.26 (2q, 4H, *J* 7.1 Hz, CH_2CH_3), 4.76 (qd, 1H, *J* 6.7, 1.5, H–4), 5.35 (d, 1H, *J* 1.2 Hz, H–6), 6.68 (d, 1H, *J* 1.4 Hz, H–2). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.1, 16.8, 61.5, 62.1, 65.4, 70.4, 77.9, 112.0, 140.8, 152.7, 160.1, 164.9; MS (HR–EI) m/z: M^+ calcd for $C_{13}H_{17}NO_7$: 299.10050. Found: 299.10010; Anal. Calcd for $C_{13}H_{17}NO_7$ (299.28): C, 52.17; H, 5.73; N, 4.68. Found: C, 53.82; H, 6.47; N, 4.43.

(4*S*, 6*R*) 3-Acetoxy-2-ethoxycarbonyl-4-methyl-5-oxa-2-cephem (14), **(3*R*, 4*S*, 6*R*) 3-acetoxy-3-cyano-4-methyl-5-oxacepham (15)** and **(3*R*, 4*S*, 6*R*) 3-cyano-3-ethoxycarbonyloxy-4-methyl-5-oxacepham (16).** To a solution of **10** (41 mg, 0.26 mmol) in THF (1.5 mL), ethyl cyanoformate (29 μL, 0.29 mmol) was added. The mixture was cooled to –78°C, treated with HMDSK (610 μL, 0.5 M solution in toluene, 0.3 mmol) and left for 1.5 h while the temperature was maintained. Subsequently, the reaction was quenched by addition of acetic acid (22 μL), pyridine (1 mL) and acetic anhydride (0.5 mL). The temperature was allowed to rise to room temperature, the mixture was poured into water and extracted with ethyl

acetate (3 x 2 mL). The combined extracts were dried over $MgSO_4$, concentrated and purified by chromatography using AcOEt/hexane as an eluant to afford compounds **14** (7 mg, 10%), **15** (7 mg, 12%) and **16** (22 mg, 33%).

14. syrup; $[\alpha]_D$ +140.35 (c 0.17, CH_2Cl_2); IR (CH_2Cl_2) 1791, 1725 cm^{-1}; ^1H NMR ($CDCl_3$): 1.32 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.41 (d, 3H, *J* 6.7 Hz, Me), 2.24 (s, 3H, Ac), 2.90 (dd, 1H, *J* 15.7, 0.8 Hz, H_a–7), 3.34 (dd, 1H, *J* 15.7, 3.8 Hz, H_b–7), 4.30, 4.25 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 4.54 (q, 1H, *J* 6.7 Hz, H–4), 5.14 (dd, 1H, *J* 3.8, 0.7 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 14.0 ($CH_2\mathbf{C}H_3$), 17.1 ($\mathbf{C}H_3$), 20.7 ($CO\mathbf{C}H_3$), 44.8 (C–7), 61.7 ($\mathbf{C}H_2CH_3$), 70.5 (C–4), 76.3 (C–6), 118 (C–2), 146.9 (C–3), 160.0 (C_2–**C**O), 165.8 (C–8), 167,8 (**C**OCH_3); MS (HR–LSIMS) m/z: $(M+H)^+$ calcd for $C_{12}H_{16}NO_6$: 270.09776. Found: 270.09871.

15. syrup; IR (CH_2Cl_2) 1786 cm^{-1}; ^1H NMR ($CDCl_3$): 1.49 (d, 3H, *J* 6.1 Hz, Me), 2.14 (s, 3H, Ac), 2.97 (dd, 1H, *J* 13.7, 1.6 Hz, H_a–2), 3.03 (dd, 1H, *J* 15.3, 0.7 Hz, H_a–7), 3.24 (ddd, 1H, *J* 15.3, 3.4, 1.6 Hz, H_b–7), 3.86 (q, 1H, *J* 6.1 Hz, H–4), 5.05 (d, 1H, *J* 13.7 Hz, H_b–2), 5.09 (br d, 1H, *J* 3.1 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 15.9, 20.5, 45.6, 46.2, 69.3, 74.8, 77.9, 114.6, 166.5, 167.8; MS (HR–LSIMS) m/z: $(M+H)^+$ calcd for $C_{10}H_{13}N_2O_4$: 225.08753. Found: 225.08819.

16. syrup; $[\alpha]_D$ +54.20 (c 0.2, CH_2Cl_2); IR (CH_2Cl_2) 1785, 1767 cm^{-1}; ^1H NMR ($CDCl_3$): 1.35 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.51 (d, 3H, *J* 6.1 Hz, Me), 3.03 (dd, 1H, *J* 13.7, 1.5 Hz, H_a–2), 3.04 (dd, 1H, *J* 15.4, 0.6 Hz, H_a–7), 3.24 (ddd, 1H, *J* 15.4, 3.3, 1.5 Hz, H_b–7), 3.84 (q, 1H, *J* 6.1 Hz, H–4) 4.29 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 5.06 (d, 1H, *J* 13.7 Hz, H_b–2), 5.08 (d, 1H, *J* 3.2 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 15.9 (CH_3), 45.6 (C–7), 46.2 (C–2), 65.8 (CH_2CH_3), 70.8 (C–3), 74.9 (C–4), 77.9 (C–6), 114.5 (CN), 151.6 (C_3–OCO), 166.4 (C–8); ^1H NMR (C_6D_6) 0.89 (t, 3H, J 7.1 Hz, CH_2CH_3), 1.35 (d, 3H, *J* 6.1 Hz, Me), 2.35 (br d, 1H, *J* 13.6 Hz, H_a–2), 2.51 (br dd, 1H, *J* 15.1, 1.8 Hz, H_a–7), 2.64 (d, 1H, *J* 15.1 Hz, H_b–7), 3.11 (q, 1H, *J* 6.1 Hz, H–4), 3.82, 3,78 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 4.13 (d, 1H, *J* 3.0 Hz, H–6), 5.13 (d, 1H, *J* 13.6 Hz, H_b–2); MS (HR–ESI) m/z: $(M+Na)^+$ calcd for $C_{11}H_{14}N_2O_5$ Na: 277.0795. Found: 277.0821. Anal. Calcd for $C_{11}H_{14}N_2O_5$ (254.24): C, 51.97; H, 5.55; N, 11.02. Found: C, 52.00; H, 5.68; N, 10.72.

(2*R*, 3*S*, 4*S*, 6*R*) 3-Acetoxy-3-cyano-2-ethoxycarbonyl-4-methyl-5-oxacepham (17). To a solution of HMDSLi (180 μL, 1 M in THF, 0.18 mmol) in THF (0.3 mL), cooled to –78°C, compound **10** (25 mg, 0.16 mmol) dissolved in THF (0.5 mL) was added dropwise. After 30 min., HMPA (20 μL) and ethyl cyanoformate (19 mg, 19 μL, 0.19 mmol) were added and the mixture was kept at –78°C for 2h. Subsequently, the reaction was quenched by addition of saturated solution of NH_4Cl (3mL) in water and the temperature was allowed to rise to room temperature. The reaction mixture was extracted with *t*–BuOMe (3 x 2 mL). The extract was dried and concentrated. The residue was acetylated with Ac_2O/pyridine mixture (1mL) in the presence of a catalytic amount of DMAP. Subsequently, the solvent was evaporated and the residue was dissolved in ethyl ether and the solution was washed with brine, dried and evaporated. The crude product was separated by chromatography using AcOEt/hexane 30:70 v/v as an eluant to afford **14** (5 mg, 10%) and **17** (16 mg, 34%).

17. syrup; $[\alpha]_D$ –30.9 (c 0.75, CH_2Cl_2); IR (CH_2Cl_2) 1790, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 (t, 3H,, *J* 7.2 Hz, CH_2CH_3), 1.48 (d, 3H, *J* 6.2 Hz, Me), 2.14 (s, 3H, Ac), 3.08 (dd, 1H, *J* 15.4, 0.7 Hz, H_a–7), 3.28 (dd, 1H, *J* 15.4, 3.4 Hz, H_b–7), 4.28, 4.22 (2q, 4H, *J* 7.2 Hz, 2 CH_2CH_3), 4.36 (q, 1H, *J* 6.2 Hz, H–4), 5.51 (br d, 1H, *J* 3.2 Hz, H–6), 5.63 (s, 1H, H–2); MS (HR–EI) m/z: M^+ calcd for $C_{13}H_{16}N_2O_6$: 296.1002. Found: 396.1008.

(4*S*, 6*R*, 4′*S*, 6′*R*) 3-Acetoxy-2-[1′-aza-4′-methyl-5′-oxa-bicyclo[4.2.0]oct-2′-en-8′-on-3′-yl]-4-methyl-5-oxa-2-cephem (19) and **(4*S*, 6*R*, 3′*R*, 4′*S*, 6′*R*) 3-acetoxy-2-[3′-acetoxy-1′-aza-4′-methyl-5′-oxa-bicyclo[4.2.0]-octan-8′-on-3′-yl]-4-methyl-5-oxa-2-cephem (18).** A solution of **10** (17 mg, 0.11 mmol) in THF (1 mL) cooled to –78°C was treated with HMDSK (260 µL, 0.5 M in toluene, 0.13 mmol). The temperature was then allowed to rise to 0°C and the mixture was left for 1 h. Subsequently, pyridine (100 µL), Ac_2O (50 µL) and a catalytic amount of DMAP were added. The mixture was refluxed for 5 min., then poured into cold water and extracted with AcOEt (3 x 2 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The crude mixture was separated by chromatography using AcOEt/hexane 20:80 v/v as an eluant to afford **19** (20 mg, 30%). A minute amount of **18** was isolated, as well.

19. syrup; $[\alpha]_D$ –57.58 (c 0.19, $CHCl_3$); IR (CH_2Cl_2) 1779, 1770 cm^{-1}; ^1H NMR ($CDCl_3$): 1.31 (d, 3H, *J* 6.6 Hz, Me (Me′)), 1.36 (d, 3H, *J* 6.7 Hz, Me′ (Me)), 2.15 (s, 3H, Ac), 2.93 (dd, 1H, *J* 15.8, 1.2 Hz, H_a–7(7′)), 3.03 (dd, 1H, *J* 16.0, 1.4 Hz, H_a–7′(7)), 3.24 (dd, 1H, *J* 15.8, 3.8 Hz, H_b–7(7′)), 3.28 (dd, 1H, *J* 16.0, 3.8 Hz, H_b–7′ (7)), 4.71 (q, 1H, *J* 6.6 Hz, H–4(4′)), 4.81 (qd, 1H, *J* 6.7, 1.6 Hz, H–4′(4)), 5.10 (dd, 1H, *J* 3.8, 1.2 Hz, H–6(6′), 5.16 (dd, 1H, *J* 3.8, 1.1 Hz, H–6′(6), 6.56 (d, 1H, *J* 1.4 Hz, H–2′); ^{13}C NMR ($CDCl_3$) δ 17.4, 18.3, 20.4, 44.4 (t), 45.4 (t), 70.5, 71.6, 76.1, 76.3, 96.1 (s), 116.2 (s), 122.2, 137.7 (s), 165.3 (s), 165.5 (s), 169.4 (s); MS (HR–EI) m/z: $(M)^+$ calcd for $C_{16}H_{18}N_2O_6$: 334.11649. Found: 334.11626.

18. syrup; IR (CH_2Cl_2) 1772 cm^{-1}; ^1H NMR ($CDCl_3$): 1.25 (d, 3H, *J* 6.6 Hz, Me (Me′)), 1.33 (d, 3H, *J* 6.5 Hz, Me′ (Me)), 2.05 (s, 3H, Ac′), 2.16 (s, 3H, Ac) 2.83 (d, 1H, *J* 14.9 Hz, H_a–7(7′)), 2.84 (dd, 1H, *J* 15.8, 0.9 Hz, H_a–7′(7)), 3.20 (ddd, 1H, *J* 14.9, 3.2, 1.2 Hz, H_b–7(7′), 3.28 (dd, 1H, *J* 15.8, 3.7 Hz, H_b–7′ (7)), 3.63 (dd, 1H, *J* 14.7, 1.1 Hz, H_a–2′), 4.40 (bq, 1H, *J* 6.5 Hz, H–4′(4)), 4.75 (d, 1H, *J* 14.7 Hz, H_b–2′), 4.94 (q, 1H, *J* 6.6 Hz, H–4(4′)), 5.12 (d, 1H, *J* 3.2 Hz, H–6(6′), 5.20 (d, 1H, *J* 3.6 Hz, H–6′(6); MS (HR–EI) m/z: M^+ calcd for $C_{18}H_{22}N_2O_8$: 394.1376. Found: 394.1386.

(6*R*) 3-Ethoxycarbonyloxy-4-methyl-5-oxa-3-cephem (20). To a solution of **10** (68 mg, 0.44 mmol) in THF (8 mL) pulverized Bu_4NHSO_4 (165 mg, 0.48 mmol) was added. The mixture was cooled to –78°C and treated with HMDSLi (1 mL,1 M in THF, 1.0 mmol). Subsequently, the temperature was allowed to rise to –40°C. After 20 min, the mixture was again cooled to –78°C and treated with *S*-phenyl *O*-ethyl thiocarbonate (77 µL, 0.48 mmol). The temperature was maintained for 20 min. and then it was allowed to rise to 0°C. The mixture was poured into cold water and extracted with *t*–BuOMe (3 x 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The crude product was separated by chromatography using AcOEt/hexane 20:80 v/v as an eluant to afford **20** (11 mg, 11%); mp 68–69°C; $[\alpha]_D$ +122.70 (c 0.22, CH_2Cl_2); IR (CH_2Cl_2) 1776, 1773 cm^{-1}; ^1H NMR ($CDCl_3$) 1.35 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.80 (t, 3H, *J*

2.0 Hz, Me), 2.90 (d, 1H, *J* 15.0 Hz, H_a–7), 3.26 (ddd, 1H, *J* 15.0, 3.1, 1.8 Hz, H_b–7), 3.61 (dm, 1H, *J* 15.8 Hz, H_a–2), 4.18 (dm, 1H, *J* 15.8 Hz, H_b–2), 4.26 (q, 2H, *J* 7.1 Hz, CH_2CH_3), 5.18 (d, 1H, *J* 3.1 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 37.8, 45.9, 65.2, 75.0, 123.9, 144.0, 153.4, 166.9; MS (EI–HR) m/z: M^+ calcd for $C_{10}H_{13}NO_5$: 227.07937. Found: 227.07992.

(4*S*, 6*R*) 3-Trimethylsiloxy-4-methyl-5-oxa-2-cephem (21). A solution of **10** (46 mg, 0.3 mmol) in THF (2.5 mL), cooled to –78°C was treated successively with LDA (160 μL 2 M in THF/heptane/ethylbenzene, 0.33 mmol) and TMSCl (55 mg, 64 μL, 0.5 mmol). The mixture was kept for 5 min at –78°C and for 1 h at room temperature. The mixture was then poured into sat. aq. sodium hydrogencarbonate and extracted with hexane (3 x 3 mL). The extracts were dried over $MgSO_4$ and concentrated to afford **21 (**47 mg, 70 %): syrup; $[\alpha]_D$ –28.80 (c 0.45, CH_2Cl_2); IR (CH_2Cl_2) 1771 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.22 (s, 9H, $SiMe_3$), 1.34 (d, 3H, *J* 6.6 Hz, Me), 2.86 (dd, 1H, *J* 15.4, 1.1 Hz, H_a–7), 3.18 (ddd, 1H, *J* 15.4, 3.5, 0.5 Hz, H_b–7), 4.37 (qd, 1H, *J* 6.6, 1.2 Hz, H–4), 4.98 (dd, 1H, *J* 3.5, 0.9 Hz, H–6), 6.01 (bs, 1H, H–2).^{13}C NMR ($CDCl_3$) δ 0.0, 17.5, 44.2, 71.8, 75.4, 102.8, 144.6, 166.0; MS (HR–EI) m/z: M^+ calcd for $C_{10}H_{17}NO_3Si$: 227.09777. Found: 227.09761.

(2*R*, 3*S*, 4*S*, 6*R*) 3-Cyano-2-ethoxycarbonyl-3-ethoxycarbonyloxy-4-methyl-5-oxacepham (22). A solution of silyl ether **21** (36 mg, 0.16 mmol) in THF (1 mL) and CH_3CN (1 mL) cooled to –78°C was treated with ethyl cyanoformate (17 mg, 18 μL, 0.17 mmol) and TASF (44 mg, 0.16 mmol). The mixture was kept at –78°C for 2.5 h. Subsequently, Ac_2O (0.3 mL), pyridyne (0.6 mL) and catalytic amount of DMAP were added. The temperature was then allowed to rise to 20°C and the mixture was left for 1 h. The reaction mixture was poured into cold water and extracted with *t*–BuOMe (3 x 3 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The crude product was separated by chromatography using *t*–BuOMe/hexane 50:50 v/v as an eluant to afford **22** (5 mg, 10%), **14** (2 mg, 5%) and **15** (8 mg, 20%).

22. syrup; IR (CH_2Cl_2) 1789, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.37, 1.28 (2t, 6H, *J* 7.2 Hz, 2 CH_2CH_3), 1.48 (d, 3H, *J* 6.2 Hz, Me), 3.05 (dd, 1H, *J* 15.4, 0.7 Hz, H_a–7), 3.26 (dd, 1H, *J* 15.4, 3.4 Hz, H_b–7), 4.32, 4.23 (2q, 4H, *J* 7.2 Hz, 2 CH_2CH_3), 4.28 (q, 1H, *J* 6.2 Hz, H–4), 5.50 (bd, 1H, *J* 2.8 Hz, H–6), 5.59 (s, 1H, H–2); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 14.0 (CH_3), 15.9 (CH_3), 45.7 (C–7), 54.7, 62.8 (CH_2CH_3), 66.1 (CH_2CH_3), 71.2, 71.4 (C–3), 77.4 (C–6), 113.8 (CN), 151.4 (C_3–CO), 165.4 (C_2–CO), 165.7 (C–8); MS (HR–ESI) m/z: $(M+Na)^+$ calcd for $C_{14}H_{18}N_2O_7Na$: 349.1006. Found: 349.1015.

(2*R*, 3*R*, 4*S*, 6*R*) 3-Hydroxy-2-ethoxycarbonyl-3-(ethoxycarbonylaminomethyl)-4-methyl-5-oxacepham (23). To a solution of **22** (5 mg, 0.016 mmol) in MeOH (0.5 mL) and AcOEt (0.5 mL) was added $Pd(OH)_2/C$ (3 mg). Upon stirring the mixture was kept under hydrogen atmosphere overnight. Subsequently the solution was filtered through Celite and evaporated. The mixture was evaporated and purified by chromatography using AcOEt/hexane 50:50 v/v as an eluant to afford **23** (3 mg, 60%): syrup; $[\alpha]_D$ +29.4 (c 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 1.30 (d, 3H, *J* 6.6 Hz, Me), 1.31 (2t, 6H,, *J* 7.1 Hz, 2 CH_2CH_3), 2.78 (d, 1H, *J* 15.1 Hz, H_a–7), 3.22 (dd, 1H, *J* 15.1, 3.3 Hz, H_b–7), 3.28 (dd, 1H, *J* 15.1, 6.7 Hz, H_a–3′), 3.65 (dd, 1H, *J* 15.1, 4.6 Hz, H_b–3′), 4.22 (4q, 4H, *J* 7.1 Hz, 2 CH_2CH_3), 4.34 (q, 1H, *J* 6.4 Hz, H–4), 4.78 (s, 1H, H–2), 5.30

(br s, 1H, OH), 5.32 (s, 1H, NH), 5.46 (d, 1H, *J* 3.3 Hz, H–6); ^{1}H NMR (C_6D_6) 0.90, 0.91 (2t, 6H,, *J* 7.1 Hz, 2 CH_2CH_3) 1.18 (d, 3H, *J* 6.7 Hz, Me), 2.37 (d, 1H, *J* 14.9 Hz, H_a–7), 2.51 (dd, 1H, *J* 14.9, 3.3 Hz, H_b–7), 2.94 (dd, 1H, *J* 15.2, 6.9 Hz, H_a–3′), 3.38 (dd, 1H, *J* 15.3, 4.6 Hz, H_b–3′), 3.86, 3.80 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 3.98, 3.95 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 4.57 (q, 1H, *J* 6.7 Hz, H–4), 5.01 (s, 1H, H–2), 5.03 (br s, 1H, NH), 5.29 (d, 1H, *J* 3.3 Hz, H–6), 5.92 (s, 1H, OH); MS (HR–ESI) m/z: $(M+Na)^+$ calcd for $C_{14}H_{22}N_2O_7Na$: 353.1319. Found: 353.1322.

(3*R*, 4*S*, 6*R*) 4-Methyl-3-spirooxirano-5-oxacepham (26). A solution of HMDSLi (340 μL, 1 M in THF) in THF (0.5 mL) was cooled to –78°C and treated with **10** (25 mg, 0.16 mmol). After 10 min, the mixture was cooled to –180°C (liquid nitrogen) and anhydrous carbon dioxide was passed through the solution for 5 min. Subsequently, the temperature was allowed to rise to –60°C and the mixture was left for 2 h. The temperature was increased to –20°C and AcOH (40 mg, 0.64 mmol) was added. After 10 min the mixture was treated with etheral solution of diazomethane. Subsequently, the mixture was poured into water and extracted with AcOEt (3x). The combined extracts were dried and concentrated. The crude product was purified by chromatography using AcOEt/hexane 30:70 v/v as an eluant to afford **26** (11 mg, 41%): syrup; $[\alpha]_D$ +15.3 (c 0.06, CH_2Cl_2); IR (film z $CHCl_3$) 1772 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.09 (d, 3H, *J* 6.4 Hz, Me), 2.74 (d, 1H, *J* 4.3 Hz, H_b–3′), 2.85 (d, 1H, *J* 15.1 Hz, H_b–7), 3.00 (dd, 1H, *J* 4.3, 1.7 Hz, H_a–3′), 3.20 (ddd, 1H, *J* 15.1, 3.3, 1.7 Hz, H_a–7), 3.32 (dd, 1H, *J* 13.7, 1.7 Hz, H_b–2), 3.58 (d, 1H, *J* 13.7 Hz, H_a–2), 4.09 (q, 1H, *J* 6.4 Hz, H–4), 5.14 (d, 1H, *J* 3.2 Hz, H–6); MS (HR–EI) m/z: M^+ calcd for $C_8H_{11}NO_3$: 169.0739. Found: 169.0731.

(±) 3-Acetoxy-2-ethoxycarbonyl-4,4-dimethyl-5-oxa-2-cephem (29) and **(±) 3-cyano-3-ethoxycarbonyloxy-4,4-dimethyl-5-oxacepham (30).** Compounds **29** and **30** were obtained from **27** (17 mg, 0.1 mmol) in THF/HMPA with HMDSK (240 μL, 0.5 M in toluene, 0.12 mmol) and ethyl cyanoformate (11 mg, 11 μL, 0.11 mmol) at –78°C according to the procedure described for **10** to afford **29** (3 mg, 10%) and **30** (7 mg, 25%).

29. syrup; IR (film z CH_2Cl_2) 1784, 1723, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.31 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.41, 1.44 (2s, 6H, 2Me), 2.24 (s, 3H, Ac), 2.87 (dd, 1H, *J* 15.6, 0.9 Hz, H_a–7), 3.35 (dd, 1H, *J* 15.6, 3.7 Hz, H_b–7), 4.24, 4.29 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 5.21 (dd, 1H, *J* 3.7, 0.9 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 20.9 ($COCH_3$), 24.6 (CH_3), 25.7 (CH_3), 44.8 (C–7), 61.7 (CH_2CH_3), 72.3 (C–6), 75.7 (C–4), 116.9 (C–2), 149.2 (C–3), 166.0 (C–8), 167.7 ($COCH_3$), 173.2 (C_2–CO); MS (HR–EI) m/z: M^+ calcd for$C_{13}H_{17}NO_6$: 283.1056. Found: 283.1035.

30. syrup; IR (film z CH_2Cl_2) 1781 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.34 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.50, 1.56 (2s, 6H, 2Me), 3.04 (dd, 1H, *J* 15.3, 0.6 Hz, H_a–7), 3.16 (dd, 1H, *J* 13.8, 1.3 Hz, H_a–2), 3.23 (ddd, 1H, *J* 15.3, 3.3, 1.5 Hz, H_b–7), 4.27, 4.28 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 5.00 (d, 1H, *J* 13.8 Hz, H_b–2), 5.22 (d, 1H, *J* 3.1 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_2CH_3), 17.6 (CH_3), 25.3 (CH_3), 26.9 (C–2), 42.9 (CH_2CH_3), 45.8 (C–7), 65.7 (C–3), 73.4 (C–6), 76.9 (C–4), 115.8 (CN), 151.8 (C_3–OCO), 167.4 (C–8); MS (HR–EI) m/z: M^+ calcd for $C_{12}H_{16}N_2O_5$: 268.1059. Found: 268.1065.

(4*S*, 6*S*) 3-Acetoxy-2-ethoxycarbonyl-4-methyl-5-oxa-2-cephem (31), **(4*S*, 6*S*) 3-cyano-3-ethoxycarbonyloxy-4-methyl-5-oxa-cepham (32)** and **(4*S*, 6*S*) 3-acetoxy-3-cyano-4-methyl-5-oxacepham (33).** Compounds **31**, **32** and **33** were obtained from **28** according to the procedure described above. The following products were isolated: **31** (5%), **32** (13%) and **33** (6%).

31. syrup; $[\alpha]_D$ –7.66 (c 0.18, CH_2Cl_2); IR (CH_2Cl_2) 1792, 1781, 1725 cm^{-1}; ^1H NMR ($CDCl_3$): 1.32 (t, 3H, *J* 7.2 Hz, CH_2CH_3), 1.41 (d, 3H, *J* 6.9 Hz, Me), 2.23 (s, 3H, $COCH_3$), 2.88 (dd, 1H, *J* 15.7, 0.8 Hz, H_a–7), 3.36 (dd, 1H, *J* 15.7, 3.5 Hz, H_b–7), 4.31, 4.26 (2q, 2H, *J* 7.2 Hz, CH_2CH_3), 4.56 (q, 1H, *J* 6.9 Hz, H–4), 5.20 (d, 1H, *J* 3.6 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 14.8 (CH_2CH_3), 17.8 (CH_3), 20.7 ($COCH_3$), 44.8 (C–7), 61.7 (CH_2CH_3), 69.8 (C–4), 71.7 (C–6), 117.9 (C–2), 147.2 (C–3), 159.2 (C_2–CO), 165.7 (C–8), 167,8 ($COCH_3$); MS (HR–ESI) m/z: $(M+Na)^+$ calcd for $C_{12}H_{15}NO_6Na$: 292.0792. Found: 292.0802.

32. syrup; $[\alpha]_D$ –87.84 (c 0.39, CH_2Cl_2); IR (CH_2Cl_2) 1785, 1766 cm^{-1}; ^1H NMR ($CDCl_3$): 1.35 (t, 3H, *J* 7.1 Hz, CH_2CH_3), 1.47 (d, 3H, *J* 6.9 Hz, Me), 3.06 (dd, 1H, *J* 15.5, 0.9 Hz, H_a–7), 3.26 (ddd, 1H, *J* 15.5, 3.4, 1.5 Hz, H_b–7), 3.29 (dd, 1H, *J* 13.9, 1.5 Hz, H_a–2),), 4.29 (2q, 2H, *J* 7.1 Hz, CH_2CH_3), 4.65 (dd, 1H, *J* 14.0, 0.8 Hz, H_b–2), 4.72 (q, 1H, *J* 6.9 Hz, H–4), 5.23 (d, 1H, *J* 3.0 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 11.3, 14.0, 41.9 (t), 45.8 (t), 65.9 (t), 72.0, 72.6, 116.7 (s), 137.5 (s), 151.7 (s), 167.4 (s); MS (HR–LSIMS) m/z: $(M+H)^+$ calcd for $C_{11}H_{15}N_2O_5$: 255.09810. Found: 255.09851.

33. syrup; IR (CH_2Cl_2) 1785 cm^{-1}; ^1H NMR ($CDCl_3$): 1.45 (d, 3H, *J* 6.9 Hz, Me), 2.15 (s, 3H, Ac), 3.06 (d, 1H, *J* 15.5 Hz, H_a–7), 3.23 (br d, 1H, *J* 12.8 Hz, H_a–2), 3.26 (ddd, 1H, *J* 15.4, 3.2, 1.4 Hz, H_b–7), 4.65 (d, 1H, *J* 14.1 Hz, H_b–2), 4.71 (q, 1H, *J* 6.9 Hz, H–4), 5.23 (d, 1H, *J* 3.1 Hz, H–6); ^{13}C NMR ($CDCl_3$) δ 11.4 (CH_3), 20.6, 42.1, 45.8 (C–7), 67.5 (C–3), 71.8 (C–4), 72.7 (C–6), 116.7 (CN), 167.3 (C–8), 167.9 (CH_3CO); MS (HR–LSIMS) m/z: $(M+H)^+$ calcd for $C_{10}H_{13}N_2O_4$: 225.08753. Found: 225.08799.

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