SEMISYNTHETIC CEPHALOSPORINS WITH α-OXIMINO ACID SIDE CHAINS

THE PREPARATION AND COUPLING OF 4-ACYLAMINO-α-OXIMINOBENZENEACETIC ACIDS AND 1,2-DIHYDRO-6-METHYL-α-OXIMINO-2-OXO-3-PYRIDINEACETIC ACID TO 7-AMINOCEPHALOSPORANIC ACID

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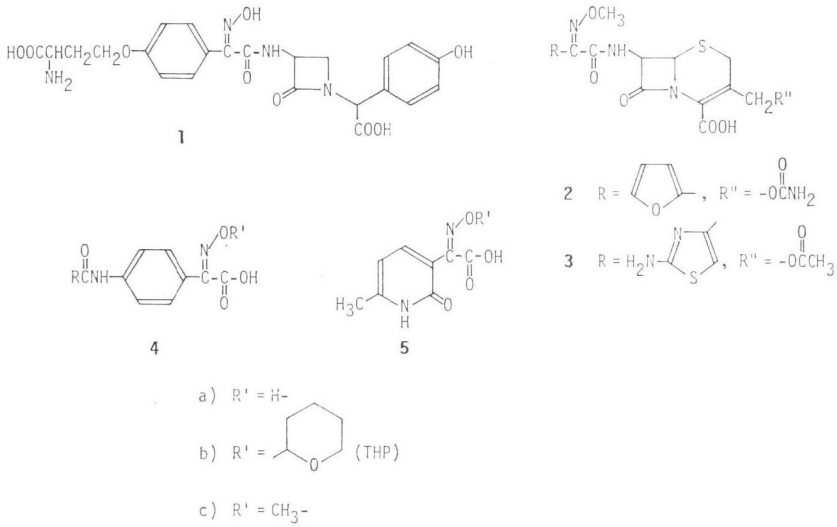
A series of 4-acylamino-α-oximinobenzeneacetic acids, and 1,2-dihydro-6-methyl-α-oximino-2-oxo-3-pyridineacetic acid were prepared and coupled to 7-aminocephalosporanic acid and its 3′-(1-methyltetrazol-5-yl)thiolo analogue. Several coupling methods and oxime protecting groups were thoroughly examined. The best coupling procedure employed dimethylchloroformiminium chloride, and the tetrahydropyranyl (THP) group was selected for oxime protection. The cephalosporins prepared were tested and compared to cefuroxime and cefotaxime. The corresponding α-keto acids, and *O*-methyl oximes were also examined.

A great deal of attention has been given in recent years, to several new and therapeutically significant antibiotics, in which a β-lactam nucleus is appended to a *Z*-α-oximino acid. Early entries in this area were nocardicin A[1] (**1**) and cefuroxime[2] (**2**), followed more recently, by the very potent cefotaxime[3] (**3**) and its derivatives[4]. These compounds possess especially good Gram-negative activity and are resistant to most β-lactamases[5]. In all known examples, the *E* (anti)-isomers were not found to be active. While the free oxime (=NOH) of **1** is essential for good activity (KAMIYA, private communication), the *O*-substituted oximes (=$NOCH_3$) of cefuroxime and cefotaxime are preferred and slightly more active than their unsubstituted derivatives[6,14].

As part of our ongoing research in the antiinfective area, we were very interested in the novel α-oximino acids of type **4** and **5** as side chains for 7-aminocephalosporanic acid (7-ACA). An unsubstituted α-oximinobenzeneacetic acid side chain has been reported to have good activity and excellent pharmacokinetic properties[7], but for our purposes the 4-acylamino-α-oximinobenzeneacetic acids (**4**) were preferred because of their spatial and electronic similarity with the 4-hydroxy-α-oximinobenzeneacetic acid portion of nocardicin A (**1**). We also envisioned that the amide group in **4** might confer different (peptide like) biological properties[8], and increased *in vivo* stability relative to a corresponding 4-acyloxy substituent. Finally, we hoped that a 4-acyl substituent could be chosen to give optimal breadth of spectrum.

The excellent broad spectrum activity of ampicillin and cephaloglycine derivatives containing various 6-substituted-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid side chains[9] prompted us to also investigate the properties of the α-oximino acid **5**, to see if the β-lactamase resistance conferred by the α-oximes in general might be combined with the overall activity associated with the 2-pyridone moiety.

When this work began, cefuroxime (**2**) was the outstanding compound in this class. It was therefore



our goal to compare and match the activity and spectrum of our derivatives with that of this cephalosporin. We now wish to report the coupling of these α-oximino acids to 7-ACA (and in select cases to its 3′-[1-methyltetrazol-5-yl]thiolo derivative) and their resultant biological activities.

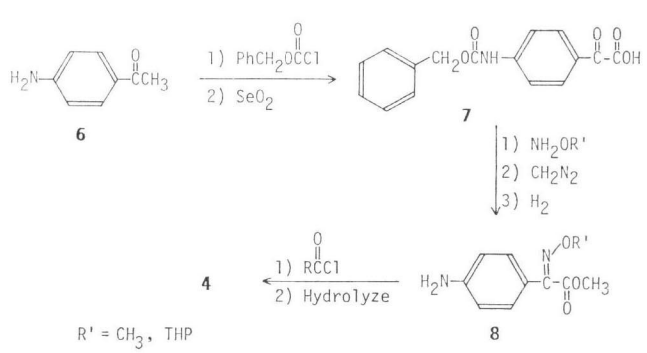
Chemistry

Preparation of α-Oximino Acids

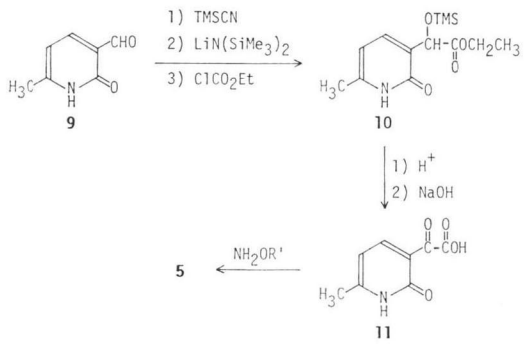
The *Z*-4-acylamino-α-oximinobenzeneacetic acids (**4**) were prepared (Scheme 1) beginning from 4-aminoacetophenone (**6**), which was converted to the α-keto acid **7** by acylation with benzyl chloroformate, followed by oxidation of the methyl ketone with selenium dioxide. The α-keto acid **7** was then oximated, esterified, and the *N*-protecting group removed with hydrogen to give **8**. Acylation of **8** and subsequent hydrolysis produced the *Z*-α-oximino acids **4**[10].

The 1,2-dihydro-6-methyl-α-oximino-2-oxo-3-pyridineacetic acid (**5**) was obtained (Scheme 2) from the 3-pyridinecarboxaldehyde **9** by acylation of the trimethylsilyl protected cyanohydrin with ethyl chloroformate, followed by hydrolysis of the adduct **10** to the α-keto acid **11**. Oximation of **11** gave the desired α-oximino acid **5**[11].

Scheme 1.

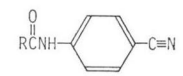


Scheme 2.



Coupling of α-Oximino Acids to 7-ACA

While the α-keto acid precursors of **4** and **5** could be readily coupled to 7-ACA *via* their acid chlorides or activated esters, this methodology was totally unacceptable for the α-oximino acids themselves. In fact, treatment of the α-oximino acids **4a** and **5a** with thionyl chloride, oxalyl chloride, *N,N'*-dicyclohexylcarbodiimide, or 1,1'-carbonyldiimidazole, under any conditions, resulted in rapid decarboxylation to the nitriles **12** and **13**. Attempts to prepare activated esters or mixed anhydrides were unsuccessful due to side reactions with the oxime OH. Protection of the oxime hydroxyl group eliminated both problems. Of all the protecting groups examined (Ph_3C–, $(CH_3)_3C$–, $CHCl_2CO$–, CH_3CO–, and $CH_3OC(CH_3)_2$–), we found that the tetrahydropyranyl group was the most easily prepared[10,11], and could be removed from the product cephalosporins with trifluoroacetic acid and a trace of water. The other protecting groups were often difficult to attach (Ph_3C– and $(CH_3)_3C$–), or required basic conditions for removal ($CHCl_2CO$– and CH_3CO–) which interfered with the 4-acylamino substituent.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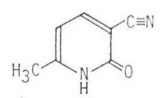
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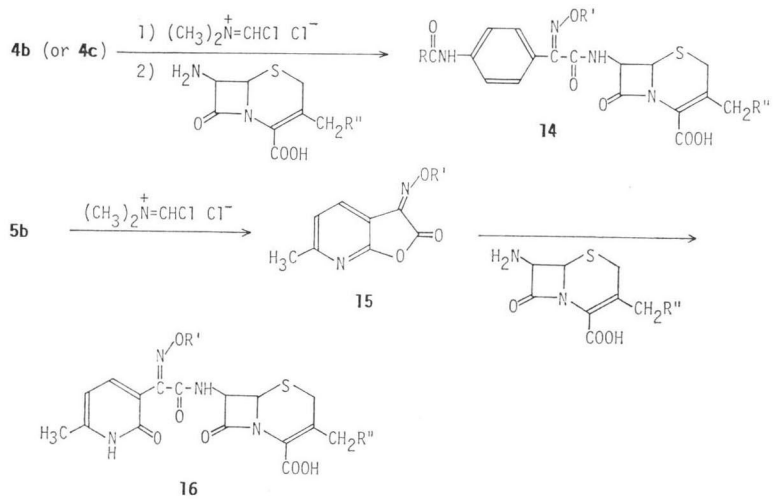
The *O*-methyl protected oximes **4c** were interesting in that the methyl groups could be removed with trimethylsilyl iodide, but only with extensive isomerization of the oxime.

The actual coupling of the protected oximes **4b** and **5b** to the β-lactam nuclei was best accomplished

Scheme 3.



using dimethylchloroformiminium chloride (VILSMEIER reagent)[12] at 0°C. In the case of **4b** (and **4c**), the crude acid chlorides formed were reacted directly with the persilylated (TMSCl and triethylamine or *N,O*-bis(trimethylsilyl)acetamide) β-lactam moiety. When **5b** was treated with dimethylchloroformiminium chloride, however, a cyclic internal activated ester **15** was obtained; which was isolated and then coupled as described above. The imidazolides and mixed anhydrides of **4b** and **4c** could be formed. These imidazolides were unreactive even at 60°C, and the mixed anhydride did not react at the desired carboxyl position. These results may be due to the large steric bulk of the substituted *Z*-α-oximino group.

Biological Activity

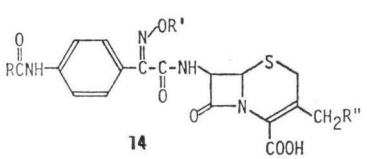
The *in vitro* activities of the cephalosporins **14** and **16**, against selected strains of Gram-negative and Gram-positive bacteria, are shown in Table 1. All the compounds prepared were active against *Staphylococcus aureus* and to a lesser extent against *Streptococcus faecalis* as well. None showed activity against *Pseudomonas aeruginosa*. *Klebsiella, Enterobacter, Escherichia coli* and *Proteus* were insusceptible to the cephalosporins **14b, d, f** featuring the 4-arylacylamino-α-oximinobenzene acetic acid side chains, whereas the 4-alkylacylamino derivatives **14a, c, e** did show activity against *Klebsiella* and *E. coli*. The 4-trifluoroacetylamino substituted side chain gave a cephalosporin, **14e**, which showed broad spectrum and potency comparable to cefuroxime (**2**). None of the other cephalosporins **14** or **16** showed this breadth of bacterial coverage when appended to 7-ACA. The 4-acetylamino side chain derivative **14a**, however, became more potent when a (1-methyltetrazol-5-yl)thio group replaced the acetoxy at the 3′ position (**14g**). The same observation was even more dramatic in the case of the pyridone side chain in **16a**, whose very disappointing activity was significantly enhanced by going from a 3′-acetoxy group to a (methyltetrazol-5-yl)thio group in **16b**. The activities conferred by the other side chains did not show significant improvement by this substitution as exemplified by going from **14i** to **14j**.

It has been suggested[13] that the α-oximino functionality is partly responsible for the β-lactamase resistance observed in the cephalosporins **1**～**3** and their derivatives[5]. Structure-activity relationships have also indicated that increased bulk at the α-oximino *O*-substituent increases this β-lactamase resistance[14]. Interestingly, the α-oximino acid side chains we prepared did not appear to lend any special β-lactamase resistance to the cephalosporins **14** and **16**, as inferred from the lack of susceptibility of the β-lactamase producer *Escherichia coli* Brig. In fact only **16b** displayed any moderate activity against this strain, and this may be a function of a cell permeability change induced by the variation in the 3′-substituent[15] and not the oxime. Furthermore, in our series, all the *O*-methyl oximes (and higher analogues) were much less active than the free oximes. Compounds **14h, i, j** were selected to illustrate this point and clearly demonstrated the complete loss of activity, especially against the Gram-negative strains. This result is similar to that seen in the nocardicins (unpublished results) and in direct contrast to cefuroxime (**2**) and cefotaxime (**3**). This implies that our substituted α-oximinophenylacetic acid side chains, as intended, behave much more like the nocardicin side chain than those of **2** or **3**.

Structure-activity relationships have also shown that the α-oximinofurylacetic acid side chain is better than the corresponding phenylacetic acid derivative when attached to 7-ACA and its analogues[14]. However we have shown that certain substitution of the phenyl ring can dramatically increase the activity of the cephalosporins to where **14e** and **14g** are perfectly comparable to the activity conferred by the furan ring in cefuroxime (**2**).

The keto acid precursors of **4** and **5** and the anti oximes were also coupled to 7-ACA. Except for

Table 1. Minimal inhibitory concentrations of compounds **14**, **16**, cefuroxime (**2**) and cefotaxime (**3**)[a].



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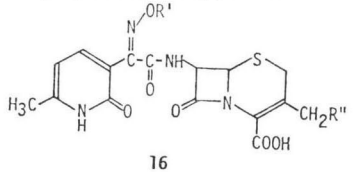

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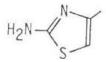
Compound	R	R′	R″	*Staph.*[b] UC-76	*Staph.*[b] S18173	*Strep.* MGH-2	*Klebs.* MGH-2	*Ent.* 1MM-11	*E. coli* Brig	*E. coli* Vogel	*Prot.* 1810
2		—	$-OCNH_2$	0.4	1.6	25	3.1	12.5	6.3	3.1	3.1
3		—	–OAc	1.6	1.6	3.1	0.05	0.2	0.2	0.05	0.05
14a	CH_3–	–H	–OAc	0.8	1.6	12.5	3.1	>50	>50	6.3	12.5
14b	$PhCH_2O$–	–H	–OAc	0.4	0.8	3.1	>50	>50	>50	>50	>50
14c	$CH_3CNHCH(CH_3)$–	–H	–OAc	3.1	6.3	25	12.5	>50	>50	25	>50
14d	Ph–	–H	–OAc	0.8	0.8	12.5	>50	>50	>50	>50	>50
14e	CF_3–	–H	–OAc	0.4	0.4	12.5	1.6	12.5	25	3.1	6.3
14f		–H	–OAc	0.8	0.8	6.3	25	>50	>50	>50	>50
14g	CH_3–	–H		1.6	1.6	12.5	1.6	25	25	3.1	12.5
14h	CH_3–	$-CH_3$	–OAc	3.1	6.3	>50	>50	>50	>50	>50	>50
14i	$CH_3CNHCH(CH_3)$–	$-CH_3$	–OAc	6.3	25	>50	>50	>50	>50	>50	>50
14j	$CH_3CNHCH(CH_3)$–	$-CH_3$		6.3	12.5	>50	>50	>50	>50	>50	>50
16a	—	–H	–OAc	3.1	6.3	>50	>50	>50	>50	>50	>50
16b	—	–H		0.8	1.6	50	1.6	12.5	12.5	3.1	6.3

[a] Antibacterial activities were determined by microtitration dilution[16] and were done in Tryptic soy broth. The minimum inhibitory concentrations (MIC) were determined after 16~18 hours incubation at 37°C.

[b] *Staph.*, *Staphylococcus aureus: Strep.*, *Streptococcus faecalis: Klebs.*, *Klebsiella pneumoniae: Ent.*, *Enterobacter cloacae: E. coli.*, *Escherichia coli: Prot.*, *Proteus vulgaris.*

some activity *vs Staphylococcus*, these compounds were uneventful. In addition, all of these α-oximino acid side chains were coupled to 3-aminonocardicinic acid (3-ANA), but like the nocardicin A side chain on 7-ACA (KAMIYA, private communication), these displayed no significant activity.

Summary

According to our goals as set forth in the introduction we have succeeded in preparing certain α-oximino acid side chains of the type **4** and **5** that are as active as cefuroxime (**2**) against both Gram-negative and Gram-positive bacteria, when coupled to 7-ACA. We have also demonstrated that the α-oximino acid side chains may not always confer β-lactamase resistance, and the preliminary evidence suggests that the 3′ substituent may be important in this regard. Furthermore, the free oximes tested here were more active than the *O*-substituted oximes—a result totally opposite to that expected from cephalosporins **2** and **3**, which are less active in their free oxime forms. Finally, the good activity *vs* Gram-negative associated with the 3-carboxyl-2-pyridone moiety in other reported cephalosporins and penicillins[7], was not completely maintained when the oximino function was inserted between the pyridone ring and the 3-carboxyl group, and the phenylglycine spacer removed. The activity of **16b**, however, shows that the phenylglycine spacer is not a requirement.

Experimental

Infrared (IR) spectra were determined on a Digilab FTS-14 instrument. Proton magnetic resonance (NMR) spectra were recorded on a Bruker WH-90 instrument, which was modified with a Nicolet Technology Corporation B-NC12 data acquisition system. Chemical shifts are reported as δ values in ppm from internal tetramethylsilane. Rotations were determined on a Perkin Elmer 141 instrument. Purifications were performed by column chromatography using E. Merck silica gel 60, 70~230 mesh with ether - acetonitrile - acetic acid, 6: 3: 1, and by preparative HPLC using a Waters Associates Prep LC System 500 equipped with a Prep Pak 500/C_{18} column. All new compounds gave satisfactory analyses.

Coupling and Deprotection of the 4-Acylamino-α-(tetrahydro-2*H*-pyran-2yl)oximinobenzeneacetic Acids (**4b**) to 7-Aminocephalosporanic Acid (7-ACA)

Preparation of **14a**, a general procedure: To 306 mg (1.00 mmole) of 4-acetylamino-α-(tetrahydro-2*H*-pyran-2-yl)oximinobenzeneacetic acid (**4b**, R=CH_3) suspended in 3 ml of dichloromethane was added 0.11 ml (1.0 eq.) of *N*-methylmorpholine. When solution was complete, the mixture was cooled to −45°C, and 140 mg (1.1 eq.) of dimethylchloroformiminium chloride (prepared from equal parts DMF and $SOCl_2$ at 50°C followed by concentration and drying the residual solid at 0.1 mmHg) was added. This mixture was stirred for 2 hours. Meanwhile, 272 mg (1.00 mmole) of 7-ACA in 3 ml of dichloromethane was treated with 0.43 ml of *N,O*-bis(trimethylsilyl)acetamide for 30 minutes. The silylated 7-ACA was added to the acid chloride solution at −45°C and the temperature brought to 0°C over 2.5 hours. The mixture was diluted with ethyl acetate and was extracted with water at pH 7.5~8.5. The aqueous phase was then acidified to pH 2.0 and extracted with ethyl acetate which was dried ($MgSO_4$) and concentrated to give 485 mg (87%) of the *O*-THP protected cephalosporin **14a** (R′=THP): $[\alpha]_D^{23}$ +57.0° (*c* 1.0, H_2O, pH 7); IR (KBr) 1790, 1730, 1680 cm^{-1}; NMR (DMSO-d_6) δ 10.1 (s, 1H, PhN*H*), 9.7 (d, *J*=8Hz, 1H, C_7N*H*), 7.65 (d, *J*=8Hz, 2H, Ph), 7.45 (d, *J*=8Hz, 2H, Ph), 5.85 (m, 1H, C_7*H*), 5.3 (s, 1H, O_2C*H*), 5.2 (d, *J*=8Hz, 1H, C_6*H*), 5.0 (d, *J*=12Hz, 1H, C_3′*H*H), 4.55 (d, *J*=12Hz, 1H, C_3′*H*H), 3.65 (m, 4H, C_4H_2 and OCH_2CH_2), 2.05 (2s, 6H, $2COCH_3$), 1.50 (m, 6H, pyranyl); HPLC 99.9%.

This product was dissolved in 3 ml of trifluoroacetic acid at 0°C and after 15 minutes, 50 mg of water was added. The mixture was brought to room temperature for 2 hours and concentrated. The oily residue was added slowly to ethyl ether and the solids collected to give 380 mg (92%) of **14a**: $[\alpha]_D^{23}$ 80.8° (*c* 1.0, H_2O, pH 7); IR (KBr) 1785, 1735, 1675 cm^{-1}; NMR (DMSO-d_6) δ 11.4 (s, 1H, O*H*), 10.5 (s, 1H, PhN*H*), 9.6 (d, *J*=7Hz, 1H, C_7N*H*), 7.65 (d, *J*=8Hz, 2H, Ph), 7.45 (d, *J*=8Hz, 2H, Ph), 5.9 (m, 1H,

C_7H), 5.2 (d, J=5Hz, 1H, C_6H), 5.05 (d, J=12Hz, 1H, $C_{3'}HH$), 4.7 (d, J=12Hz, 1H, $C_{3'}HH$), 3.55 (m, 2H, C_4H_2), 2.1 (2s, 6H, $2COCH_3$).

All the cephalosporins **14** were prepared in identical fashion. Yields given are total yields after coupling and deprotection.

Preparation of **14b**: Cephalosporin **14b** was obtained in 60% yield and was analyzed as the sodium salt: $[\alpha]_D^{23}$ 80.5° (*c* 1.0, H_2O, pH 7); IR (KBr) 1770, 1700, 1620 cm^{-1}; NMR (DMSO-d_6) δ 9.90 (m, 2H, 2NH), 7.35 (m, 9H, Ph), 5.6 (m, 1H, C_7H), 4.9 (m, 5H, C_6H, $C_{3'}H_2$, PhCH_2), 3.3 (m, 2H, C_4H_2), 2.0 (s, 3H, $COCH_3$).

Preparation of **14c**: The cephalosporin **14c** was obtained in 50% yield, and was analyzed as the sodium salt; IR (KBr) 1770, 1670, 1610 cm^{-1}; NMR (DMSO-d_6) δ 11.4 (s, 1H, OH), 10.2 (s, 1H, NH), 9.5 (s, 1H, NH), 8.25 (d, J=8Hz, 1H, C_7NH), 7.6 (d, J=8Hz, 2H, Ph), 7.4 (d, J=8Hz, 2H, Ph), 5.4 (m, 1H, C_7H), 4.8 (m, 3H, C_6H, $C_{3'}H_2$), 4.35 (t, J=7Hz, 1H, CH_3CH), 3.3 (m, 2H, C_4H_2), 2.0 (s, 3H, $COCH_3$), 1.9 (s, 3H, $COCH_3$), 1.25 (d, J=7Hz, 3H, $CHCH_3$).

Preparation of **14d**: Cephalosporin **14d** was obtained in 35% yield after column chromatography and was analyzed as the sodium salt: $[\alpha]_D^{25}$ 59.3° (*c* 1.0, H_2O, pH 7); IR (KBr) 1780, 1660 cm^{-1}; NMR (DMSO-d_6) δ 10.4 (s, 1H, NH), 7.6 (m, 10H, Ph and C_7NH), 5.6 (d, J=5Hz, 1H, C_6H), 4.8 (m, 3H, C_7H and $C_{3'}H_2$), 3.5 (m, 2H, C_4H_2), 2.0 (s, 3H, $COCH_3$).

Preparation of **14e**: Cephalosporin **14e** was obtained in 49% yield: $[\alpha]_D^{23}$ 74.0° (*c* 1.0, H_2O, pH 7); IR (KBr) 1785, 1730, 1675, 1610 cm^{-1}; NMR (DMSO-d_6) δ 11.6 (s, 1H, OH), 11.3 (s, 1H, NH), 9.6 (d, J=8Hz, 1H, C_7NH), 7.7 (d, J=8Hz, 2H, Ph), 7.5 (d, J=8Hz, 2H, Ph), 5.8 (m, 1H, C_7H), 5.2 (d, J=5Hz, 1H, C_6H), 4.95 (d, J=12Hz, 1H, $C_{3'}HH$), 4.65 (d, J=12Hz, 1H, $C_{3'}HH$), 3.6 (m, 2H, C_4H), 2.0 (s, 3H, $COCH_3$).

Preparation of **14f**: Cephalosporin **14f** was obtained in 63% yield: $[\alpha]_D^{25}$ 128.0° (*c* 1.0, H_2O, pH 7); IR (KBr) 3300, 1785, 1730, 1670, 1590 cm^{-1}; NMR (DMSO-d_6) δ 11.5 (s, 1H, OH), 10.3 (s, 1H, NH), 9.6 (d, J=9Hz, 1H, C_7NH), 7.3 (m, 7H, Ar), 5.8 (m, 1H, C_7H), 5.0 (m, 3H, C_6H and $C_{3'}H_2$), 2.5 (m, 2H, C_4H_2), 2.0 (s, 3H, $COCH_3$).

Preparation of **14g**: Cephalosporin **14g** was prepared in 59% and was analyzed as the sodium salt: $[\alpha]_D^{25}$ 19.2° (*c* 1.0, H_2O, pH 7); IR (KBr) 1770, 1680 cm^{-1}; NMR (DMSO-d_6) δ 10.3 (d, J=9Hz, 1H, C_7NH), 7.5 (m, 5H, Ph and PhNH), 5.65 (d, J=6Hz, 1H, C_6H), 5.0 (m, 1H, C_7H), 4.3 (m, 2H, $C_{3'}H_2$), 3.9 (s, 3H, NCH_3), 3.5 (m, 2H, C_4H_2), 2.1 (s, 3H, $COCH_3$).

Preparation of **14h**: The cephalosporin **14h** was obtained from **4c** (R=CH_3) in 65% yield: $[\alpha]_D^{23}$ 53.9° (*c* 1.0, H_2O, pH 7); IR (KBr) 1790, 1735, 1675 cm^{-1}; NMR (DMSO-d_6) δ 10.1 (s, 1H, PhNH), 9.7 (d, J=8Hz, 1H, C_7NH), 7.55 (m, 4H, Ph), 5.85 (m, 1H, C_7H), 5.2 (d, J=5Hz, 1H, C_6H), 4.8 (m, 2H, $C_{3'}H_2$), 3.9 (s, 3H, OCH_3), 3.55 (m, 2H, C_4H_2), 2.05 (s, 3H, $COCH_3$), 2.0 (s, 3H, $COCH_3$).

Preparation of **14i**: The cephalosporin **14i** was prepared in 20% yield after purification, and was analyzed as the sodium salt: IR (KBr) 1770, 1670, 1610, 1530 cm^{-1}; NMR (DMSO-d_6) δ 10.35 (s, 1H, PhNH), 9.65 (d, J=8Hz, NH), 8.35 (d, J=8Hz, 1H, NH), 7.7 (d, J=9Hz, 2H, Ph), 7.5 (d, J=9Hz, 2H, Ph), 5.6 (m, 1H, C_7H), 5.0 (m, 3H, $C_{3'}H_2$ and C_6H), 4.4 (m, 1H, $CHCH_3$), 3.9 (s, 3H, OCH_3), 3.3 (m, 2H, C_4H_2), 2.0 (s, 3H, $COCH_3$), 1.9 (s, 3H, $COCH_3$), 1.3 (d, J=7, 3H, $CHCH_3$).

Preparation of **14j**: The cephalosporin **14j** was prepared in 27% yield after purification and was analyzed as the sodium salt: IR (KBr) 1765, 1665, 1610 cm^{-1}; NMR (DMSO-d_6) δ 10.3 (s, 1H, PhNH), 9.65 (d, J=7Hz, 1H, NH), 9.3 (d, J=5Hz, 1H, C_7NH), 7.7 (d, J=8Hz, 2H, Ph), 5.6 (m, 1H, C_7H), 5.0 (d, J=5Hz, 1H, C_6H), 4.3 (m, 2H, $C_{3'}H_2$), 3.9 (s, 6H, OCH_3 and NCH_3), 3.5 (m, 3H, C_4H_2 and $CHCH_3$), 1.9 (s, 3H, $COCH_3$), 1.2 (d, J=7 Hz, 3H, $CHCH_3$).

The Coupling of 1,2-Dihydro-6-methyl-α-(tetrahydro-2H-pyran-2-yl)oximino-2-oxo-3-pyridine-acetic Acid **5b** to 7-ACA

Preparation of **16a**, a general procedure: To 210 mg (0.75 mmole) of the pyridone acid **5b** in 5 ml of dichloromethane was added 0.17 ml (1.0 eq.) of *N*-methylmorpholine. At 0°C 105 mg (1 eq.) of dimethylchloroformiminium chloride was added and the mixture stirred for 1 hour. The mixture was extracted with water, dried ($MgSO_4$) and concentrated to give 192 mg (92%) of a crystalline residue **15** (R′=THP): IR ($CHCl_3$) 1810, 1620, 1400 cm^{-1}, which was used directly for coupling.

To 152 mg (0.58 mmole) of the anhydride **15** (R′=THP) in 2 ml of DMF was added 166 mg (0.61 mmole) of 7-ACA (silylated as above) in 2 ml of DMF. The mixture was stirred for 1.5 hours at 25°C. Workup and deprotection as described above gave cephalosporin **16a** (29% after purification) which was analyzed as the sodium salt: $[\alpha]_D^{23}$ 53.9° (*c* 1.0, H_2O, pH 7); IR (KBr) 1765, 1655, 1615 cm^{-1}; NMR (DMSO-d_6) δ 11.5 (s, 1H, N*H*), 9.0 (d, *J*=7Hz, 1H, C_7NH), 7.39 (d, *J*=8Hz, 1H, pyridone *H*), 6.0 (d, *J*=8Hz, 1H, pyridone *H*), 5.5 (m, 1H, C_7H), 4.7 (m, 3H, C_6H and $C_{3'}H_2$), 3.4 (m, 2H, C_4H_2), 2.2 (s, 3H, CH_3), 1.9 (s, 3H, $COCH_3$).

Preparation of **16b**: Cephalosporin **16b** was prepared in 57% yield, and was analyzed as the sodium salt: $[\alpha]_D^{23}$ −14.0° (*c* 1.0, H_2O, pH 7); IR (KBr) 1775, 1660, 1625 cm^{-1}; NMR (DMSO-d_6) δ 11.7 (s, 1H, N*H*), 9.0 (d, *J*=5Hz, 1H, C_7NH), 7.38 (d, *J*=8Hz, 1H, pyridone *H*), 6.0 (d, *J*=8Hz, 1H, pyridone *H*), 5.7 (m, 1H, C_7H), 4.9 (d, *J*=6Hz, 1H, C_6H), 4.28 (m, 2H, $C_{3'}H_2$), 3.88 (s, 3H, NCH_3), 3.40 (m, 2H, C_4H_2), 2.17 (s, 3H, CH_3).

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