Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 349–352

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis of a Dihydroxythiophene Analogue of Catechosporines

C. Dini* and J. Aszodi

Medicinal Chemistry Department, Hoechst Marion Roussel, France102 rte de Noisy 93235, Romainville Cedex, France

Received 13 September 1999; accepted 14 December 1999

Abstract—A vinylogous cephalosporine bearing a dihydroxythiophene moiety as a potential catechol surrogate has been synthesised (**I-e-β**). Even if the anti staphylococcus spectrum displayed by this compound is of interest, its activity against *Pseudomonas* species, expected for such a structure, remains disappointing.

Catechol containing β-lactams has attracted a lot of interest during the last 10 years. They penetrate into Gram negative bacteria via an illicit transport by using a Ton B dependent iron transport system.[1] RU 59863 (**I-a-β**),[2] a vinylogous catechosporin displays a very broad spectrum of Gram positive and Gram negative activity, including *Pseudomonas* strains which are resistant to various β-lactams including carbapenems. Hydroxypyridones (**b**) have successfully been used as catechol surrogates[2,3] (Fig. 1). In the present paper, we wish to report the synthesis of a vinylogous cephalosporin **I-e-β** bearing a dihydroxythiophen moiety as potential isoster of a catechol group. This function has been designed on the basis of a very strong anti-pseudomonal activity of the corresponding 3-cyano-4,5-dihydroxy (**I-c-α**) and 2-cyano-3,4-dihydroxybenzene (**I-d-α**) containing cephalosporins.[2]

Before synthesising the aimed molecule (**I-e-β**), we had checked that 2-cyano-3, 4-dihydroxythiophene predominantly existed in the dihydroxy tautomeric form (**7a**), as expected for such compounds.[4] This compound was prepared according to Scheme 1.

The intermediate **3** was obtained by reaction of ethyl thioglycolate **1** with bromoacetonitrile **2** in the presence of sodium ethoxide in ethanol. After in situ addition of two additional equivalents of sodium ethylate and diethyl oxalate, the disodium salt of **4** was precipitated by addition of methylene chloride. This compound was solubilized in water and **4** was precipitated by subsequent addition of 2N HCl.

*Corresponding author. Fax: +33-1-49-91-50-87; e-mail: christophe.dini@hmag.com

Hydroxyl groups were protected using methoxyethoxymethyl chloride in the presence of diisopropylethylamine affording **5**, which could be used without further purification. Saponification of **5**, followed by decarboxylation in refluxing ethanol, led to **6**. This compound was in equilibrium between its tautomeric forms (**6a** and **6b**).[6] Cleavage of the remaining protection was accomplished with TFA in CH_2Cl_2, leading to **7**.

^{13}C and ^{1}H NMR studies performed in methanol, as well as IR analysis demonstrated that this compound was present only in the dihydroxy thiophene tautomeric form **7a**.[7]

Consequently, we undertook the synthesis of **I-e**, by using the same synthetic scheme as previously described for the synthesis of cathecosporines (Scheme 2). The challenge was the construction of the dihydroxythiophen moiety **[I]**.

Reduction of **5** using tri-*ter*-butoxyalumino hydride in THF gave the alcohol **8** without affecting either the cyano function or the thiophene ring. MnO_2 oxydation of **8** provided the aldehyde **9**, which was purified by chromatography.

As the classical techniques, previously developed in catechol series, for the synthesis of α-chloroesters starting from aldehydes[5] were unsuccessful, we envisaged the use of a modified version of the approach developed by Robert et al.[8] (Scheme 3). To our knowledge, it has never been applied on thiophene derivatives.

The olefinic derivative **10** was obtained by condensation of malononitrile on **9** with a catalytic amount of piperidine, in the presence of molecular sieves. Epoxydation using a stoichiometric amount of triethylamine and *ter*-butylhydroperoxide afforded the desired epoxyde **11**.

0960-894X/00/$ - see front matter
PII: S0960-894X(99)00697-6

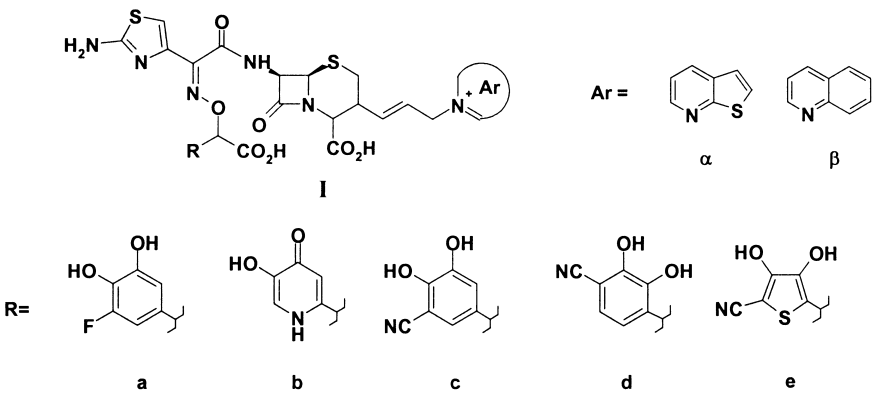


Figure 1.

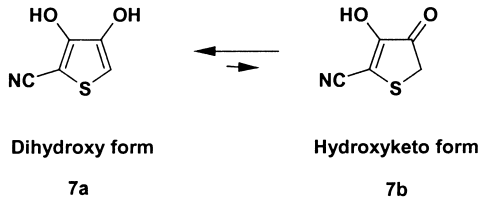


Figure 2.

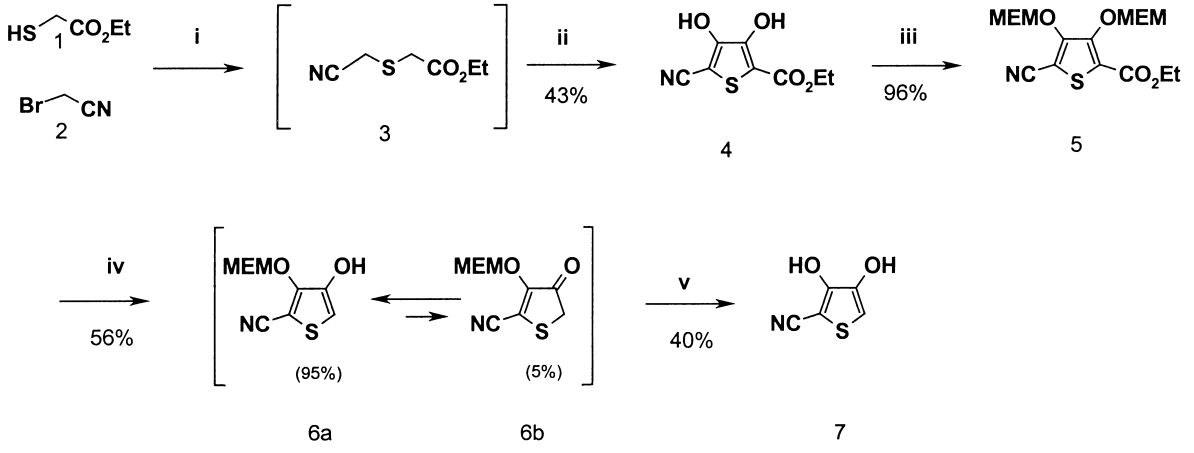
After filtration and evaporation of the solvent, **11** was treated by 1 N HCl in THF (1.3 equivalent) affording **12** which was immediately esterified by addition of an excess of diphenyldiazomethane to provide **13**.[9]

By carrying out the reaction sequence from **9** to **13** without any purification of the intermediates, **13** was obtained in 64% overall yield, after silica gel chromatography.

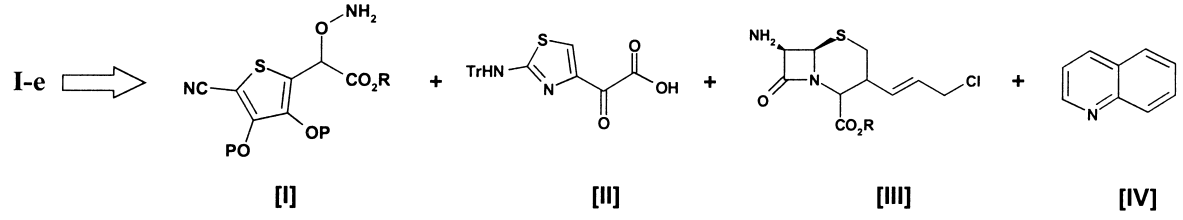
Substitution of chlorine with hydroxyphthalimide on **13** under phase transfer catalysis conditions provided **14a** in 50% yield. These conditions limited the formation of **14b**.

Deprotection of **14a** at −10 °C with hydrazine in methanol afforded the unstable hydroxylamine **15**, which had to be reacted in situ with the ketoacid **20** to give **16** after chromatographic purification. Coupling of **16** with **21** in the presence of EDC provided, after purification, the desired **17** as a syn-oxime in 16% overall yield from **14a**.

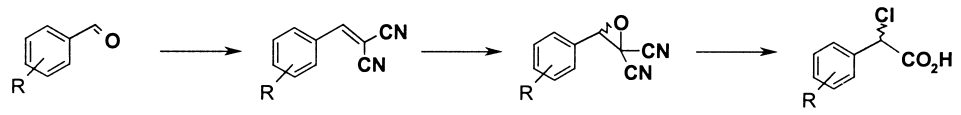
The use of sodium iodide in the presence of iodine led to the formation of the fragile iodo analogue **18** (mixture E/Z isomers). The coupling of **18** with quinoline furnished **19** which was then fully deprotected with TFA in the presence of anisole to provide **I-e** in a (70:30) E:Z ratio.[5]



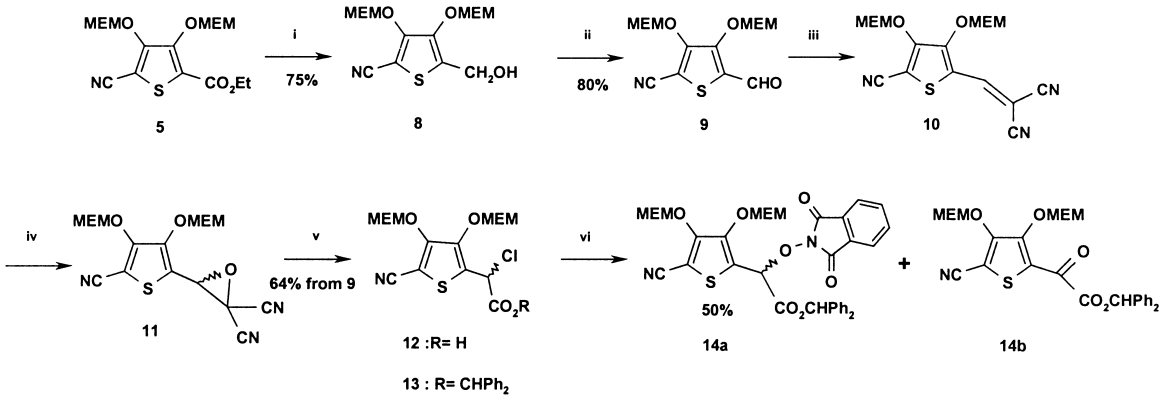
Scheme 1. (i) EtONa (1.1 equiv), EtOH; (ii) 1. $(CO_2Et)_2$, EtONa (2 equiv), EtOH; 2. HCl 2N; (iii) MEMCl, $(iPr)_2NEt$, CH_2Cl_2; (iv) KOH, EtOH, then H^+, then EtOH rfx; (v) TFA/CH_2Cl_2 (1/2) 20 min rt then neutralised.



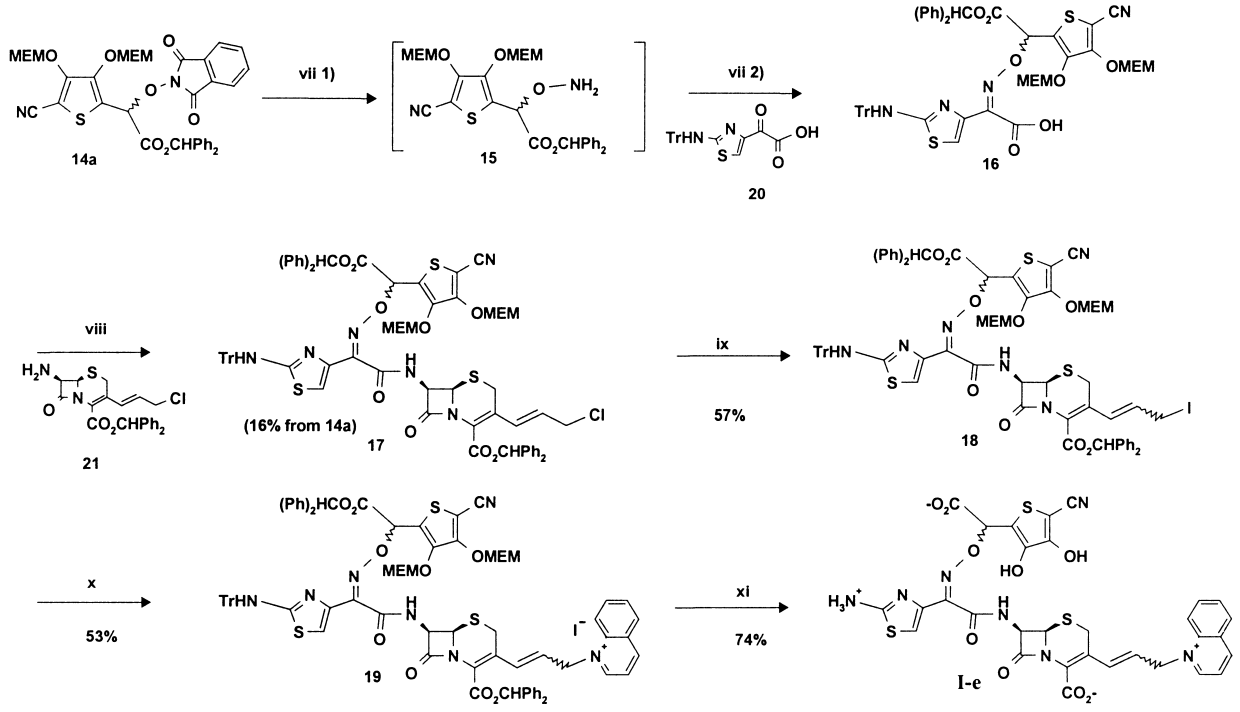
Scheme 2.



Scheme 3.



Scheme 4. (i) $(tBuO)_3AlH$ 6 equiv THF 24 h rt; (ii) MnO_2, CH_2Cl_2, 5 °C; (iii) $NCCH_2CN$, piperidine 0.1 equiv, dioxane, MS 4Å, 5 °C 40 min; (iv) *t*BuOOH, Et_3N, dioxane, 20 min 5–10 °C; (v) 1. HCl 1 N (1.3 equiv), THF, 1 h, rt; 2. Ph_2CN_2, 2 h, rt; (vi) Et_3NBn^+ Cl^- (0.1 equiv), $NaHCO_3$, *N*-hydroxyphthalimide, CH_2Cl_2, H_2O, 13 h rt.



Scheme 5. (vii) 1. $H_2NNH_2.H_2O$, MeOH −10 °C 45 min, 2. 20 , CH_2Cl_2 rt 2 h; (viii) 21, EDC, CH_2Cl_2, 45 min rt; (ix) NaI, I_2 (cat.), acetone, 1 h rt; (x) Quinoline, CH_2Cl_2, 1 h 30 rt; (xi) TFA - anisole (9–1), 1 h rt.

The final product (**I-e**) was tested in vitro against a panel of Gram positive and Gram negative strains, using **I-b**, **I-c** and **I-d** as comparators (Table 1).

Contrary to the expectations, this molecule is almost inactive against *Pseudomonas* strains. Also, the compound displays highly potent activity against *Staphylococci*,

Table 1.[a]

	I-b-α	I-c-α	I-d-α	I-e-β
S. aureus (20 strains)	0.92	1.40	3.6	0.17
P. aeruginosa (40 strains)	3.12	0.06	0.12	38

[a]Geometric mean of MICs (μg/mL).

which is unusual for either a catechol or hydroxypyridone derivative.

References and Notes

1. Guerinot, M.-L. *Annu. Rev. Microbiol.* **1994**, *48*, 743.
2. Aszodi, J.; Bonnefoy, A.; Chantot, J.-F.; Dini, C.; Fauveau, P.; Humbert, D. *Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy* **1994**, *34*, 161.
3. Dobbin, P. S.; Hider, R. C.; Hall, A. D.; Taylor, P. D.; Sarpong, P.; Porter, J. B.; Xiao, G.; Van der Helm, D. *J. Med. Chem.* **1993**, *36*, 2448.
4. Melvin, Jr., L. S.; Hada, W. A.; Rusek, F. W.; Bordner, J. *Tetrahedron Lett.* **1993**, *34*, 8229.
5. Aszodi, J.; Chantot, J.-F.; D'Ambrières, S.; Dini, C.; Fauveau P.; Humbert D. EP: 94/628562/A1 1994.
6. Data for the tautomeric mixture **6a**/6b (95/5): ^{1}H NMR ($CDCl_3$): 3.43 (s, OCH_3) 3.44 (s, OCH_3) total 3H, 3.67 (m, 2H, OCH_2CH_2O), 4.02 (m, 2H, OCH_2CH_2O), 4.59 (s, S–CH_2-C=O), 5.28 (s), 2H, OCH_2O), 6.61 (s, <1H, S–CH=C), 7.91 (sl, ~1H, OH). IR ($CHCl_3$): 3550, 3290 cm^{-1} (OH), 2220 cm^{-1} (CN), 1578,1492 cm^{-1} (heterocycle); **6a** major tautomer. MS (ES): 229^+ ($M+H^+$).
7. Data for **7**: ^{1}H NMR (CD_3OH): 6.46 (s, =CH-). ^{13}C NMR (CD_3OH): 83.4 (CN), 105.7(=CH-); 115.0, 145.2, 156.0 other C. IR (Nujol): 3100–2300 cm^{-1} (general absorption); 2226 cm^{-1} (CN); 1590 cm^{-1}, 1512 cm^{-1} (heterocycle). MS (EI): 141^+ ($M+H^+$).
8. Guinamant, J.-L.; Jaguelin, S.; Robert, A. *Tetrahedron* **1986**, *42*, 2275–2281.
9. Data for **13**: ^{1}H NMR ($CDCl_3$): 3.31 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.48 (m, 2H, OCH_2CH_2O), 3.58 (m, 2H, OCH_2-CH_2O), 3.82 (m, 2H, OCH_2CH_2O; MEM), 3.92 (m, 2H, OCH_2CH_2O), 5.17 to 5.41 (m, 4H, OCH_2O), 5.98 (s, 1H, $ArCHClCO_2$), 6.91 (s, 1H, C (O)$OCHPh_2$), 7.34 (m, 10H, Ph). IR ($CHCl_3$): 2221 cm^{-1} (CN), 1746 cm^{-1} (CO_2R) MS (SIMS): 576^+ ($M+H^+$).