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1-PHOSPHACEPHALOSPORIN. II.[1]
SYNTHESIS OF OPTICALLY ACTIVE 7-SUBSTITUTED-1-PHOSPHADETHIA-3-CEPHEM 1-OXIDES

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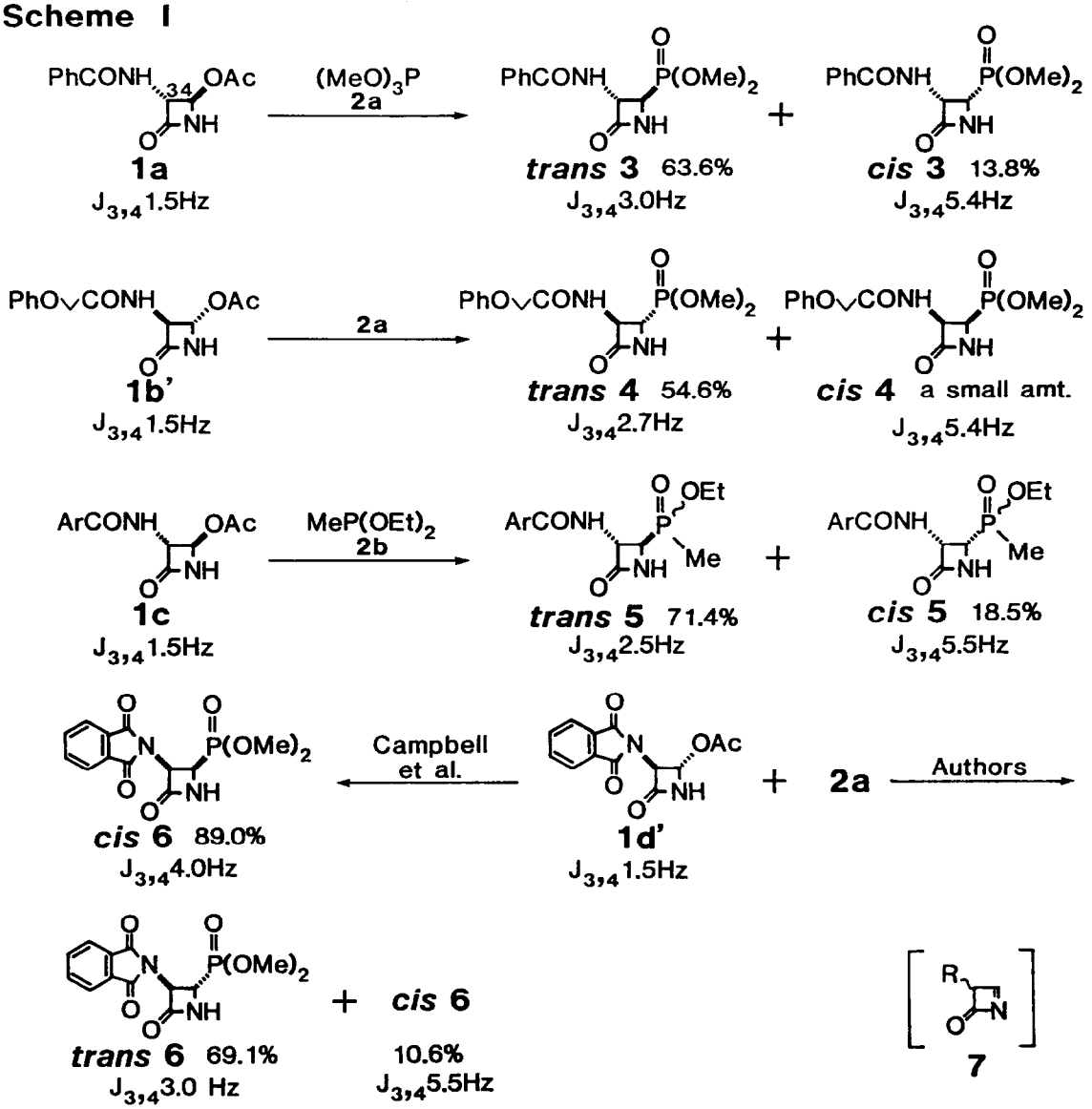
Abstract: The synthesis of optically active 7-substituted-1-phosphadethia-3-cephems is described. The stereochemistry in the displacement reaction at C-4 of chiral 3-acylamino-4-acetoxy-2-azetidinones toward trivalent phosphorus nucleophiles is also discussed briefly.

In the preceding paper,[1] we reported the first synthesis of the novel racemic 7-unsubstituted-1-phosphadethia-3-cephem 1-oxides. As these compounds were devoid of antibacterial activity, we tried to improve their biological activity by introducing some substituents into the C-7 position. We report here the synthesis of optically active 1-phosphadethia-3-cephem 1-oxides having acylamino- and α-hydroxyethyl side-chains at C-7.

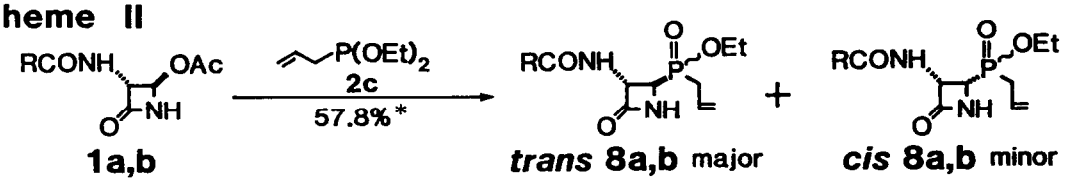
In the synthesis of the title compound, the R-configuration at C-6 is important stereochemically for the biological activities.[2] Accordingly, we investigated the mode of the displacement reaction at C-4 of chiral 3-acylamino-4-acetoxy-2-azetidinones 1a, 1b' and 1c toward phosphorus nucleophiles such as a $(MeO)_3P$ (2a) and $(EtO)_2PMe$ (2b). In all reactions, the trans-substituted product was obtained as a major product as shown in Scheme I. Stereochemical assignments for the products were determined from coupling constants correlation ($J_{3,4\text{-cis}} > J_{3,4\text{-trans}}$) in ^1H NMR spectra. Contrary to our results, Campbell et al.[3] recently reported the reaction of 4α-acetoxy-2-azetidinone bearing a bulky phthalimido group at C-3β, 1d' with 2a giving cis-phosphonate (cis-6) in 89.0% yield. Our careful reinvestigation revealed that the major product obtained was the trans-isomer (trans-6), as expected.[3,4]

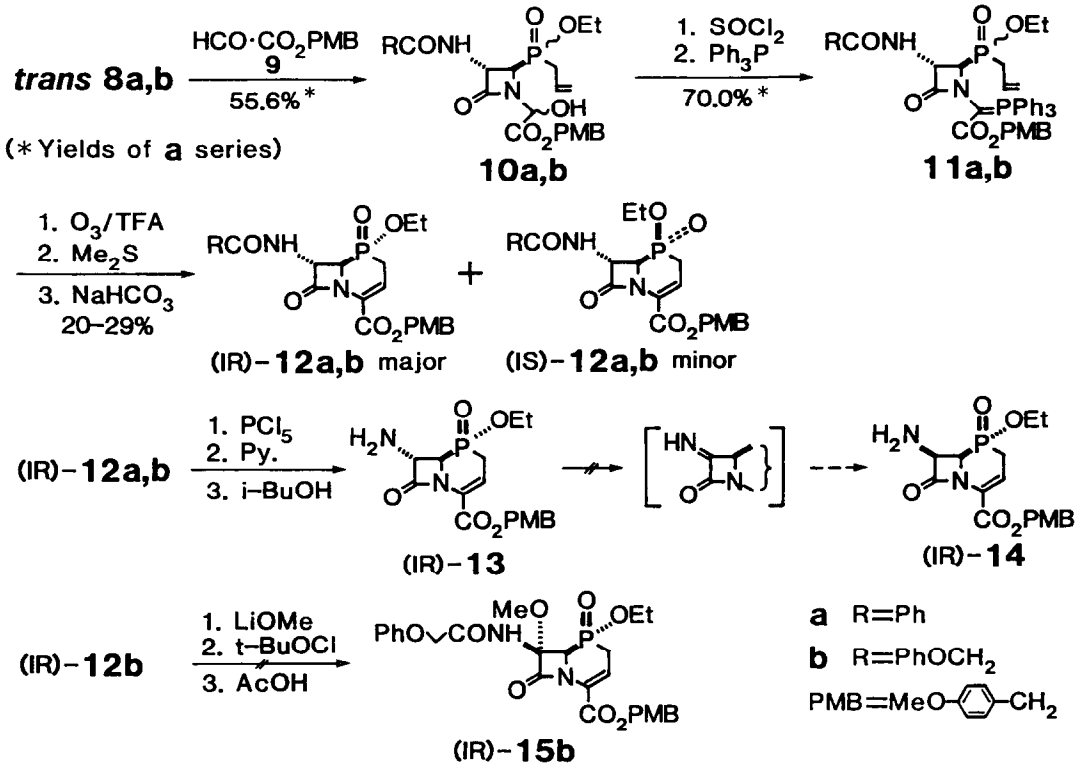
These preliminary reactions suggested that displacement reactions of these substrates involve the imine 7 as an intermediate which may undergo nucleophilic attack by phosphorus reagents preferentially from the less-hindered side and that chiral "3α"-acylamino-4β-acetoxy-2-azetidinones 1a and 1b are suitable starting materials. The method established in the preceding paper[1] was successfully extended to the synthesis of 1-phosphacephems (1R)-12a,b and (1S)-12a,b as shown in Scheme II.[5] The configurational assignments at the P atom of (1R)-12a,b and (1S)-12a,b were made based on the diagnostically useful chemical shift of a proton at C-3 and a characteristic signal pattern of the protons at C-2 in their ^1H NMR spectra as described in the preceding paper.[1] (1R)-12a: foam; λ_{max}^{EtOH} 226.5, 266(sh.) nm; $\nu_{max}^{CHCl_3}$ 1785 cm^{-1}; δ ($CDCl_3$) 6.23 (t-d, $^3J_{HH}$ 5.0, $^3J_{HP}$ 28.5 Hz, 1H, C-3). (1S)-12a: foam; λ_{max}^{EtOH} 227.5, 266(sh) nm; $\nu_{max}^{CHCl_3}$ 1780 cm^{-1}; δ ($CDCl_3$) 6.10 (t-d, $^3J_{HH}$ 5.0, $^3J_{HP}$ 28.0 Hz, 1H, C-3). $[\alpha]_D^{21}$ +26.5° (c 0.31, $CHCl_3$). (1R)-12b: foam; λ_{max}^{EtOH} 222.5, 266 nm; $\nu_{max}^{CHCl_3}$ 1790 cm^{-1}. (1S)-12b: foam; λ^{EtOH} 222(sh), 268 nm; $\nu_{max}^{CHCl_3}$ 1790 cm^{-1}; $[\alpha]_D^{21}$ +19.3° (c 0.312, $CHCl_3$). Sub-

Scheme I

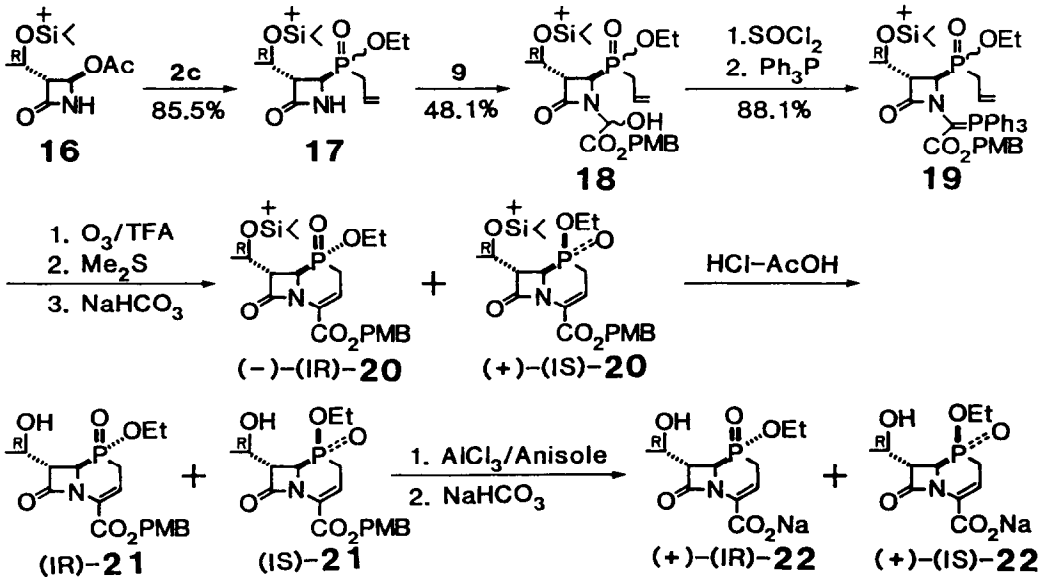


Scheme II




trans 8a,b
HCO·CO2PMB
9
55.6%*
(*Yields of a series)
10a,b
1. SOCl2
2. Ph3P
70.0%*
11a,b
1. O3/TFA
2. Me2S
3. NaHCO3
20–29%
(IR)-12a,b major
(IS)-12a,b minor
1. PCl5
2. Py.
3. i-BuOH
(IR)-13
(IR)-14
(IR)-12b
1. LiOMe
2. t-BuOCl
3. AcOH
(IR)-15b
a R=Ph
b R=PhOCH2
PMB=MeO-C6H4-CH2

Scheme III


16
2c
85.5%
17
9
48.1%
18
1.SOCl2
2. Ph3P
88.1%
19
1. O3/TFA
2. Me2S
3. NaHCO3
(-)-(IR)-20
(+)-(IS)-20
HCl-AcOH
(IR)-21
(IS)-21
1. AlCl3/Anisole
2. NaHCO3
(+)-(IR)-22
(+)-(IS)-22

sequently, epimerization of the 7α-amide side-chain is necessary because in biologically active cephalosporins, the amide group is always located on the β-face. Unfortunately, we could not isomerize[6] the 7α-amide side-chain in (1R)-12a,b to the 7β-amino orientation, i.e., (1R)-14, via 7α-amino compound (1R)-13 (gum; $\nu_{max}^{CHCl_3}$ 1775 cm^{-1}; δ ($CDCl_3$) 6.25 (t-d, $^3J_{HH}$ 5.0, $^3J_{HP}$ 27.0 Hz, 1H, C-3)) and the 7-imino compound. Epimerization of the 7α-amide isomer (1R)-12b to the 7β-amide isomer, (1R)-15b, by stereoselective 7α-methoxylation[7] was also unsuccessful, resulting in formation of a mixture of non-β-lactams.

Although homothienamycin[8] is a very weak antibacterial agent, incorporation of the electron-withdrawing P(O)(OEt) group into the ring fused with the β-lactam was expected to enhance the β-lactam reactivity and to lead to potent antibiotics. We thus investigated the synthesis of 1-phosphacephem derivatives bearing the (1R)-hydroxyethyl side chain at C-7 (Scheme III).[5] The target compounds were synthesized by the reaction sequence developed for the synthesis of the aforementioned7α-acylamino-1-phosphacephem system. (-)-(1R)-20: gum; λ_{max}^{EtOH} 227 (ε 14700), 265 (ε 8340) nm; $\nu_{C=O}^{CHCl_3}$ 1779, 1728 cm^{-1}; $[\alpha]_D^{21.5}$ -4.2° (c 0.342, $CHCl_3$). (+)-(1S)-20: gum; λ_{max}^{EtOH} 227.4 (ε 13295), 264.5 (ε 8048) nm; $\nu_{C=O}^{CHCl_3}$ 1776, 1726 cm^{-1}; $[\alpha]_D^{21.5}$ +14.2° (c 0.340, $CHCl_3$). Both compounds were desilylated to hydroxyethylphosphacephems, (1R)-21 and (1S)-21, by treatment with HCl-AcOH in CH_3CN, and subsequent removal of the PMB protecting group of both products with $AlCl_3$-anisole[9] followed by treatment with aq. $NaHCO_3$ afforded the sodium salts (+)-(1R)-22 (powder; $\lambda_{max}^{H_2O}$ 252 nm (ε 7511); $\nu_{C=O}^{KBr}$ 1754 cm^{-1}; $[\alpha]_D^{22.0}$ +44.4° (c 0.225, H_2O); 72.6% from (-)-(1R)-20) and (+)-(1S)-22 (powder; $\lambda_{max}^{H_2O}$ 251.5 nm (ε 7878); $\nu_{C=O}^{KBr}$ 1750 cm^{-1}; $[\alpha]_D^{22.5}$ +73.4° (c 0.224, H_2O); 79.9% from (+)-(1S)-20), respectively. Unfortunately, neither (+)-(1R)-22 nor (+)-(1S)-22 possessed significant antibacterial activity or β-lactamase inhibitory properties.

References and Notes

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4. This opposite result is attributed to the erroneous stereochemical assignment by Campbell et al. based on the coupling constant ($J_{3,4}$) in the ^1H NMR spectrum of the product in addition to no isolation of the other epimeric isomer.
5. All new compounds showed IR, UV and ^1H NMR (90 MHz) spectra consistent with the proposed structure. No special effort was made to improve the yield.
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