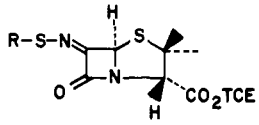
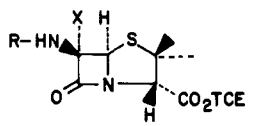
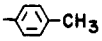
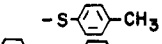
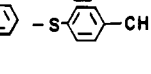
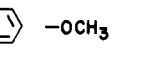
of **10** or **15**, but the preferred procedure is a modification of the sulfenyl transfer rearrangement in which either thiooxime is reacted with triphenylphosphine (3 equiv), mercuric acetate (1 equiv), methanol, and methylene chloride (26 °C, 3–5 h). Following removal of methanol, acylation of this mixture ($PhCH_2COCl$, propylene oxide, −10 °C) afforded 7α-methoxycephem ester **17** (90% from **7**) as a white foam: NMR ($CDCl_3$) δ 3.46 (s, 3 H), 3.50 (s, 2 H), 3.66 (s, 2 H), 3.93 (s, 3 H), 4.20, 4.50 (d of d, 2 H, J = 13 Hz), 5.00 (s, 1 H), 6.33 (br s, 1 H), 6.90 (s, 1 H), 7.33 (s, 15 H); IR ($CHCl_3$) 1780, 1715, 1690 cm^{-1}. It is noteworthy that no β-methoxylation is observed.[14] A proposed pathway for this transformation is illustrated in Scheme I (**3** → **11** → **12** → **13** → **17**).

The methodology discussed above has been generalized to include the penam nucleus. Thus, trichloroethyl 6-aminopenicillanate *p*-toluenesulfonate salt was converted to thiooximes **18** (80%)[15a] and **19** (43%).[15b] Substance **18**, in





	R
18	
19	$-CH_3$

	R	X
20	−H	
21		
22		$-OCH_3$

analogy with the cephalosporin example, underwent sulfenyl transfer rearrangement to **20** (≃90% by NMR, one isomer) which was acylated ($PhCH_2COCl$, $PhN(Et)_2$, CH_2Cl_2, 0 °C) to yield **21**. In addition, subjection of thiooxime **18** to the above modified rearrangement conditions, followed by acylation, afforded 6α-methoxypenam **22** (91% from **18**).[16,17] We are continuing to investigate the scope and mechanism of these transformations.

Acknowledgment. The authors wish to express their gratitude to Dr. William H. Koster and Dr. William A. Slusarchyk for useful discussions during the course of this research. We also wish to thank the Squibb Institute Analytical Department for their assistance, especially Dr. M. Puar for obtaining and interpreting NMR data.

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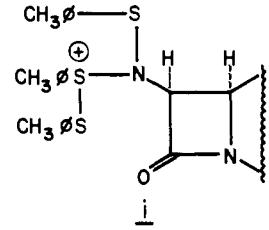
(4) For a different synthesis of 7α-methoxycephalosporins from thiooximes, see the accompanying paper of Dr. Tetsuo Hiraoka and his colleagues at Sankyo Company, Japan.

(5) T. L. Cairns, Ed., *Org. Synth.*, **35**, 99, 1955.

(6) All new compounds gave satisfactory elemental analyses and spectral data.

(7) All yields refer to quantities actually isolated, unless otherwise stated.

(8) Similar sulfenimides (of 6-APA) have been isolated by Welch;[9] however, these reactions were performed in aqueous media and did not lead to thiooxime products. An alternate route to **3** might involve activation of sulfenimide **4** toward β elimination through a structure of type **i**.



i

(9) W. M. Welch, *J. Org. Chem.*, **41**, 2220 (1976).

(10) I. B. Douglass, *J. Org. Chem.*, **24**, 2004 (1959).

(11) There is ample analogy for insertion of trivalent phosphorous between an N–S bond in sulfenamide chemistry. See T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **15**, 94 (1976).

(12) Mallinckrodt SilicAR CC-4 was used, although numerous brands were satisfactory.

(13) Personal communication from Dr. W. A. Slusarchyk of these laboratories. We thank him for providing this sample.

(14) The α configuration of methoxyl at C-7 is confirmed by comparison of **18** with an authentic sample prepared by a route known to give exclusive α-methoxylation.[3k,13]

(15) (a) Yellow crystals; mp 77–79 °C; NMR ($CDCl_3$) δ 1.60 (br s, 6 H), 2.36 (s, 3 H), 4.73 (s, 1 H), 4.80 (s, 2 H), 5.73 (s, 1 H), 7.16, 7.46 (d of d, 4 H, J = 8 Hz); IR ($CHCl_3$) 1780, 1760 cm^{-1}; UV (MeOH) 226 nm (ε 8300), 267 (3600), 338 (3600); mass spectrum *m/e* 466 (M^+). (b) White crystals; mp 129–130 °C; NMR ($CDCl_3$) δ 1.60 (s, 6 H), 2.91 (s, 3 H), 4.76 (s, 1 H), 4.86 (s, 2 H), 5.81 (s, 1 H); IR (KBr) 1770, 1755 cm^{-1}; mass spectrum *m/e* 390 (M^+). Both **18** and **19** form stereospecifically and are stable entities at 26 °C.

(16) Introduction of C-6 methoxyl occurs stereospecifically, the configuration of which was expected to be α on the basis of steric effects and analogy with the cephalosporin example. This was confirmed by conversion of **22** to the known 7α-methoxy-7-phenylacetamidodeacetoxycephalosporanic acid.[3d] Details will be given in the full paper.

(17) A typical procedure for rearrangement of **18** to **22** is as follows. Thiooxime **18** (16.1 g, 34.5 mmol) and triphenylphosphine (27.6 g, 103.6 mmol) are dissolved in methylene chloride (600 ml) and stirred at 26 °C. A solution of mercuric acetate (11.0 g, 34.5 mmol) in methanol (150 ml) is immediately added and the reaction mixture is allowed to stir for 3.5 h. The mixture is evaporated to dryness under reduced pressure and then redissolved in methylene chloride (600 ml) and propylene oxide (150 ml). This solution is chilled to −10 °C and phenylacetyl chloride (25.8 g) in methylene chloride (80 ml) is added dropwise with stirring. After 3 h, the reaction mixture is concentrated to an oil and chromatographed on silica gel (Mallinckrodt SilicAR CC-7) to yield **22** as a clear, colorless oil (15.49 g, 91%).

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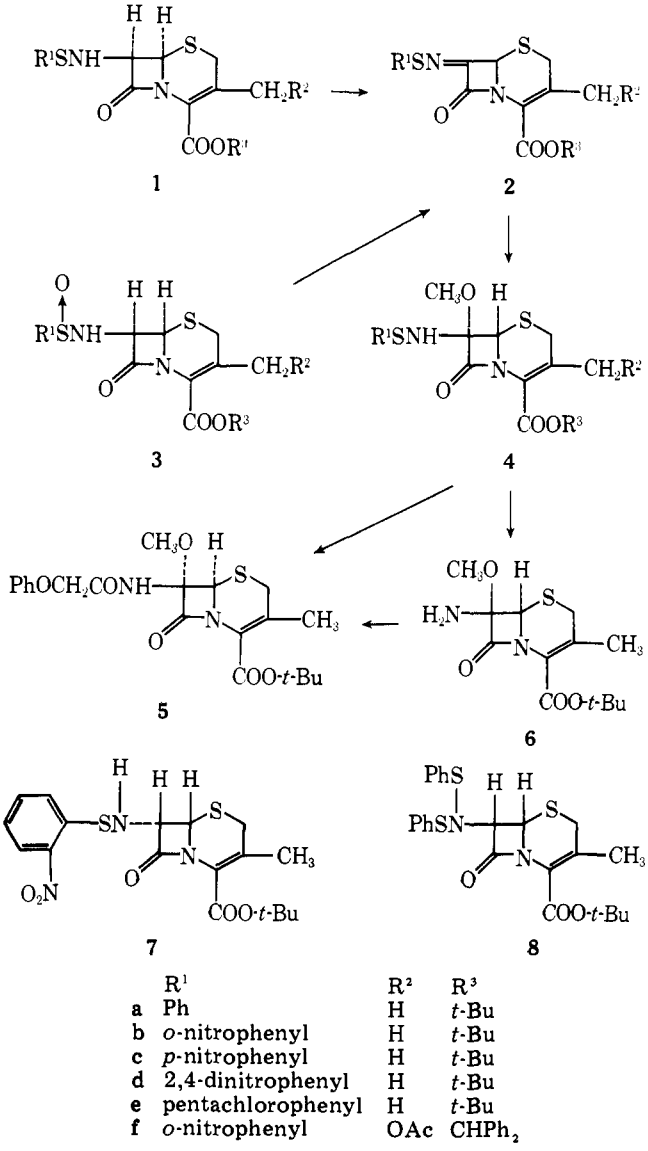
A Novel Synthetic Route to 7α-Methoxycephalosporins

Sir:

Much attention has been focused on 7-methoxycephalosporins after isolation of the cephamycin group from cultures of a *streptomyces* species[1] and subsequent modification of the original compound to those with enhanced activity.[2] Several methods have been developed for introduction of a methoxy group at the seven position of cephalosporins starting from 7-aminocephalosporins or 7-acylaminocephalosporins.[3] However, some difficulty still remains in the synthesis of 7α-methoxycephalosporins having a complex 7β-acylamino side chain.[4] Our object was directed toward the synthesis of



	R^1	R^2	R^3
a	Ph	H	*t*-Bu
b	*o*-nitrophenyl	H	*t*-Bu
c	*p*-nitrophenyl	H	*t*-Bu
d	2,4-dinitrophenyl	H	*t*-Bu
e	pentachlorophenyl	H	*t*-Bu
f	*o*-nitrophenyl	OAc	$CHPh_2$

7α-methoxycephalosporins with a masked 7β-amino group which can act as an activated amine in a peptide synthesis. The 7α-methoxy-7β-sulfenamide moiety is very attractive for this purpose since a sulfenamide group may be converted to an amide by reaction with a carboxylic acid.[5] Now we wish to report an efficient synthesis of 7α-methoxy-7β-sulfenylaminocephalosporins.

Reaction of *tert*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate with 1 equiv of phenylsulfenyl chloride in the presence of triethylamine at room temperature gave the sulfenamide **1a** (76% yield), **8** (8%),[6] and the sulfenimine **2a** (7%)[7] after silica gel chromatography. Isolation of **2a** as a stable compound encouraged us to examine the oxidation of **1a.** Thus treatment of **1a** with manganese dioxide at room temperature for 1 h afforded the sulfenimine **2a** in 83% yield. Other oxidative reagents such as trichloroisocyanuric acid, *N*-chlorosuccinimide, or *tert*-butyl hypochlorite with triethylamine were less effective than MnO_2. Analogously, **1b, 1c, 1d,** and **1f** were converted into the exo imine **2b, 2c, 2d,** and **2f,** respectively, in high yields (68–86%) by treatment with MnO_2. In the case of the pentachloro derivative **1e,** the oxidation was rather slow and a lower yield (20%) was obtained with recovery of the starting material after reaction for 1 h. The compound **2b** was also synthesized from the sulfinamide **3b** using thionyl chloride and quinoline at 0 °C in 54% yield. To our knowledge, this is the first example of a Pummerer-type reaction of a sulfinamide. This reaction also proceeded well starting from **3f** to give **2f.** Although the sulfinamides **3b** and **3f** were a mixture of diastereomers (epimeric at the sulfinyl sulfur) both isomers were smoothly converted to sulfinimine. Reduction of **2b** with sodium borohydride in tetrahydrofuran–dimethyl sulfoxide (1:1) at 0 °C gave back **1b** (52% yield) together with a small amount of the stereoisomer **7** (5.6% yield), confirming the structure of **2.** Methoxylation of the imine **2** was smoothly conducted on treatment with lithium methoxide in methanol or potassium *tert*-butoxide in methanol when the benzene ring of R^1 possessed electron-withdrawing group(s). Thus, the 2,4-dinitrophenyl derivative **2d** was methoxylated at −78 °C to furnish **4d**[8] stereospecifically in 83% yield. In the case of mononitro and pentachlorophenyl derivatives (**2b,c,e**) methoxylation was slower and moderate yields (50–63%) were obtained, while **2a** afforded a trace of **4a** with methoxide anion. Interestingly, methoxylation with an acid catalyst such as methanesulfonic acid or *p*-toluenesulfonic acid at room temperature gave a mixture of 7α- and 7β-methoxy derivatives. The methoxysulfenamide **4c** was converted to the free amine **6** on treatment with sodium iodide in methanol–methylene chloride in the presence of acetic acid at 0 °C for 20 min in 53% yield. Removal of the sulfenyl group from **4c** with thiophenol or hexamethylphosphorus triamide took a longer time (overnight); however, acylation with phenoxyacetyl chloride without isolation of **6** afforded the amide **5** in good yield (80–90%) with some amount of Δ^2 isomer. Application of a known coupling method[5] for peptide formation to the methoxysulfenamide **4c** was unsatisfactory. This is not unusual based on the observation that there was a great difference in reactivity between 7αH-7β-aminocephalosporins and the 7α-methoxy-7β-amino series. For example, the 7αH-sulfenamide **1c** was reacted with phenoxyacetyl chloride without a base to afford the corresponding 7β-phenoxyacetamide in 90% yield, whereas the same reaction using the 7α-methoxysulfenamide **4c** gave **5** in only 5% yield.

This oxidation and methoxylation reaction also proceeded well in penicillin series with some ring opening of β-lactam in the methoxylation step.

Although the direct condensation of the 7α-methoxysulfenamides **4** with a carboxylic acid is disappointing, the method demonstrated here provides a versatile, useful alternative to functionalization at the seven position of cephalosporins.

Acknowledgments. We are very grateful to Dr. K. Arima, the director of our research laboratories, and to Dr. Y. Kishida, the director of chemical research for their interest and discussions throughout this work.

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(3) For methods of preparation of 7α-methoxycephalosporins, see Y. Sugimura, K. Iino, Y. Iwano, T. Saito, and T. Hiraoka, *Tetrahedron Lett.*, 1307 (1976), and references cited therein.

(4) Acylation of 7α-methoxy-7β-aminocephalosporins with a carboxylic acid having complex functional group(s) using DCC or mixed anhydride methods gave poor results. So a carboxylic acid whose acid chloride can not be prepared is difficult to condense with 7α-methoxy-7β-aminocephalosporins.

(5) (a) T. Mukaiyama, M. Ueki, H. Maruyama, and R. Matsueda, *J. Am. Chem. Soc.*, **90,** 4490 (1968), (b) M. Ueki, H. Maruyama, and T Mukaiyama, *Bull. Chem. Soc. Jpn.*, **44,** 1108 (1971).

(6) In the case of *o*- or *p*-nitrophenylsulfenyl chloride no bisnitrophenylsulfenimide was formed. Cf. W. M. Welch, *J. Org. Chem.*, **41,** 2220 (1976).

(7) Mp 170–171 °C; IR 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (9 H, s), 2.08 (3 H, s), 3.12 and 3.48 (2 H, AB q, J = 19 Hz), 5.27 (1 H, s), 7.16–7.70 (5 H, m).

(8) Amorphous powder; IR 3300, 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.49 (9 H, s), 2.12 (3 H, s), 3.20 and 3.40 (2 H, AB q, J = 18 Hz), 3.58 (3 H, s), 4.58 (1 H, s), 4.93 (1 H, s), 8.35–9.08 (3 H, m).

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Icosahedral Boron Frameworks. The Structure of γ-AlB_{12}

Sir:

We have determined the structure of γ-AlB_{12}. The solution to this long-standing problem has contributed significantly to our understanding of the structural chemistry of elementary boron and icosahedral borides. The structure is based upon a framework of boron icosahedra that is intimately related to the frameworks in α-AlB_{12}[1] and BeB_6.[2] Moreover, we have determined that all of these structures are derivative from a parent framework, that of β-rhombohedral boron,[3] the thermodynamically stable form of the element.[4] We also suggest that such derivative frameworks will be appropriate for the description of another preparation of boron[5] and for a variety of nonstoichiometric borides.[6]

A single crystal of γ-AlB_{12} was kindly provided by Dr. J. A. Kohn.[7] Diffraction symmetry and extinctions corresponded to $P2_12_12_1$ with $a = 16.623 \pm 0.005$, $b = 17.540 \pm 0.005$, and $c = 10.180 \pm 0.005$ Å. The densities $D_m = 2.56$ and $D_x = 2.55$ g cm^{-3} correspond to a unit cell content of $B_{352}Al_{27.9}$. Intensities were measured in a θ-2θ scan mode with Mo Kα radiation on a Picker card controlled diffractometer; of 5539 nonabsent independent reflections investigated ($\sin\theta/\lambda \leq 0.7456$), a total of 5439 were statistically observable. With 427 independent parameters in the refinement, this provided a data-parameter ratio of 12.7. No corrections were made for extinction or absorption.

The structure was solved by iterative Fourier methods using initial models derived from stereochemical principles for icosahedral boron framework structures that were developed in this laboratory.[8] Final block diagonal least-squares refinement of the structure yielded a standard residual $R = 0.059$ for the observed data; a weighted residual $R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2} = 0.078$ was obtained with unit weights. Isotropic thermal parameters were used for all boron atoms but six fully occupied and two partially occupied aluminum sites were refined anisotropically. Final difference Fourier syntheses were featureless with background noise at a level of ~0.5 e $Å^{-3}$.

Icosahedral structures can be described in remarkably diverse but nevertheless complementary ways depending upon the basic unit of structure that is selected for emphasis.[4] Because of this diversity we now introduce a nomenclature that characterizes the symmetry of selected boron subunits with standard Schoenflies notation. Thus, the now conventional representation[9] of the β-rhombohedral boron structure, β-B_{105}-($R\bar{3}m$), would be described as a rhombohedral (quasi-cubic) framework of B_{84}-(I_h) units interbonded through rhombohedrally directed pentagonal faces with holes in the framework filled by B_{10}-(C_{3v}) units that fully interlink the equatorial pentagonal faces. This succinct statement provides a graphic description of a complex structure that requires only a moderate familiarity with the B_{84}-(I_h) unit. An alternative description is required, however, to reveal the hitherto unnoted relationships to the framework structures of α-AlB_{12} and γ-AlB_{12}.

Boron icosahedra can be centered at all of the vertices of a regular *3636* kagomé plane net[10] with twofold axes perpendicular to the net and then oriented so as to fully satisfy the symmetry of the plane group *p6m*; indeed, the resulting sheet of icosahedra also possesses mirror symmetry in the net plane. If additional boron icosahedra (with threefold axes perpendicular to the plane net) are suitably centered at the tetrahedral apices above one of the two subsets of triangular sites in the kagomé net, the effective plane group symmetry of the array becomes *p3m1*. A tetrahedron of four boron icosahedra possesses the full symmetry of the tetrahedral group and is designated as the B_{48}-(T_d) unit. The bi-layered sheet of icosahedra comprised of a kagomé layer of interconnected B_{48}-(T_d) units is the basic layer of structure in the frameworks of γ-AlB_{12}, α-AlB_{12}, and β-rhombohedral boron. The frameworks are simply generated by appropriately stacking these layers and it is important to emphasize that in every case *all* intericosahedral bonds in the frameworks closely satisfy the preferred pentagonal pyramidal bonding for elementary boron.[4]

There are two distinct stacking operators that relate successive B_{48}-(T_d) kagomé layers so as to preserve the directed geometry of icosahedral bonding. The first, a 2_1 operator normal to the layer and colinear with the "local" threefold axes of the B_{48}-(T_d) units, generates the framework of γ-AlB_{12} as depicted in Figure 1. The appropriate metrics of the orthorhombic cell are preserved in a framework of symmetry

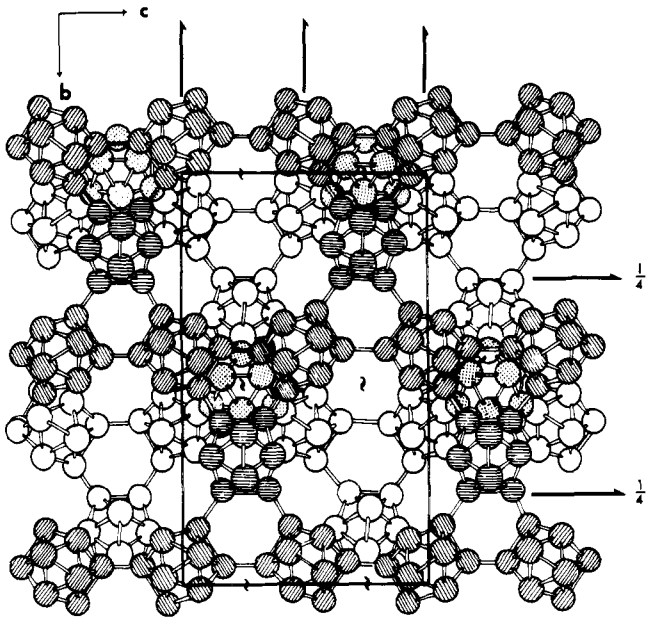

Figure 1. A projection along the *a* axis of the framework of boron icosahedra in γ-AlB_{12}. Two kagomé nets and the interleaving triangular net frame the truncated tetrahedral holes.

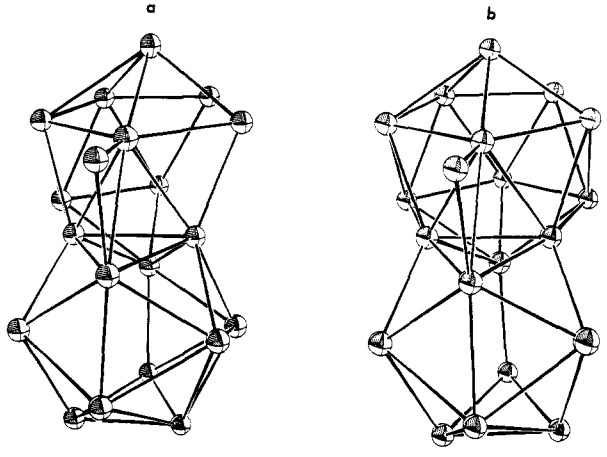

Figure 2. Condensed units of boron icosahedra and icosahedral fragments: a, B_{20}-(C_2) unit, found in α-AlB_{12} and γ-AlB_{12}; b, B_{20}-(C_s) unit, found in γ-AlB_{12}.