The most striking feature of Table I is the high activity of the catalyst prepared from the mixed metal cluster $H_2FeRu_3(CO)_{13}$. Similarly, mixtures of $Fe(CO)_5$ and $Ru_3(CO)_{12}$ form catalysts in alkaline solution considerably more active than either metal carbonyl individually (Table II). Spectral characterization as well as isolation of various reaction components indicate the presence of several mixed-metal clusters including $H_2FeRu_3(CO)_{13}$ in these solutions. The source of the synergetic behavior of the iron/ruthenium mixtures is uncertain. However, the key may lie with the stabilities of the mixed-metal hydridocarbonyl clusters toward reductive elimination of dihydrogen. For example, $H_4FeRu_3(CO)_{12}$ is reportedly[8] less stable toward loss of H_2 than is $H_4Ru_4(CO)_{12}$; thus, if reductive elimination were rate limiting, this difference could have a marked effect on the relative catalytic activities. We are investigating this hypothesis with kinetics studies of H_2 elimination from several of these complexes and the role of CO in this reaction.

Ruthenium carbonyl forms active catalysts in other reaction media including aqueous piperidine/ethoxyethanol, aqueous pyridine, and acidic aqueous diglyme solutions[9] (Table II) and, according to a recent report,[10] in aqueous trimethylamine/tetrahydrofuran. Notably, marked enhancement of activity is again seen for the mixed Fe/Ru catalysts in the piperidine and pyridine solutions but not in the acidic diglyme solutions.

The greater activities of the ruthenium and Fe/Ru amine solutions compared with alkali base solutions may be the result of several perturbations. One possibility is that the amines are participating in direct attack on coordinated carbonyl, as previously reported[11] for $Fe(CO)_5$, thus accelerating the activation step (step A in Scheme I). However, solvent effects alone may play a major role given that the amine concentrations are sufficient to change markedly the medium properties. Such effects on a rate-determining step or key equilibrium in a cycle such as Scheme I would have major consequences on the catalytic activity.

The high activity of the ruthenium catalysts in acidic solution may be simply the result of shifts in pH dependent equilibria. The key steps in Scheme I are likely to be activation of CO by nucleophilic attack on M–CO and reductive elimination of H_2 from MH_2. If M–CO is either $HRu_4(CO)_{13}^-$ or $H_2Ru_4(CO)_{13}$, the latter species (which is favored by lowering the pH) should be the more susceptible to nucleophilic attack by H_2O or OH^-. We have demonstrated that after the first day the alkaline catalyst solutions prepared with KOH are ca. pH 10; thus H_2O (6 M) is probably the important nucleophile under this condition and at lower pH. In addition it is likely that $H_4Ru_4(CO)_{12}$ is more reactive toward reductive elimination than is the deprotonated analogue $H_3Ru_4(CO)_{12}^-$. The failure of the mixed-metal system to show enhanced activity in acidic solution is unexplained; however, qualitative comparison of the reaction solutions (color, IR spectra, etc.) show, as expected, these systems to have considerably different characters in the acidic and basic media. These are mechanistic aspects of the various catalysts under further study in these laboratories.

Acknowledgments. This work was supported by the Department of Energy, Office of Basic Energy Sciences. Howard Walker and Professor Ralph G. Pearson contributed significantly to the discussion and interpretation of these results.

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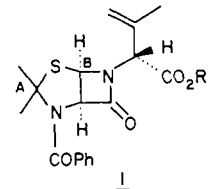
Stereospecific Synthesis of Penicillins. Stereoelectronic Control in the Conversion of a Peptide into a Penicillin

Sir:

Recently we described the stereospecific total synthesis of a penicillin from a dipeptide,[1] in which the thiazolidine β-lactam **1**[2] was converted via a seven-step sequence into a penicillin. This lengthy sequence resulted from the intrinsically



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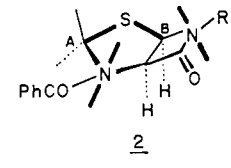

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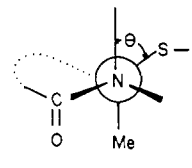

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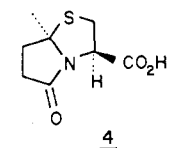

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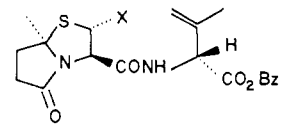
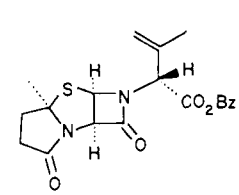


5 a : X = H
b : X = OCOPh
c : X = Cl



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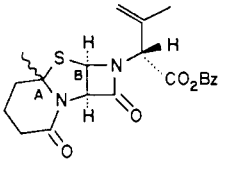
stronger C_A–S bond relative to the C_B–S bond in **1**, a situation which always resulted in the undesired preferential cleavage of the latter. The origin of this difference almost certainly derives from a stereoelectronic factor, i.e, the C_B–S bond is more nearly orthogonal to the β-lactam amide plane than the C_A–S bond is, with respect to the thiazolidine amide plane, as in **2** (darkened perpendiculars). We argued that this ordering of bond lability could be reversed by constructing a ring bridging the thiazolidine moiety which would render the C_A–S bond more nearly orthogonal to the thiazolidine amide plane. The projection **3** attempts to illustrate how reduction in size of the bridging ring (dotted line) reduces the angle θ. We now report the successful realization of this stereoelectronic control, which enables us to selectively cleave the C_A–S bond and hence obtain the shortest stereocontrolled entry to the penam system.

Cysteine was condensed with methyl levulinate[3] (neat, $MeSO_3H$, 120 °C, 4 h) to provide the bicyclic thiazolidine **4**:[4] mp 193–194.5 °C; 16%;[5] $[\alpha]^{27}_D$ −202.2° (*c* 2.51, Me_2SO); ν_{max} 3300–2500, 1735, 1660 cm^{-1}; NMR δ 1.65 (3 H, s), 2.10–2.78 (4 H, m), 3.46 (1 H, br s), 3.59 (1 H, s), 4.87 (1 H, dd, *J* = 6, 10 Hz, 1 H). Compound **4** represents a single isomer at the angular methyl group and has been assgined the α configuration, although this assignment is not critical to the above hypothesis.[6] Bicycle **4** was coupled with D-isodehydrovaline[7] as its benzyl ester (DCC–1-hydroxybenzotriazole,[8] CH_2Cl_2, room temperature) to the dipeptide **5a:** oil; 93%; $[\alpha]^{24}_D$ −117.8° (*c* 4.85, CH_2Cl_2); ν_{max} 3400, 1730, 1715, 1685 cm^{-1}; NMR δ 1.60 (3 H, s), 1.71 (3 H, d, *J* = 1 Hz), 1.98–2.82 (4 H, m), 3.40 (1 H, dd, *J* = 9, 12 Hz), 3.86 (1 H, dd, *J* = 6.5, 12 Hz), 4.83 (1 H, dd, *J* = 6.5, Hz, partially obscured), 4.97–5.20 (5 H, m), 7.33 (6 H, s, contains NH). Stereospecific functionalization with benzoyl peroxide[2] (2.5 equiv, CCl_4, 65 °C, 1 h) provided the benzoate **5b** (oil; 22%; $[\alpha]^{25}_D$ +112.8° (*c* 2.65, CH_2Cl_2); ν_{max} 3400, 1722 (br), 1690 cm^{-1}; NMR δ 1.61 (3 H, s), 1.65 (3 H, s), 2.22–2.80 (4 H, m), 5.02–5.17 (5 H, m), 5.57 (1 H, s), 6.98 (1 H, d, *J* = 8 Hz), 7.05 (1 H, s), 7.20–7.55 and 7.80–8.00 (5 H, m), 7.32 (5 H, s)) which was smoothly converted to the chloride **5c** (HCl gas,[2] CH_2Cl_2, 0 °C, 2 h) (mp 79–80.5 °C; 72%; NMR δ 1.69 (3 H, s), 1.72 (3 H, s), 2.40–2.88 (4 H, m), 4.96–5.18 (5 H, m), 5.42 (1 H, s), 6.38 (1 H, s), 6.95 (1 H, d, *J* = 8 Hz), 7.30 (5 H, s)). This compound was unstable and highly sensitive to moisture. Treatment of chloride **5c** with sodium hydride[2] (0.95 equiv, as 60% oil dispersion, 0 °C, 25 min) provided a quantitative yield of the tricyclic β-lactam **6** as an oil, which could be crystallized from ether: mp 133.5–135 °C; $[\alpha]^{25}_D$ −256.8° (*c* 0.31, CH_2Cl_2); ν_{max} 1765, 1730, 1710 cm^{-1}; NMR δ 1.73 (3 H, s), 1.88 (3 H, s), 2.00–2.62 (4 H, m), 4.82 (1 H, s), 4.95–5.25 (4 H, m), 5.80 (2 H, s, β-lactam), 7.30 (5 H, s). Reaction of β-lactam **6** with *tert*-butyl hypochlorite[9] in wet THF (1.0 equiv, −78 °C, 1.5 h) provided the 2β-chloromethylpenam **7a** (oil; 55%; $[\alpha]^{25}_D$ +91.7° (*c* 1.83, CH_2Cl_2); ν_{max} 3400, 1780, 1740, 1710, 1690 cm^{-1}; NMR δ 1.50 (3 H, s), 2.20 (3 H, s), 2.40–2.85 (4 H, m), 3.60 (2 H, s), 4.97 (1 H, s), 5.21 (2 H, s), 5.51–5.75 (2 H, m), 6.80 (1 H, d, *J* = 8 Hz), 7.36 (5 H, s)), presumably through the intermediacy of the sulfenyl chloride **8a.**[10] Penam **7a** was stable to chromatographic purification (silica gel), in contrast to compounds where X is a better leaving group.[10,11] If allowed to stand as the neat oil at room temperature, penam **7a** was converted quantitatively to the 3β-chlorocepham **9a:** oil; $[\alpha]^{25}_D$ +25.3° (*c* 2.30, CH_2Cl_2); ν_{max} 3400, 1772, 1738, 1708, 1692 cm^{-1}; NMR δ 1.58 (3 H, s), 2.18 (3 H, s), 2.44–2.90 (5 H, m), 3.61 (1 H, d, *J* = 14 Hz), 4.72 (1 H, s), 5.18 (2 H, s), 5.23 (1 H, d, *J* = 4.5 Hz), 5.60 (1 H, dd, *J* = 9 Hz), 6.79 (1 H, d, *J* = 4.5, 9 Hz), 7.37 (5 H, s). The isomerization to cepham **9a** was more rapid in DMF[12] at 45 °C.

The structure of penam **7a** was proven by synthesis from natural sources. Thus, condensation of benzyl 6-aminopenicillinate[13] with levulinic acid via the mixed carbonic anhydride (ethyl chloroformate, THF, −18 °C) provided the penam **10** (oil; 96%; $[\alpha]^{26}_D$ +155.8° (*c* 1.44, CH_2Cl_2); ν_{max} 3410, 1780, 1740, 1708, 1692 cm^{-1}; NMR δ 1.42 (3 H, s), 1.64 (3 H, s), 2.20 (3 H, s), 2.40–2.83 (4 H, m), 4.43 (1 H, s), 5.19 (2 H, s), 5.55 (1 H, m), 5.75 (1 H, d, *J* = 4 Hz), 6.64 (1 H, d, *J* = 7 Hz), 7.37 (5 H, s)), which was oxidized to the sulfoxide **11** (MCPBA, CH_2Cl_2, −78 °C) (oil; 78%; $[\alpha]^{27}_D$ +159.2° (*c* 5.88, CH_2Cl_2); ν_{max} 3380, 1795, 1748, 1708, 1693 cm^{-1}; NMR δ 1.04 (3 H, s), 1.66 (3 H, s), 2.18 (3 H, s), 2.32–2.83 (4 H, m), 4.65 (1 H, s), 4.98 (1 H, d, *J* = 5 Hz), 5.10 and 5.31 (2 H, AB q, *J* = 11 Hz), 5.98 (1 H, d, *J* = 5, 11 Hz), 7.13 (1 H, d, *J* = 11 Hz), 7.33 (5 H, s)). Thermolysis of sulfoxide **11** in the presence of 2-mercaptobenzothiazole[13] gave the disulfide **12,** used without further purification: oil; 94%; NMR δ 1.90 (3 H, s), 2.15 (3 H, s), 2.50–2.84 (4 H, m), 4.96 (1 H, s), 5.14 (2 H, s), 5.38 (1 H, dd, *J* = 4.5, 8 Hz), 5.54 (1 H, d, *J* = 4.5 Hz), 7.15–7.85 (10 H, m). When this disulfide was treated with chlorine[12] (0.90 equiv, THF, −78 °C), the penam **7a** was produced and isolated in 40% yield after chromatography. This material was identical spectroscopically with that prepared from β-lactam **6.**

Similar treatment of β-lactam **6** with *N*-bromosuccinimide and disulfide **12** with bromine provided the 2β-bromopenam **7b** and 3β-bromocepham **9b.** The stereoelectronic effect observed here is analogous to those described by Deslongchamps in the selective decomposition of tetrahedral intermediates.[14] In accord with our suggestion that the required orbital alignment depends on the size of the bridging ring, *of* **3** above, we found that neither of the diastereomers **13** provided the selective C_A–S cleavage.[15]



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(15) These two diastereomes **13** were prepared analogously to **6**, i.e., from the respective cis and trans isomers of the bicyclic thiazolidine.

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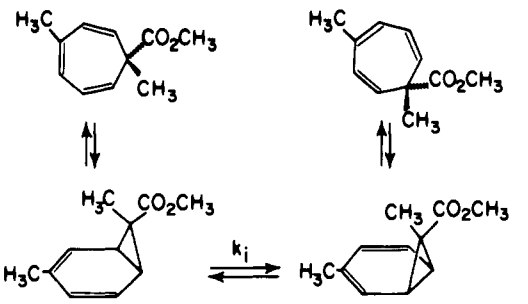
Kinetics of the Stereomutations of (+)-2-Deuterio-3,7-dimethyl-7-methoxymethylcyclohepta-1,3,5-triene: One-Centered Epimerization at C(7) and [1,5] Carbon Migration with Retention of Configuration in a Norcaradiene

Sir:

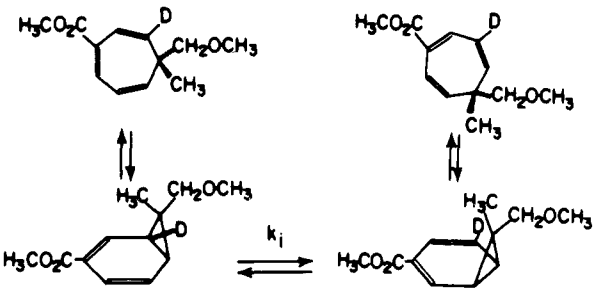
The ring-walk interconversions of the *n*,7,7-trimethyltropilidenes discovered by Berson and Willcott in 1965[1] involve tropilidene–norcaradiene valence isomerizations and [1,5] carbon migrations. The stereochemical features of such [1,5] shifts are the concern of this communication.

Optically active 3,7-dimethyl-7-methoxycarbonylcycloheptatriene has been shown to undergo thermal racemization as well as isomerization to 2,7-dimethyl-7-methoxycarbonylcycloheptatriene[2] (Scheme I), an observation taken as evidence for [1,5] carbon migrations with highly stereoselective inversion stereochemistry. This finding diametrically opposed to expectations based on orbital symmetry theory[3] has been validated through molecular orbital calculations: the [1,5] "forbidden" shift with inversion was held to be favored over the [1,5] "allowed" shift with retention of configuration by some 1.4 kcal/mol, thanks to subjacent orbital effects.[4]

Scheme I



Scheme II



Very recent work, which came to our attention just as our own experimental efforts were nearly completed,[5] supported the conclusion that the [1,5] shift involves inversion of stereochemistry. Hansen found that optically active 1-deuterio-3-methoxycarbonyl-7-methyl-7-methoxymethylcycloheptatriene racemized thermally at approximately the same rate as its degenerate deuterium-scrambling isomerization took place (Scheme II).

Our approach was based on synthesis of optically active (+)-2-deuterio-3,7-dimethyl-7-methoxymethylcycloheptatriene and determination of its kinetics of degenerate rearrangement, with cognizance of the possible intrusion of one-centered epimerization at C(7) of the norcaradiene form of the substrate.[6] We sought experimental measures of the rate constants k_e, k_i, and k_r defined in Scheme III.

The required synthesis began with selective epoxidation of carvone with *m*-chloroperbenzoic acid; the keto epoxide[7] was isomerized with lithium diisopropylamide to provide 2,6-dimethyl-6-hydroxymethylcyclohepta-2,4-dien-1-one. Its hemiphthalate was resolved through recrystallizations of the related (−)-α-methylbenzylamine salt from ether–chloroform; the amine salt had mp 132–133 °C, $[\alpha]^{CHCl_3}_D$ +60.2°. Reduction of the resolved hemiphthalate with sodium borodeuteride, followed by dehydration catalyzed by *p*-toluenesulfonic acid in methylene chloride at reflux, gave the hemiphthalate of one antipode of 2-deuterio-3,7-dimethyl-7-hydroxymethylcycloheptatriene. Hydrolysis with 3 N sodium hydroxide, followed by methylation using *n*-butyllithium and methyl iodide in Me_2SO, gave the desired compound 96.4% optically pure (according to NMR analysis in the presence of an optically active shift reagent) and containing 94% of one deuterium at C(2).

Table I. Calculated[a] and Observed Mole Percent Concentrations of 2- and 4-Deuterio-3,7-dimethyl-7-methoxymethylcyclohepta-1,3,5-trienes at 223.4 °C

Time, min	(+)-2-*d*		(−)-2-*d*		(+)-4-*d*		(−)-4-*d*	
	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd
0	92.3	92.3	1.7	1.7	0	0	0	0
300	80.4	80.0	8.2	8.6	4.3	4.7	1.1	0.7
679	68.5	70.7	14.1	11.9	8.4	6.2	3.0	5.2
1500	50.9	51.2	21.6	21.3	14.0	13.7	7.5	7.8

[a] According to Scheme III and the rate constants $k_e = 0.45 \times 10^{-5}$ s^{-1}; $k_r = 0.29 \times 10^{-5}$ s^{-1}; and $k_i = 0.05 \times 10^{-5}$ s^{-1}.

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