Nuclear analogs of β-lactam antibiotics. XVIII.[1] A short synthesis of 2-alkylthiocarbapen-2-em-3-carboxylate

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A short synthesis of (±)-2-alkylthiocarbapen-2-em-3-carboxylic acid (**2**) from sorbic acid via a key intermediate **4** is described.

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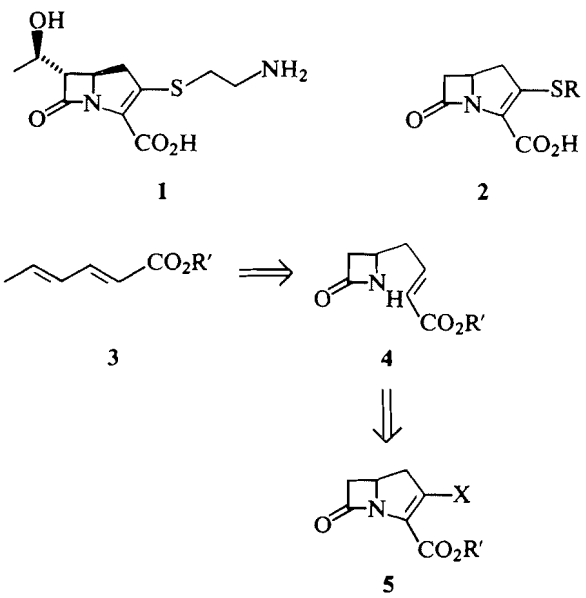
On décrit une synthèse courte de l'acide (±)-alkyl-2-thiocarbapenem-2-carboxylique-3 (**2**) à partir de l'acide sorbique via l'intermédiaire-clé **4**.

[Traduit par le journal]

The discovery of thienamycin **1** (1), a potent and broad spectrum β-lactam antibiotic, has initiated considerable effort in the synthesis of the carbapenem ring system (2). Several methods have recently been developed for the synthesis of thienamycin (3) and its 6-unsubstituted analogs (4). Some of these methods (4) require long synthetic sequences or the starting materials are not readily available. We wish to report a short synthesis of 6-unsubstituted 2-alkylthiocarbapen-2-em-3-carboxylic acid (**2**) from an inexpensive starting material, sorbic acid (**3***a*), through a key intermediate **4**.[3] The carbon skeleton necessary for the synthesis of a carbapenem nucleus such as **5** is built-in to this intermediate.



1 **2** **3** **4** **5**

Thus, methyl sorbate (**3***b*) was converted to methyl 3,5-hexadienoate (**6***a*) in 77% yield by kinetic protonation of the enolate generated with lithium diisopropylamide at −78°C in THF–HMPA (6). *p*-Nitrobenzyl 3,5-hexadienoate (**6***b*) was prepared from sorbic acid (**3***a*) as follows: since *p*-nitrobenzyl esters generally suffer from treatment with a strong base such as LDA, sorbic acid (**3***a*) was converted to 3,5-hexadienoic acid (**6***c*) by kinetic protonation of the enolate generated at −10°C with 2 equiv. of LDA in THF (7). This acid was immediately esterified at 0–5°C with *p*-nitrobenzyl bromide and triethylamine to obtain *p*-nitrobenzyl 3,5-hexadienoate (**6***b*) in 65.7% overall yield from sorbic acid (**3***a*).

Addition of chlorosulfonyl isocyanate (8) to these conjugated dienes **6***a* and **6***b* at room temperature in CH_2Cl_2 cleanly provided azetidinone sulfonyl chlorides **7***a* and **7***b* which were, without isolation, reduced by a modification (Na_2SO_3–$NaHCO_3$) of the Durst method (9) to yield azetidinones **8***a* and **8***b* in 63% and 49% yield, respectively. Use of NaOH instead of $NaHCO_3$ caused destruction of the molecule. Isomerization of the double bond in **8***a* to the conjugated system **4***a* was studied in various base–solvent systems. Triethylamine in CH_2Cl_2 did not effect the isomerization at an appreciable rate at room temperature. Triethylamine in polar aprotic solvents, such as DMSO, DMF, or CH_3CN, gave, after weeks, the desired isomerization product **4***a* together with a white solid which consisted of β-lactam opened products.[4]

These fragmentation materials were the major products when **8***a* was treated with strong bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in CH_2Cl_2, sodium methoxide in MeOH, or potassium *tert*-butoxide in *t*-BuOH. The best result was obtained by using 1,4-diazabicyclo[2.2.2.]octane (DABCO) in CH_3CN at room temperature. Thus, **8***a* and **8***b* were treated with DABCO in CH_3CN at room temperature for 3–4 days to produce the conjugated esters **4***a* and **4***b* in 87% and 73% yield, respectively.

Although intermediates **4** could be used, after protection of

[1]For Part XVII of this series see ref. 14.

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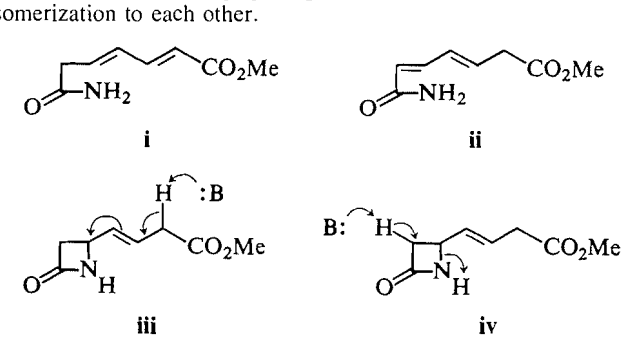
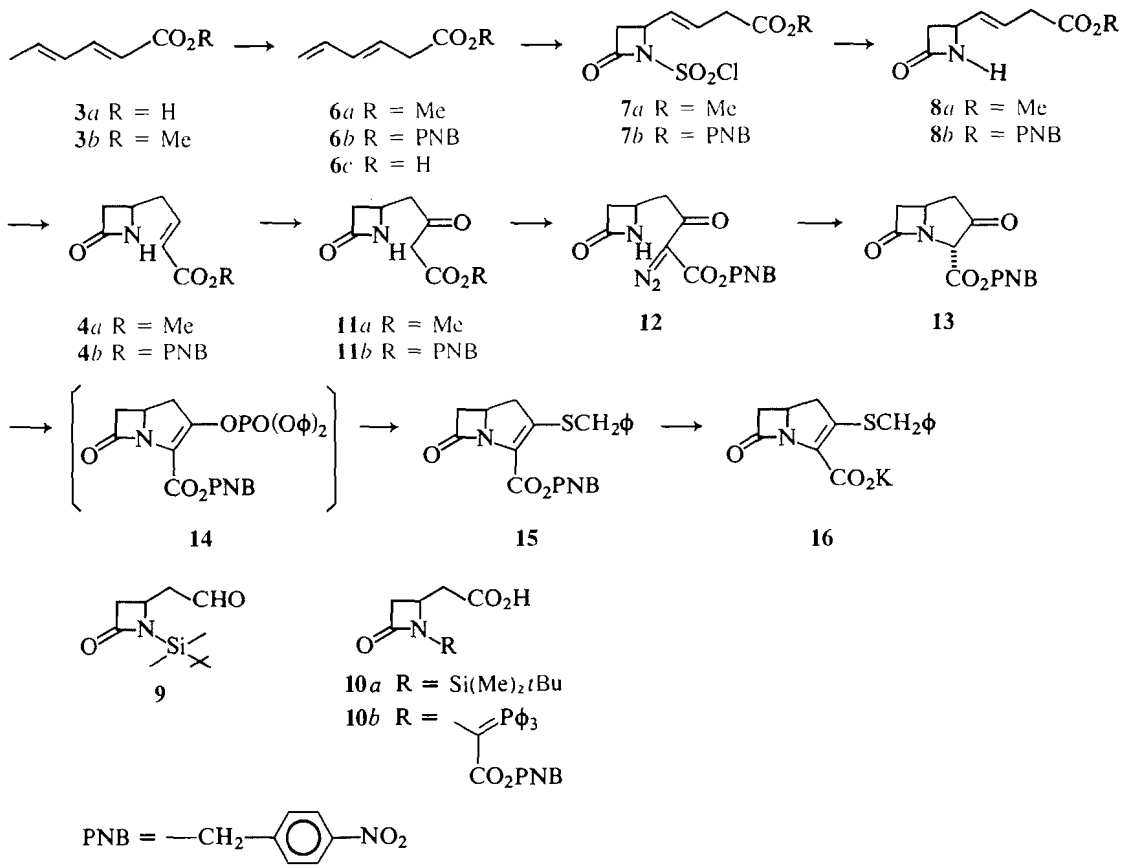
[3]After a major part of this work was completed, the Smith Kline & French group described a similar approach in their recent publication (5).

[4]These by-products were tentatively characterized as a mixture of **i** and **ii** based on the ^{1}Hmr spectrum, which exhibited two different methyl signals at around 3.7 ppm, and the uv spectrum, which showed a λ_{max} at 256 nm. These were presumably formed by proton abstraction, followed by the ring opening as shown in **iii** and/or **iv**, and then isomerization to each other.



i **ii** **iii** **iv**



SCHEME 1

the amide, for the synthesis of carbapenems[5] by oxidation of the double bond to the aldehyde **9** (*4a*, *g*) or the carboxylic acids **10** (*3d*, *4d–f*), since they contain the carbon framework needed for the synthesis of carbapenem carboxylates, we decided to use this advantage without breaking down the molecule.

Conversion of α, β-unsaturated esters **4***a*, and **4***b* to β-keto esters **11***a* and **11***b* was readily achieved in 30% and 36% yield, respectively, by the oxypalladation method (*t*-BuOOH/$NaPdCl_4$) which was recently developed by Tsuji *et al.* (10) and employed in the synthesis of a carbapenem intermediate (*4g*). Teatment of β-keto ester **11***b* with *p*-carboxybenzenesulfonyl azide (11) gave diazo compound **12** in 88% yield, which was cyclized by $Rh_2(OAc)_4$, the Merck method (*4a*), to produce cleanly the bicyclic β-keto ester **13**. Transformation of this type of keto ester to 2-alkylthiocarbapenem was reported by the Merck group (*4a*). One example is demonstrated here. Thus **13**, treated with diphenyl chlorophosphate (diisopropylethylamine/CH_3CN, 0°C), gave enol phosphate **14** which was, without isolation, converted to 2-benzylthiocarbapenem **15** in 34% yield by reaction with benzyl mercaptan in the presence of diisopropylethylamine. Catalylic hydrogenolysis of **15** (H_2/Pd–C, $KHCO_3$) afforded carbapenem potassium salt **16**, the presence of which was confirmed by an ir absorption band at 1765 cm^{-1} and its uv spectrum (λ_{max} 299 nm). Due to the instability of this type of molecule (*4c–e*), we were unable to isolate it in a pure form.

This approach offers the following advantages over the methods previously reported. (a) The starting material is commercially available and inexpensive. (b) A variety of carboxylic acid protecting groups, particularly the *p*-nitrobenzyl group, can be easily introduced: *p*-nitrobenzyl ester is most commonly used in the penem or carbapenem synthesis since it can be cleaved to the corresponding carboxylic acid by catalytic hydrogenolysis without destruction of the labile ring system. (c) Since all the necessary carbon skeleton is constructed in one step, this is the most direct route known so far to the carbapenem ring system.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are not corrected. The infrared spectra were recorded on a Perkin–Elmer 267 grating infrared spectrometer. The ^1H nuclear magnetic resonance spectra were taken with either the Varian EM-360 (60 MHz) or a Varian CFT-20 (80 MHz) nmr spectrometer. Tetramethylsilane (for solutions other than D_2O) and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (for solutions of D_2O) were used as internal standards and chemical shifts are reported in parts per million (δ) relative to the internal standards. The ultraviolet spectra were recorded on an Unicam SP8-100 uv spectrophotometer. Tetrahydrofuran was freshly distilled from lithium aluminum hydride. Anhydrous diethyl ether (Mallinkrodt or Fisher) was used without further treatment. All other solvents were reagent grade and had been stored over molecular sieves before use. n-Butyllithium (n-BuLi) in hexane (Aldrich) was titrated periodically by the diphenylacetic acid method. Triethylamine, diisopropylamine, and diisopropylethylamine were distilled from CaH_2 and stored over NaOH. Analytical thin layer chromatography (tlc) was conducted on precoated plates (Silica Gel 60F-254, E. Merck). Visualization was effected by uv light and iodine. Preparative layer chromatography (plc) was performed on silica gel plates prepared from Silica Gel 60 GF-254 (E. Merck). For column chromatography, 70–230 mesh Silica Gel 60 (E. Merck) was

[5]The versatility of this type of intermediate **4** in the synthesis of carbapenems will be reported in a forthcoming paper.

used. The analyses were performed by Micro-Tech Laboratories, Skokie, Illinois, U.S.A. The abbreviations for ^{1}Hmr multiplicities are used as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet, dt, doublet of triplets; td, triplet of doublets; m, multiplet; br, broad.

*Methyl 2,4-hexadienoate (methyl sorbate) (**3**b)*

Through a stirred suspension of 2,4-hexadienoic acid (**3***a*) (sorbic acid; 112 g, 1.00 mol) in methanol (0.5 L) was bubbled dry hydrogen chloride gas for 5 min, and then the mixture was heated at reflex for 4 h. After cooling, the methanol was evaporated *in vacuo* and the residual oil was diluted with CH_2Cl_2 (0.4 L), removing water which separated out. The CH_2Cl_2 solution was washed carefully with saturated $NaHCO_3$ and then brine, dried (Na_2SO_4), and evaporated. The residue was distilled under reduced pressure to obtain 98.5 g (0.782 mol, yield 78.2%) of the title compound **3***b* as a colourless liquid; bp 69°–71°C/12 Torr (lit. (12) bp 60°C/12 Torr); ir (neat) ν_{max}: 1720 (C=O), 1650 (C=C), and 1620 (C=C) cm^{-1}; R_f 0.72 (Et_2O); ^{1}Hmr ($CDCl_3$) δ: 1.87 (3H, d, J = 5 Hz, 5-Me), 3.74 (3H, s, —CO_2Me), 5.6–6.5 (3H, m, olefinic protons), and 7.05–7.5 (1H, m, 5-H) ppm.

*Methyl 3,5-hexadienoate (**6**a)*

To a stirred solution of diisopropylamine (85 mL, 0.61 mol) in THF (1.4 L) was added, at 0°–5°C under a nitrogen atmosphere, n-BuLi (396 mL, 0.61 mol; 1.54 *M* in hexane) over a period of 45 min. The resulting pale yellow solution was stirred at 0°–5°C for 15 min and then cooled to −75° to −78°C. A solution of hexamethylphosphoramide (115 mL, 0.66 mol) in THF (30 mL) was added in 30 min, and stirring continued for 30 min. To this mixture was added a solution of methyl 2,4-hexadienoate (**3***b*) (64.0 g, 0.508 mol; methyl sorbate) in THF (30 mL) during a period of 1 h at −78°C and stirred for 30 min. The dark red mixture was poured into 2 *N* HCl (900 mL) with stirring. The mixture was extracted with pentane (200 mL × 3) and these extracts combined, washed successively with H_2O (600 mL × 3), saturated $NaHCO_3$ (600 mL) and brine (600 mL), dried (Na_2SO_4), and evaporated to a yellow oil. This was distilled under reduced pressure to give 49.0 g (0.389 mol, yield 76.6%) of the title compound **6***a* as a clear liquid: bp 58°–60°C/12 Torr (lit. (6*b*) bp 73°–75°C/12 Torr); ir (neat) ν_{max}: 1735 (C=O) and 1640 (C=C) cm^{-1}; R_f 0.67 (benzene–Et_2O 4:1); ^{1}Hmr ($CDCl_3$) δ: 3.12 (2H, d, J = 6 Hz, —CH_2—), 3.69 (3H, s, —CO_2Me), 5.14 (2H, t, J = 8 Hz, olefinic protons), and 5.5–6.7 (3H, m, olefinic protons) ppm.

p-*Nitrobenzyl 3,5-hexadienoate (**6**b)*

To a stirred solution of diisopropylamine (76.5 mL, 0.55 mol) in THF (0.5 L) was added at 0°–5°C n-BuLi (344 mL, 0.55 mol; 1.6 *M* in hexane), over a period of 0.5 h under a nitrogen atmosphere, and stirred at 0°–5°C for 0.5 h. To this was added at −15° to −10°C a solution of 2,4-hexadienoic acid (**3***a*) (28.0 g, 0.25 mol) in THF (125 mL) over a period of 0.5 h. The cooling bath was removed and the mixture stirred at room temperature for 1 h. This was poured into a cold solution of concentrated HCl (125 mL) in water (500 mL). The aqueous layer was saturated with sodium chloride and extracted with EtOAc (150 mL × 3). All organic layers were combined, washed with brine (200 mL × 2), dried ($MgSO_4$), and evaporated, yielding 29.0 g of 3,5-hexadienoic acid as a crude oil: bp 61°–63°C/0.2 Torr (lit. (13) bp 102°–103°C/6 Torr); ir (neat) ν_{max}: 2500–3500 (br, CO_2H) and 1710 (CO_2H) cm^{-1}; R_f 0.57 (Et_2O); ^{1}Hmr ($CDCl_3$) δ: 3.15 (2H, d, J = 6 Hz, 2-H) and 5–6.7 (5H, m, olefinic protons) ppm. The distilled material polimerized on standing.

To a solution of this crude material (29.0 g) in DMF (250 mL) was added at 0°–5°C *p*-nitrobenzyl bromide (54.0 g, 0.25 mol) followed by triethylamine (34.75 mL, 0.25 mol). The mixture was stirred at 0°–5°C overnight (ca. 18 h). This was poured into cold water (1 L) and extracted with EtOAc (250 mL × 2), then brine (250 mL), dried ($MgSO_4$), and evaporated to yield 52.7 g of a brown oil. A major portion (30.88 g) of this crude oil was purified[6] by column chromatography (600 g, Et_2O–hexanes 1:4) to obtain 25.28 g of a yellowish oil which was crystallized from Et_2O–pentane (1:2, 15 mL) to give 23.78 g (96.3 mmol, yielded 65.7% based on 2,4-hexadienoic acid) of the title compound **6***b* as pale yellow crystals: mp 40°–41°C; ir (film) ν_{max}: 1740 (C=O), 1525 and 1350 (NO_2) cm^{-1}; R_f 0.46 (Et_2O–hex 1:1); ^{1}Hmr ($CDCl_3$) δ: 3.22 (2H, J = 6 Hz, 2-H), 5.23 (2H, s, —CO_2CH_2Ar), 5.0–6.7 (5H, m, olefinic protons), 7.48 (2H, d, J = 9 Hz, aromatic protons), and 8.16 (2H, d, J = 9 Hz, aromatic protons) ppm. *Anal.* calcd. for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, N 5.67; found: C 63.02, H 5.32, N 5.56.

*Methyl 4-(2-azetidinon-4-yl)-3-butenoate (**8**a)*

To a stirred solution of methyl 3,5-hexadienoate (**6***a*) (48.85 g, 0.388 mol) in CH_2Cl_2 (1.2 L) was added, at 0°–5°C under a nitrogen atmosphere, chlorosulfonyl isocyanate (38.0 mL, 0.430 mol) in 15 min. The mixture was stirred at room temperature for 21 h. A small portion (1 mL) of the reaction mixture was added to a mixture of cold water (3 mL) and CH_2Cl_2 (3 mL), and the CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated to yield methyl 4-(*N*-chlorosulfonyl-2-azetidinon-4-yl)-3-butenoate (**7***a*) as a yellowish oil: ir (neat) ν_{max}: 1815 (β-lactam) and 1730 (ester) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 3.07 (1H, dd, J_{gem} = 16 Hz, $J_{3-4\,trans}$ = 4 Hz, 3-H_b), 3.20 (2H, d, J = 6 Hz), 3.55 (1H, dd, J_{gem} = 16 Hz, $J_{3-4\,cis}$ = 6 Hz, 3-H_a), 3.70 (3H, s, —CO_2Me), 4.80 (1H, m, 4-H), 5.5–6.4 (2H, m, olefinic protons) ppm. The rest of the reaction mixture was added slowly to a mechanically stirred slurry of sodium sulfite (242 g, 1.93 mol) in water (0.5 L), ice (0.6 L), and CH_2Cl_2 (0.5 L) at 0°–5°C. During the addition, the mixture was maintained at a pH of 7–8 by addition of saturated $NaHCO_3$ (total 1.8 L). The foaming, milky reaction mixture thus obtained was warmed to room temperature during 1.5 h. The organic layer was collected and the aqueous layer saturated with NaCl and then extracted with CH_2Cl_2 (×2). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to yield 66.0 g of milky yellow oil, which was purified[6] by column chromatography (1.2 kg, EtOAc) to obtain 41.3 g (0.244 mol, yield 63.0%) of the title compound **8***a* as a colourless oil: bp 126°–130°/0.01 Torr; ir (neat) ν_{max}: 3280 (NH), 1760–1730 (br, β-lactam and ester), 1670 (C=C), and 970 (*trans*-disubstituted olefin) cm^{-1}; R_f 0.32 (EtOAc); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.70 (1H, ddd, J_{gem} = 14.9 Hz, $J_{3'-4'\,trans}$ = 2.6 Hz, $J_{3'-1'}$ = 1.3 Hz, 3'-H_b), 3.11 (2H, d, J = 5.7 Hz, —CH_2CO_2—), 3.23 (1H, ddd, J_{gem} = 14.9 Hz, $J_{3'-4'\,cis}$ = 5.1 Hz, $J_{3'-1'}$ = 2.2 Hz, 3'-Ha), 3.69 (3H, s, —CO_2Me), 4.15 (1H, m, 4'-H), 5.5–6.1 (2H, m, olefinic protons), and 5.8 (br, 1'-H) ppm. *Anal.* calcd. for $C_8H_{11}NO_3$: C 56.79, H 6.55, N 8.28; found: C 56.77, H 6.59, N 8.39.

p-*Nitrobenzyl 4-(2-azetidinon-4-yl)-3-butenoate (**8**b)*

To a stirred solution of *p*-nitrobenzyl 3,5-hexadienoate (**6***b*) (2.47 g, 10 mmol) in CH_2Cl_2 (30 mL) was added, at 0°–5°C under a nitrogen atmosphere, chlorosulfonyl isocyanate (0.98 mL, 11 mmol), and the mixture was stirred at room temperature for 3 days. A small portion (1 mL) of the reaction mixture was shaken with a mixture of water (5 mL) and CH_2Cl_2 (5 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated to yield *p*-nitronbenzyl 4-(*N*-chlorosulfonyl-2-azetidinon-4-yl)-3-butenoate as a yellowish oil: ir (neat) ν_{max}: 1825 (β-lactam), 1745 (ester), 1520, and 1350 (NO_2) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 3.08 (1H, dd, J_{gem} = 16.7 Hz, $J_{3'-4'\,trans}$ = 4.1 Hz, 3'-H_b), 3.28 (2H, d, J = 6.1 Hz, —CH_2CO_2—), 3.54 (1H, dd, J_{gem} = 16.7 Hz, 3'-H_a), 4.79 (1H, ddd, $J_{4'-4}$ = 7.5 Hz, $J_{4'-3'\,cis}$ = 6.5 Hz, $J_{4'-3'\,trans}$ = 4 Hz, 4-H), 5.23 (2H, s, —CO_2CH_2Ar), 5.6–6.4 (2H, m, olefinic protons), 7.50 (2H, d, J = 8.7 Hz, aromatic protons), and 8.21 (2H, d, J = 8.7 Hz, aromatic protons) ppm. The rest of the reaction mixture was added slowly at room temperature to a stirred mixture of sodium sulfite (12 g, 95 mmol), water (60 mL), and CH_2Cl_2 (60 mL). During the addition, the reaction mixture was maintained at a pH of 7–9 by simultaneous addition of saturated $NaHCO_3$ (70 mL). This was stirred for another 3 h, and the CH_2Cl_2 layer washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*, yielding 1.99 g of a crude oil. This was purified by column chromatography (80 g, EtOAc) to yield 1.41 g (4.86 mmol, yield 48.6%)

[6]Distillation under reduced pressure caused serious decomposition.

of the title compound **8***b* as an oil which crystallized on standing: mp 85°–87°C (recrystallized from CH_2Cl_2–Et_2O); ir (film) ν_{max}: 1745 (β-lactam and ester), 1525, and 1350 (NO_2) cm^{-1}; R_f 0.32 (EtOAc); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.70 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'trans}$ = 2.6 Hz, $J_{3'-1'}$ = 1.3 Hz, 3′-H_b), 3.19 (2H, d, J = 5.4 Hz, —CH_2CO_2—), 3.23 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'cis}$ = 5 Hz, $J_{3'-1'}$ = 2.2 Hz, 3′-H_a), 4.16 (1H, m, 3′-H), 5.22 (2H, s, —CO_2CH_2Ar), 5.5–6.1 (2H, m, olefinic protons), 7.51 (2H, d, J = 8.7 Hz, aromatic protons), and 8.23 (2H, d, J = 8.7 Hz, aromatic protons) ppm. *Anal.* calcd. for $C_{14}H_{14}N_2O_5$: C 57.93, H 4.86, N 9.65; found: C 57.61, H 4.79, N 9.57.

*Methyl 4-(2-azetidinon-4-yl)-2-butenoate (**4**a)*

A solution of methyl 4-(2-azetidinon-4-yl)-3-butenoate (**8***a*) (16.9 g, 0.100 mol) and 1,4-diazabicyclo[2.2.2]octane (22.4 g, 0.200 mol; DABCO) in CH_3CN (100 mL) was stirred at room temperature under a nitrogen atmosphere for 4 days. The solvent was evaporated at room temperature *in vacuo*, and the residue mixed with EtOAc (20 mL). The precipitates, formed were filtered and washed with cold EtOAc (20 mL). The filtrate and the washings were combined, evaporated, and the residual oil purified by column chromatography (300 g, EtOAc) to obtain 14.68 g, (86.9 mmol, yield 86.9%) of the title compound **4***a* as an amber coloured oil. This was crystallized from Et_2O at 0°C; mp 51°–52°C; ir ($CHCl_3$) ν_{max}: 3420 (NH), 1765 (β-lactam), 1720 (ester), and 1660 (C=C) cm^{-1}; R_f 0.32 (EtOAc); ^{1}Hmr ($CDCl_3$) δ: 2.55 (2H, dt, J = 6.8 Hz, J_{4-2} = 1.4 Hz, 4-H), 2.63 (1H, ddd, J_{gem} = 14.8 Hz, $J_{3'-4'trans}$ = 2.4 Hz, $J_{3'-1'}$ = 1.2 Hz, 3′-H_b), 3.14 (1H, ddd, J_{gem} = 14.8 Hz, $J_{3'-4'cis}$ = 4.8 Hz, $J_{3'-1'}$ = 2.2 Hz, 3′-H_a), 3.74 (3H, s, —CO_2Me), 3.5–3.8 (1H, m, 4′-H), 5.90 (1H, td, J_{2-3} = 16 Hz, J_{2-4} = 1.4 Hz, 2-H), 6.87 (1H, br, 1′-H), and 6.94 (1H, td, J_{3-2} = 16 Hz, J_{3-4} = 6.8 Hz, 3-H) ppm; *Anal.* calcd. for $C_8H_{11}NO_3$: C 56.79, H 6.55, N 8.28; found: C 57.00, H 6.49, N 8.13.

*Isomerization of **8**a with Et_3N in DMSO*

A mixture of methyl 4-(2-azetidinon-4-yl)-3-butenoate (**8***a*) (4.05 g, 24.0 mmol) and triethylamine (1.50 g, 15.0 mmol) in DMSO (24 mL) was stirred at room temperature for 18 days. The rection mixture was poured into a cold mixture of 1 *N* HCl (15 mL), water (85 mL), and CH_2Cl_2 (100 mL). The aqueous layer was saturated with sodium chloride and extracted with CH_2Cl_2 (35 mL × 3). All CH_2CH_2 layers were combined, washed with brine, dried (Na_2SO_4), and evaporated, yielding 3.83 g of crude oily solid. This was purified by column chromatography (60 g, MeOH–benzene 2:98) to obtain 2.12 g (12.5 mmol, yield 52.4%) of **4***a* as a colourless oil: R_f 0.33 (MeOH–benzene 1:4), and 1.32 g (7.81 mmol, yield 32.5%) of β-lactam opened materials **i** and **ii** as a white solid: mp 127°–133°C; ir (Nujol) ν_{max}: 3390, 3190 (—$CONH_2$), 1720 (ester) and 1645 (amide) cm^{-1}; uv (EtOH) λ_{max}: 256 nm (ε 26 000); R_f 0.22 (MeOH–benzene 1:4); ^{1}Hmr ($CHCl_3$, 80 MHz) δ: 3.14 (d, J = 5.7 Hz, —CH_2—), 3.21 (d, J = 5.2 Hz, —CH_2—), 3.70 (s, —CO_2Me), 3.74 (2, —CO_2Me), 5.5 (br, —$CONH_2$), 5.87 (d, J = 15.3 Hz, olefinic proton), 6.1–7.4 (m, olefinic protons) ppm.

*p-Nitrobenzyl 4-(2-azetidinon-4-yl)-2-butenoate (**4**b)*

A solution of *p*-nitrobenzyl 4-(2-azetidinon-4-yl)-3-butenoate (**8***b*) (1.16 g, 4.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (900 mg, 8.00 mmol; DABCO) in CH_3CN (8 mL) was stirred at room temperature for 3 days. After evaporation of the solvent *in vacuo*, the residue, dissolved in EtOAc (40 mL), was washed with 1 *N* HCl (10 mL), then brine, dried (Na_2SO_4), and evaporated to yield 1.05 g of yellow solid. This was purified by column chromatography (50 g, EtOAc) to obtain 850 mg (2.93 mmol, yield 73.2%) of the title compound **4***b* as white crystals: mp 126°–128°C (recrystallized from EtOAc); ir (film) ν_{max}: 3200 (NH), 1755 (β-lactam), 1720 (ester), 1655 (C=C), 1510, and 1350 (NO_2) cm^{-1}; R_f 0.31 (EtOAc); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.57 (2H, dt, J = 7.1 Hz, J_{4-2} = 1.3 Hz, 4-H), 2.65 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'trans}$ = 2.4 Hz, $J_{3'-1'}$ = 1 Hz, 3′-H_b), 3.15 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'cis}$ = 5 Hz, $J_{3'-1'}$ = 2.3 Hz, 3′-H_a), 3.74 (1H, m, 4′-H), 5.27 (2H, s, —CO_2CH_2Ar), 5.97 (1H, td, J_{2-3} = 15.7 Hz, J_{2-4} = 1.3 Hz, 2-H), 6.97 (1H, dt, J_{3-2} = 15.6 Hz, J_{3-4} = 7.1 Hz, 3-H), 7.53 (2H, d, J = 8.7 Hz, aromatic protons), and 8.23 (2H, d, J = 8.7 Hz, aromatic protons) ppm. *Anal.* calcd. for $C_{14}H_{14}N_2O_5$: C 57.93, H 4.86, N 9.65; found: C 58.01, H 4.81, N 9.59.

*Methyl 4-(2-azetidinon-4-yl)-3-oxobutanoate (**11**a)*

To a mixture of sodium tetrachloropalladate (58 mg, 0.2 mmol) and *tert*-butyl hydroperoxide (193 mg, 1.5 mmol; 70% aqueous solution) in 50% aqueous HOAc (1 mL) was added a solution of methyl 4-(2-azetidinon-4-yl)-2-butenoate (**4***a*) (169 mg, 1.0 mmol) in 50% aqueous HOAc (1 mL), and the mixture was heated at 50°C for 10 h. The solvents were evaporated by a vacuum pump at 50°C and the residue was purified by plc (EtOAc) to yield 55 mg (0.30 mmol, yield 30%) of the title compound **11***a* as a yellowish oil: ir (neat) ν_{max}: 3320 (NH), 1745 (β-lactam and ester), and 1715 (C=O) cm^{-1}; R_f 0.20 (EtOAc); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.59 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'trans}$ = 2.5 Hz, $J_{3'-1'}$ = 1 Hz, 3′-H_b), 2.77 (1H, dd, J_{gem} = 18 Hz, $J_{4-4'}$ = 8 Hz, 4-H_a), 3.08 (1H, dd, J_{gem} = 18 Hz, $J_{4-4'}$ = 4.6 Hz, 4-H_b), 3.16 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'cis}$ = 5.0 Hz, $J_{3'-1'}$ = 2.4 Hz, 3′-H_a), 3.47 (2H, s, 2-H), 3.74 (3H, s, —CO_2Me), 3.9 (1H, m, 4′-H), and 6.15 (br, NH) ppm.

*p-Nitrobenzyl 4-(2-azetidinon-4-yl)-3-oxobutanoate (**11**b)*

To a mixture of sodium tetrachloropalladate (58 mg, 0.2 mmol) and *tert*-butyl hydroperoxide (193 mg, 1.5 mmol; 70% aqueous solution) in 50% aqueous HOAc (3 mL) was added a solution of *p*-nitrobenzyl 4-(2-azetidinon-4-yl)-2-butenoate (290 mg, 1.0 mmol) in 50% aqueous HOAc (3 mL) and the mixture was heated at 60°–65°C for 6 h. The resulting reddish mixture, diluted with EtOAc (30 mL), was neutralized by careful addition of saturated $NaHCO_3$ (ca. 50 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to yield 187 mg of a crude oil. This was purified by column chromatography (10 g, EtOAc) to obtain 109 mg (0.356 mmol, yield 36%) of the title compound as a clear oil. This was crystallized by trituration with i-PrOH: mp 46°–48°C; ir (film) ν_{max}: 3300 (br, NH), 1745 (β-lactam and ester), 1715 (C=O), 1520, and 1350 (NO_2) cm^{-1}; R_f 0.19 (EtOAc); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.59 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'trans}$ = 2.5 Hz, $J_{3'-1'}$ = 1 Hz, 3′-H_b), 2.77 (1H, ddd, J_{gem} = 18 Hz, $J_{4-4'}$ = 8 Hz, 4-H_a), 3.08 (1H, dd, J_{gem} = 18 Hz, $J_{4-4'}$ = 5 Hz, 4-H_b), 3.18 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'cis}$ = 5 Hz, $J_{3'-1'}$ = 2.5 Hz, 3′-H_a), 3.55 (2H, s, 2-H), 3.93 (1H, m, 4′-H), 5.27 (2H, s, —CO_2CH_2Ar), 6.0 (br, NH), 7.52 (2H, d, J = 8.7 Hz, aromatic protons), and 8.24 (2H, J = 8.7 Hz, aromatic protons) ppm. *Anal.* calcd. for $C_{14}H_{14}N_2O_6$: C 54.90, H 4.61, N 9.15; found: C 54.70, H 4.80, N 9.06.

*p-Nitrobenzyl 4-(2-azetidinon-4-yl)-3-oxo-2-diazobutanoate (**12**)*

To a mixture of *p*-nitrobenzyl 4-(2-azetidinon-4-yl)-3-oxobutanoate (**11***b*) (1.38 g, 4.51 mmol) and *p*-carboxybenzenesulfonyl azide (1.27 g, 5.59 mmol) in CH_3CN (30 mL) was added, at 0°–5°C under a nitrogen atmosphere, Et_3N (2.70 mL, 19.4 mmol), causing dissolution followed by precipitation. The mixture was diluted with CH_3CN (15 mL) and stirred at room temperature for 30 min. The precipitate was filtered and washed with EtOAc. The filtrate and washings were combined and evaporated to yield 2.0 g of a greenish oil. This was purified by column chromatography (160 g, EtOAc) to give 1.32 g (3.97 mmol, yield 88.1%) of the title compound **12** as yellowish crystals: mp 109°–110°C (recrystallized from EtOAc); ir (film) ν_{max}: 3370 (NH), 2140 (C=N_2), 1760 (β-lactam), 1720 (ester), 1650 (C=O), 1520, and 1350 (NO_2) cm^{-1}; R_f 0.41 (EtOAc); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.65 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'trans}$ = 2.5 Hz, $J_{3'-1'}$ = 1 Hz, 3′-H_b), 2.99 (1H, dd, J_{gem} = 18 Hz, $J_{4-4'}$ = 8.5 Hz, 4-H_a), 3.17 (1H, ddd, J_{gem} = 15 Hz, $J_{3'-4'cis}$ = 5 Hz, $J_{3'-1'}$ = 2.4 Hz, 3′-H_a), 3.38 (1H, dd, J_{gem} = 18 Hz, $J_{4-4'}$ = 4.4 Hz, 4-H_b), 3.95 (1H, m, 4′-H), 5.35 (2H, s, —CO_2CH_2Ar), 6.07 (br, NH), 7.53 (2H, d, J = 8.8 Hz, aromatic protons), and 8.25 (2H, d, J = 8.8 Hz, aromatic protons) ppm; *Anal.* calcd. for $C_{14}H_{12}N_4O_6$: C 50.61, H 3.64, N 16.86; found: C 50.72, H 3.81, N 16.80.

*p-Nitrobenzyl 2-oxocarbapenam-3-carboxylate (**13**)*

Through a suspension of *p*-nitrobenzyl 4-(2-azetidinon-4-yl)-3-oxo-

2-diazobutanoate (49 mg, 0.15 mmol) and $Rh_2(OAc)_4$ (0.1 mg) in benzene (2 mL) was bubbled dry nitrogen for 10 min, and this mixture was heated at gentle reflux under a nitrogen atmosphere for 30 min. The catalyst was filtered and washed with EtOAc. The filtrate and washings were cobmined and evaporated to yield a crude oil which was purified by column chromatography (short column, EtOAc) to obtain 37 mg (0.12 mmol, yield 81%) of the title compound **13** as an oil: ir (film) ν_{max}: 1765 (β-lactam), 1745 (ester and ketone), 1520, and 1350 (NO_2) cm^{-1}; R_f 0.60 (EtOAc); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.40 (1H, dd, J_{gem} = 19 Hz, J_{1-5} = 8 Hz, 1-H_a), 2.94 (1H, dd, J_{gem} = 19 Hz, J_{1-5} = 6.2 Hz, 1-H_b), 2.96 (1H, dd, J_{gem} = 16 Hz, $J_{6-5\,trans}$ = 2 Hz, 6-H_b), 3.67 (1H, dd, J_{gem} = 16 Hz, $J_{6-5\,cis}$ = 5 Hz, 6-H_a), 4.15 (1H, m, 5-H), 4.77 (1H, s, 3-H), 5.30 (2H, s, —CO_2CH_2Ar), 7.53 (2H, d, J = 8.8 Hz, aromatic protons), and 8.24 (2H, d, J = 8.8 Hz, aromatic protons) ppm.

p-*Nitrobenzyl 2-benzylthiocarbapen-2-em-3-carboxylate (15)*

To a stirred solution of freshly prepared *p*-nitrobenzyl-2-oxo-carbapenam-3-carboxylate (**13**) (151 mg, 0.496 mmol) in CH_3CN (10 mL) was added, at 0°–5°C under a nitrogen atmosphere, diisopropylethylamine (0.095 mL, 0.55 mmol), followed by diphenyl chlorophosphate (0.11 mL, 0.55 mmol). The mixture was stirred at 0°–5°C for 30 min, by which time the tlc (EtOAc–hex 1:1) indicated that the reaction was over. The enol phosphate **14** could be isolated as an off-white solid: mp 105°–111°C (dec.); ir (film) ν_{max}: 1790 (β-lactam), 1730 (ester), and 1640 (C=C) cm^{-1}; R_f 0.20 (EtOAc–hex 1:1); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.96 (1H, dd, J_{gem} = 17 Hz, $J_{6-5\,trans}$ = 3 Hz, 6-H_b), 3.0–3.3 (2H, m, 1-H), 3.55 (1H, dd, J_{gem} = 17 Hz, $J_{6-5\,cis}$ = 5.5 Hz, 6-H_a), 4.15 (1H, m, 5-H), 5.20 (1H, d, J = 13.8 Hz, —CO_2CH_2Ar), 5.43 (1H, d, J = 13.8 Hz, —CO_2CH_2Ar), 7.26 (10H, s, aromatic protons), 7.54 (2H, d, = 8.8 Hz, aromatic protons), and 8.15 (2H, d, J = 8.8 Hz, aromatic protons) ppm. Without isolation of the enol phosphate **14**, to this reaction mixture was added, at 0°–5°C, diisopropylamine (0.086 mL, 0.50 mmol), and then benzyl mercaptan (0.058 mL, 0.50 mmol). The mixture was stirred at room temperature (N_2) for 1 h. The solvent was evaporated *in vacuo* at room temperature and the residue (yellowish solid), dissolved in CH_2Cl_2, was washed with diluted brine, dried (Na_2SO_4), and evaporated to yield crystalline solid. This was rinsed with a small amount of cold EtOAc to obtain 70 mg (0.17 mmol, yield 34%) of the title compound **15** as yellowish crystals: mp 124°–128°C (dec.); ir (film) ν_{max}: 1765 (β-lactam), 1690 (ester), 1515, and 1340 (NO_2) cm^{-1}; uv (EtOH) λ_{max}: 319 (ε 13 300) and 266 nm (ε 11 000); R_f 0.27 (EtOAc–hex 1:1); ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 2.90 (1H, dd, J_{gem} = 16.5 Hz, $J_{6-5\,trans}$ = 3.0 Hz, 6-H_b), 2.95 (1H, dd, J_{gem} = 18 Hz, J_{1-5} = 8.5 Hz, 1-H_a), 3.29 (1H, J_{gem} = 18 Hz, J_{1-5} = 8.5 Hz, 1-H_b), 3.49 (1H, dd, J_{gem} = 16.5 Hz, $J_{6-5\,cis}$ = 5.3 Hz, 6-H_a), 4.08 (2H, s, —$SCH_2\phi$), 4.15 (1H, m, 5-H), 5.23 (1H, d, J = 13.6 Hz, —CO_2CH_2Ar), 5.50 (1H, d, J = 13.6 Hz, —CO_2CH_2Ar), 7.33 (5H, s, aromatic protons), 7.63 (2H, d, J = 8.8 Hz, aromatic protons), and 8.19 (2H, d, J = 8.8 Hz, aromatic protons) ppm. This material decomposed during preparative layer chromatography on silica gel.

Potassium 2-benzylthiocarbapen-2-em-3-carboxylate (16)

A solution of *p*-nitrobenzyl 2-benzylthiocarbapen-2-em-3-carboxylate (35 mg, 0.085 mmol) in THF (6 mL) was mixed with Et_2O (6 mL), a solution of K_2HPO_4 (15 mg, 0.085 mmol) and $KHCO_3$ (8.5 mg, 0.085 mmol) in water (6 mL), and 10% Pd–C (35 mg). This mixture was shaken in a Parr apparatus under hydrogen pressure of 30 psi at room temperature for 30 min. The aqueous layer, separated, was filtered over Celite and the filtrate washed with Et_2O. Lyophilization of the aqueous phase gave 10 mg of the title compound as greyish powder: ir (KBr disc) ν_{max}: 1765 (β-lactam) and 1630 (br, —CO_2^-) cm^{-1}; uv (H_2O) λ_{max}: 299 nm (ε 1800); ^{1}Hmr (D_2O, 80 MHz) δ: 2.7–3.5 (m, 1-H and 6-H), 3.37 (dd, J_{gem} = 16 Hz, $J_{6-5\,cis}$ = 4 Hz, 6-H_a), 4.05 (s, —$CH_2\phi$), 4.1 (m, 5-H), and 7.35 (s, aromatic protons) ppm.

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1. (*a*) G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen. J. Am. Chem. Soc. **100**, 6491 (1978); (*b*) J. S. Kahan, F. M. Kahan, R. Geogelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochaks, S. Hernandez, H. B. Woodruff, and J. Birnbaum. J. Antibiot. **32**, 1 (1979).
2. (*a*) T. Kametani and M. Ihara. J. Synth. Org. Chem. Jpn. **38**, 1025 (1980); (*b*) R. D. G. Cooper. *In* Topics in antibiotic chemistry. Vol. 3. *Edited by* P. G. Sammes. Ellis Horwood Ltd., Chichester. 1980. pp. 101–138; (*c*) T. Kametani, K. Fukumoto, and M. Ihara. Heterocycles, **17**, 463 (1982); (*d*) R. W. Ratcliffe and G. Albers-Schönberg. *In* Chemistry and biology of β-lactam antibiotics. Vol. 2. *Edited by* R. B. Morin and M. Gorman. Academic Press, New York. 1982. pp. 227–313.
3. (*a*) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen. J. Am. Chem. Soc. **100**, 313 (1978); (*b*) S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen. J. Org. Chem. **45**, 1142 (1980); (*c*) D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger. Tetrahedron Lett. **21**, 2783 (1980); (*d*) T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard. J. Am. Chem. Soc. **102**, 6161 (1980); (*e*) S. Karady, J. S. Amato, R. A. Reamer, and L. M. Weinstock. J. Am. Chem. Soc. **103**, 6765 (1981).
4. (*a*) R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen. Tetrahedron Lett. **21**, 31 (1980); (*b*) S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen. J. Org. Chem. **45**, 1135 (1980); (*c*) S. Oida, A. Yashida, and E. Ohki. Chem. Pharm. Bull. **28**, 3494 (1980); (*d*) R. J. Ponsford, P. M. Roberts, and R. Southgate. Chem. Commun. 847 (1979); (*e*) L. Cama and B. G. Christensen. Tetrahedron Lett. **21**, 2013 (1980); (*f*) M. J. Basker, J. H. Bateson, A. J. G. Baxter, R. J. Ponsford, P. M. Roberts, R. Southgate, T. C. Smale, and J. Smith. J. Antibiot. **34**, 1224 (1981), and references therein; (*g*) S. Takano, C. Kasahara, and K. Ogasawara. Chem. Lett. 631 (1982); (*h*) M. Shibasaki, A. Nishida, and S. Ikegami. Tetrahedron Lett. **23**, 2875 (1982).
5. D. A. Berges, E. R. Snipes, G. W. Chan, W. D. Kingsburry, and C. M. Kinig. Tetrahedron Lett. **22**, 3557 (1981).
6. (*a*) K. Torssell. Tetrahedron Lett. 623 (1974); (*b*) R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, and R. Lapalme. J. Am. Chem. Soc. **98**, 6317 (1976).
7. S. F. Martin, C. Tu, and T. Chou. J. Am. Chem. Soc. **102**, 5274 (1980).
8. (*a*) J. K. Rasmussen and A. Hassner. Chem. Rev. **76**, 389 (1976); (*b*) W. A. Szabo. Aldrichimica Acta, **10**, 23 (1977).
9. T. Durst and M. J. O'Sullivan. J. Org. Chem. **35**, 2043 (1970).
10. J. Tsuji, H. Nagashima, and K. Hori. Chemistry Lett. 257 (1980).
11. J. B. Hendrickson and W. A. Wolf. J. Org. Chem. **33**, 3610 (1968).
12. D. H. Wheeler. J. Am. Chem. Soc. **70**, 3467 (1948).
13. R. Paul and S. Tchelitcheff. Bull. Soc. Chim. Fr. 108 (1948).
14. A. Martel, J.-P. Daris, C. Bachand, M. Ménard, T. Durst, and B. Belleau. Can. J. Chem. **61**, 1899 (1983).