# β-Lactam Antibiotics: A Formal Stereocontrolled Total Synthesis of (±)-Thienamycin

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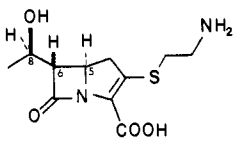
*Received February 21, 1984*

**Abstract:** A formal total synthesis of (±)-thienamycin is described which features the transformation of aldehyde **3** into alcohol **4** and subsequent elaboration of **4** into azetidinone **2**.

Since the structure and absolute configuration of thienamycin[2,3] (**1**) were first reported in 1978 by the Merck Sharp & Dohme



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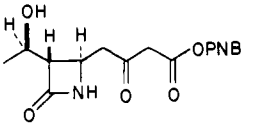

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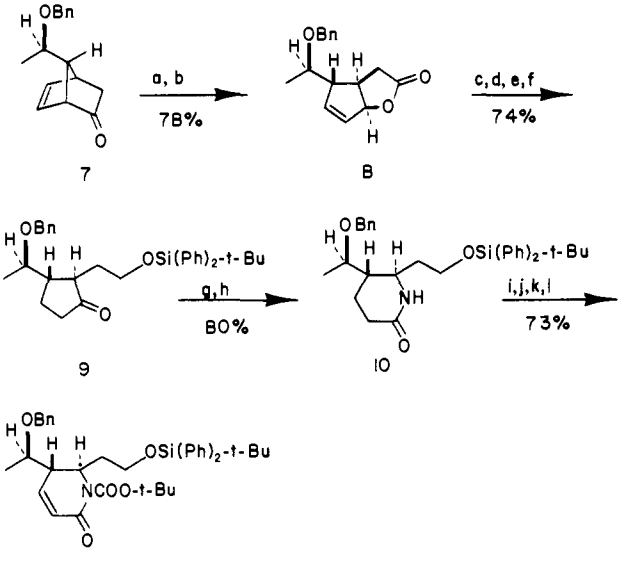
Research group, there have been extensive synthetic studies aimed at construction of the carbapenem system of thienamycin.[4,5] The synthetic activity has been due, in part, to its unique structure. However, the major interest in **1** stems from its unusually high potency against both Gram-positive and Gram-negative bacteria.

Whereas early synthetic studies focused primarily on the novel ring system of **1** with minimum attention devoted to construction of the hydroxy ethyl side chain, it was apparent that future synthetic efforts would have to concentrate on (1) developing stereocontrolled approaches for elaboration of the three contiguous chiral centers located at C(5), C(6), and C(8)[6] and (2) incorporating substituents into the C(6) position of thienamycin. We report below on a stereocontrolled synthesis of azetidinone **2**, a known precursor to (±)-thienamycin.[3d] A major feature of the formal synthetic route to thienamycin is the ability, at an early state in the synthesis, to incorporate a variety of substituents into the C(6) position.

Scheme I. Preparation of Unsaturated Lactam 11[a]



[a] (a) 10% NaOH (3.0 equiv), 30% $H_2O_2$ (2.5 equiv), MeOH, 0 °C, 48 h; (b) $BF_3 \cdot Et_2O$ (0.4 equiv), $CH_2Cl_2$, 0 °C, 45 min; (c) $LiAlH_4$ (2.0 equiv), $Et_2O$, 0 °C, 90 min; (d) $NaBH_4$ (2.0 equiv), $NiCl_2 \cdot 6H_2O$ (0.2 equiv), MeOH, −10 °C, 2.5 h; (e) *t*-Bu(Ph)$_2$SiCl (1.5 equiv), $Et_3N$ (1.5 equiv), DMAP (catalyst), $CH_2Cl_2$, 0 °C, 12 h; (f) PCC (2.0 equiv), NaOAc (1.5 equiv), $CH_2Cl_2$, Celite, 3 h; (g) $H_2NOH \cdot HCl$ (1.2 equiv), NaOAc (1.2 equiv), absolute EtOH, 42 h; (h) TsCl (2.5 equiv), DMAP (catalyst), Py, 30 min (room temperature) → 65 °C (3 h); (i) *t*-Bu$O_2$C)$_2$O (10 equiv), $Et_3N$ (10 equiv), DMAP (1.0 equiv), $CH_2Cl_2$, 20 h; (j) (a) LDA (2.0 equiv), THF-HMPA (1:1), −78 °C (30 min) → 0 °C; (b) PhSSPh (1.1 equiv), THF-HMPA (2:1), 0 °C → room temperature (30 min); (k) MCPBA (1.5 equiv), $CH_2Cl_2$, −78 °C, 2 h; (l) $PhCH_3$, 100 °C, 70 min.

Our synthetic strategy was dictated by two observations. The first involved the reaction ($Me_2Cu(CN)Li_2$, $Et_2O$, −78 °C, 1.5 h) of aldehyde **3**[7] with a higher order, mixed organocuprate[10]

(1) Lubrizol Graduate Research Fellow, 1983–1984.

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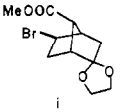
(3) For the first synthesis of (±)-thienamyci, see: (a) Johnston, D. B. R.; Schmitt, S. M.; Bouffard, F. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313. Also see: (b) Schmitt, S. M.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1142. (c) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A *J. Am. Chem. Soc.* **1980**, *102*, 6161. (d) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.

(4) For formal syntheses of thienamycin in both chiral and racemic form, see: (a) Ponsford, R. J.; Southgate, R. *J. Chem. Soc., Chem. Comm.* **1979**, 846. (b) Shiozaki, M.; Hiraoka, T. *Tetrahedron Lett.* **1980**, *21*, 4473. (c) Bouffard, F. A.; Johnston, D. B. R; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1130. (d) Kametani, T.; Huang, S.-P.; Yokohama, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060. (e) Shibasaki, M.; Nishida, A.; Kegami, S. *J. Chem. Soc., Chem. Comm.* **1980**, 1324. (f) Miyashita, M.; Chida, N.; Yoshikoshi, A. *Ibid.* **1980**, 1354. (g) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Vanagisawa, H. *Tetrahedron Lett.* **1981**, *22*, 5205. (h) Kametani, T.; Huang, S.-P.; Nagahara, T.; Yokohama, S.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 964. (i) Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913. (j) Ikota, N.; Yoshino, O.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 1929. (k) Hanessian, S.; Desilets, D.; Rancourt, G.; Fortin, R. *Can. J. Chem.* **1982**, *60*, 2292. (l) Shinkai, I.; Liu, T.; Reamer, R. A.; Sletzinger, M. *Tetrahedron Lett.* **1982**, *23*, 4899. (m) Shibasaki, M.; Nishida, A.; Ikegami, S. *Ibid.* **1982**, *23*, 2875. (n) Reider, P. J.; Grabowski, E. J. J. *Ibid.* **1982**, *23*, 2293. (o) Okano, K.; Izawa, T.; Ohno, M. *Ibid.* **1983**, *24*, 217.

(5) Tufariello, J. J.; Lee, G. E.; Senaratne, P. A.; Al-Nuri, M. *Tetrahedron Lett.* **1979**, 4359. Stevens, R. V.; Albizati, K. *J. Chem. Soc., Chem. Commun.* **1982**, 104.

(6) Despite extensive synthetic studies on thienamycin, few stereospecific methods for the elaboration of the three contiguous centers at C(5), C(6) and C(8) have been reported (see ref 3d, 4f, 4j, 4k).

(7) Aldehyde **3** and ketone **6** were prepared in straightforward manner from the bromo ketal ester i which is available in bulk in either racemic[8] or chiral[9] form.



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(8) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.

(9) Grieco, P. A.; Owens, W.; Wang, C.-L. J.; Williams, E.; Schillinger, W. J.; Hirotsu, K.; Clardy, J. *J. Med. Chem.* **1980**, *23*, 1072.

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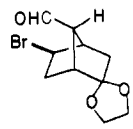

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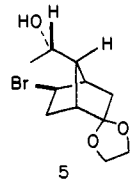

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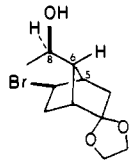

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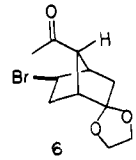

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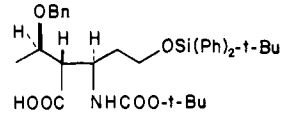
which gave rise to diastereomer **4**, mp 93–94 °C, in 79% isolated yield. Approximately 8% of the diastereomeric alcohol **5** was obtained. Reaction of **3** with methyllithium gave a 1:1 mixture of **4** and **5**. The second significant finding was that reduction ($LiAlH(OMe)_3$, THF, −100 °C, 1.0 h) of ketone **6**[7] afforded in 91% isolated yield the same diastereomer **4**. Less than 4.0% of diastereomer **5** was detected.

Analysis of **4** immediately reveals the presence of the hydroxyethyl structural unit of thienamycin bearing the proper configuration at C(8). However, upon careful scrutiny of **4**, one finds that both C(5) and C(6) of thienamycin are embedded in the bicyclo[2.2.1]heptane nucleus. Having made this realization, we embarked on a program to transform **4** into azetidinone **2**.

Our initial goal was to convert norbornane derivative **4** into unsaturated δ-lactam **11** (Scheme I) so as to more fully expose the relationship between C(5), C(6), and C(8). The availability of lactam **11** would permit access via oxidative cleavage to the protected β-amino acid **12**, a logical precursor to thienamycin.



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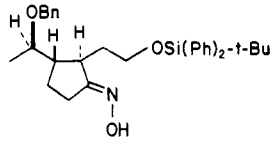
Toward this end, **4** was smoothly transformed [(1) DBU, $PhCH_3$, reflux; (2) NaH, HMPA, THF, BnBr, $n$-$Bu_4NI$, 50 °C; (3) 10% HCl–THF (1:10)] in 85% overall yield into norbornenone **7**.

Baeyer–Villiger oxidation of **7** (Scheme I) followed by treatment of the resultant hydroxy carboxylic acid with a Lewis acid afforded bicyclic lactone **8** as a crystalline material, mp 69–70 °C. In a straightforward manner, lactone **8** was converted into cyclopentanone **9**,[11] which upon exposure to hydroxylamine hydrochloride gave rise in 70% yield to *anti*-oxime **13**, along with 28% of *syn*-oxime **14**. After it stands at room temperature, the



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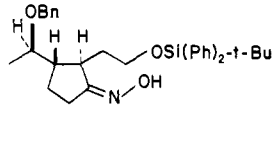

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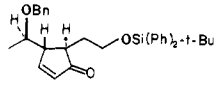
(10) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(11) Reduction[12] of the olefin in bicyclic lactone **8** and subsequent reintroduction of the double bond into lactam **10** proved necessary due to the fact that cyclopentenone ii was extremely sensitive toward migration of the double bond.



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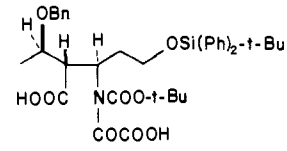
(12) Satoh, D.; Hashimoto, J. *Chem. Pharm. Bull.* **1976**, *24*, 1950.

*syn*-oxime slowly equilibrates to a 7:3 mixture in favor of the desired oxime **13**. Subjection of **13** to Beckman rearrangement provided saturated δ-lactam **10** as a crystalline compound, mp 114.5–116.0 °C, in 80% yield. Prior to introduction of the necessary unsaturation into the lactam ring, lactam **10** was converted into this corresponding *N*-*t*-Boc derivative.[13] Phenyl sulfenylation of the *N*-*t*-Boc derivative of **10** followed by oxidation with *m*-chloroperbenzoic acid and subsequent loss of benzenesulfenic acid provided unsaturated lactam **11**.

The transformation of unsaturated lactam **11** into protected β-amino acid **12** was achieved via a two-step process. Treatment (1.5 h) of **11** with 0.3 equiv of potassium permanganate and 6.0 equiv of sodium metaperiodate in 50% aqueous tertiary butanol[14] containing 5.0 equiv of sodium bicarbonate gave rise to dicarboxylic acid **15**, which upon treatment with 1.0 M sodium



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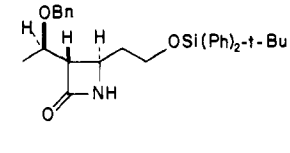

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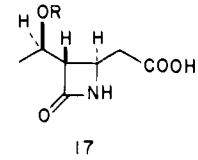
methoxide in methanol[15] at 0 °C for 1.5 h afforded in 65% overall yield crystalline acid **12**, mp 147–149 °C.

The fully protected β-amino acid derivative **12**, bearing the three contiguous chiral centers and the necessary appendage at C(5) to construct the carbapenem system of thienamycin, set the stage for conversion of **12** into azetidinone **2**.

Cleavage (TFA, 0 °C, 20 min) of the *t*-Boc group in **12** afforded the corresponding ammonium trifluoroacetate, which was cyclized [(a) $Et_3N$ (3.0 equiv), $CH_3CN$; (b) DCC (2.0 equiv), 65 °C, 5 h] to the fully substituted azetidinone **16** in 84% overall yield. A solution of azetidinone **16** in tetrahydrofuran was cleanly desilylated (93%) at room temperature in 30 min, employing 2.0 equiv of tetra-*n*-butylammonium fluoride. The resultant alcohol upon treatment with Jones reagent (3.0 equiv, acetone, 0 °C, 45 min) provided in 80% yield carboxylic acid **17** (R = Bn) as a crystalline



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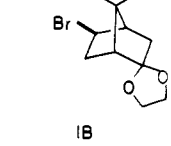

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substance, mp 103–104 °C. Hydrogenolysis [$H_2$ (40 psi), 20% by weight Pd black, MeOH] of **17** (R = Bn) afforded in quantitative yield the corresponding alcohol **17** (R = H), which was dissolved in a mixture of acetonitrile and dimethylformamide (3:1), cooled to 0 °C, and treated sequentially with 1.0 equiv of *N*,*N*′-carbonyldiimidazole and, after 50 min, with 0.55 equiv of the magnesium salt of *p*-nitrobenzoyl hydrogen malonate.[4i,16] The crude product upon crystallization provided in 50% yield β-keto ester **2**, mp 105–106 °C, whose spectra (NMR, IR) were identical in all respects with spectra kindly supplied by Dr. Melillo (Merck). Since **2** has been transformed on a previous occasion into (±)-thienamycin, the preparation of **2** constitutes a formal total synthesis of the antibiotic. The general strategy developed above allows for incorporation of substituents into the C(6) position of thienamycin at an early stage in the synthesis starting from the known bromo ketal ester **18** (where X = fluorine,[9] methyl,[8] or hydroxyl[17]).

(13) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730.

(14) Cf.: Lemieux, R. U.; von Rudloff, E. *Can. J. Chem.* **1955**, *33*, 1714.

(15) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(16) Cf.: Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.

(17) Grieco, P. A.; Tuthill, P. A.; Sham, H. L. *J. Org. Chem.* **1981**, *46*, 5005.

## Experimental Section

**[1*R*-(α*R**,1α,4α,5α,7*S**)]-5-Bromo-α-methylspiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-methanol (4). Reaction of Aldehyde 3 with $Me_2Cu(CN)Li_2$.** To a suspension of 10.34 g (0.115 mol) of copper(I) cyanide in 120 mL of dry ether at 0 °C under argon was added 144 mL (0.230 mol) of a 1.6 M solution of methyllithium in ether. After 10 min at 0 °C, the clear solution was cooled to −78 °C and 20.0 g (76.6 mmol) of aldehyde **3** in 60 mL of dry ether was added slowly via cannula. After 1.5 h at −78 °C, the reaction was warmed to room temperature and was quenched with 300 mL of a saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 × 50 mL). The combined extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. Separation on a Waters Prep 500A LC/system, using two Prep PAK-500/silica cartridges (57 mm × 30 cm, ethyl acetate–hexane, 1:3, flow rate 300 mL/min) afforded in order of elution 900 mg of recovered aldehyde (retention time 2.3 min) and 16.80 g (79%) of alcohol **4** (3.3 min) as a crystalline substance: mp 93.0–94.0 °C; [$R_f$ 0.42 (ether–hexane, 2:1); IR ($CHCl_3$) 3575, 3525–3475, 2965, 2880, 1475, 1450, 1435, 1400, 1380, 1360, 1330, 1255, 1235, 1200, 1160, 1100, 1065, 1050, 1015, 985, 945, 905, 895, 875, 840 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 4.28 (qd, 1 H, $J$ = 6.0, 12.0 Hz), 4.01 (dd, 1 H, $J$ = 4.0, 8.0 Hz), 3.92–3.70 (m, 4 H), 2.69 (d, 1 H, $J$ = 5.0 Hz), 2.55 (dd, 1 H, $J$ = 5.0, 14.0 Hz), 2.42 (br s, 1 H), 2.11–1.97 (m, 3 H), 1.90 (dd, 1 H, $J$ = 5.0, 14.0 Hz), 1.47 (d, 1 H, $J$ = 14.0 Hz), 1.22 (d, 3 H, $J$ = 6.0 Hz). Anal. Calcd for $C_{11}H_{17}O_3Br$: C, 47.67; H, 6.18. Found: C, 48.01; H, 6.26. Continued elution provided 1.61 g (8%) of alcohol **5** (10.4 min): mp 102–103 °C; $R_f$ 0.24; IR ($CHCl_3$) 3590, 3525–3350, 2965, 2880, 1450, 1440, 1375, 1335, 1235, 1225, 1210, 1170, 1140, 1105, 1090, 1065, 1020, 990, 950, 905, 895, 875, 840 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 4.33 (qd, 1 H, $J$ = 6.0, 11.0 Hz), 3.99 (dd, 1 H, $J$ = 4.0, 8.0 Hz), 3.09–2.86 (m, 4 H), 2.53 (dd, 1 H, $J$ = 8.0, 14.0 Hz), 2.47–2.36 (m, 3 H), 2.16 (td, 1 H, $J$ = 4.0, 14.0 Hz), 2.00–1.91 (m, 2 H), 1.50 (d, 1H, $J$ = 14.0 Hz), 1.31 (d, 3 H, $J$ = 6.0 Hz).

**Reaction of Ketone 6 with $LiAlH(OMe)_3$.** To a suspension of 1.04 g (0.027 mol) of lithium aluminum hydride in 30 mL of dry tetrahydrofuran at 0 °C under argon was added dropwise 3.3 mL (0.082 mol) of dry methanol followed by warming to room temperature. After 30 min at room temperature, the reaction was cooled to −100 °C and a solution of 250 mg (0.91 mmol) of ketone **6** in 5 mL of dry tetrahydrofuran was added via syringe. After 30 min at −100 °C, the reaction was warmed to −78 °C. After an additional 30 min, the reaction was quenched by the addition of 5 mL of a 50% aqueous tetrahydrofuran solution. The reaction was filtered and concentrated in vacuo. The residue was chromatographed on 20 g of silica gel. Elution with ether–hexane, 1:4, afforded 230 mg (91%) of alcohol **4**, which was identical in all respects with the sample of 4 prepared above. Continued elution afforded 9 mg (3.5%) of alcohol **5**, which was identical in all respects with the sample of **5** prepared above.

**[5*S*-[5α(*S**),6β]]-6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-5-[1-(phenylmethoxy)ethyl]-2-piperidinone (10).** To a stirred solution of 4.50 g (8.74 mmol) of *anti*-oxime **13** in 145 mL of dry pyridine were added 4.15 g (21.6 mmol) of *p*-toluenesulfonyl chloride and 20 mg of 4-(dimethylamino)pyridine. The reaction was stirred for 30 min at room temperature, followed by heating at 65 °C for 3 h. The resulting dark brown solution was cooled to room temperature, and the pyridine was removed in vacuo. The residue was dissolved in 300 mL of ethyl acetate and was washed with 100 mL of a 10% hydrochloric acid solution and 100 mL of a saturated solution of sodium bicarbonate. The organic phase was dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo. Chromatography of the residue on 200 g of silica gel (elution with ether to remove excess *p*-toluenesulfonyl chloride, followed by elution with ether–ethyl acetate, 9:1), afforded 3.68 g (82%) of lactam **10** as an oil, which crystallized on standing. Recrystallization from ether afforded analytically pure lactam **10**: mp 114.5–116.0 °C; $R_f$ 0.31 (ether–ethyl acetate, 3:2); IR ($CHCl_3$) 3480, 3460, 3060, 2980, 2950, 2925, 2850, 1650, 1588, 1468, 1460, 1425, 1378, 1360, 1335, 1305, 1255, 1210, 1285, 1108, 1090, 1030, 1010, 940, 908, 860, 820, 695, 660 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 7.75–7.25 (m, 15 H), 6.46 (br s, 1 H), 4.51 (AB q, 2 H, $J$ = 12.0 Hz, $\Delta\nu_{AB}$ = 35.0 Hz), 3.84–3.55 (m, 3 H), 2.27 (m, 2 H), 2.05–1.77 (m, 6 H), 1.16 (d, 3 H, $J$ = 6.0 Hz), 1.05 (s, 9 H); high-resolution MS, calcd for $C_{32}H_{41}NO_3Si$, 515.2856; found, 515.2856.

**1,1-Dimethylethyl [2*R*-[2α,3β(*R**)]]-2-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-3,6-dihydro-6-oxo-3-[1-(phenylmethoxy)ethyl]-1-(2*H*)-pyridinecarboxylate (11).** To a solution of 573 μL (4.10 mmol) of dry diisopropylamine in 6.5 mL of dry tetrahydrofuran at −78 °C under argon was added 3.07 mL (3.90 mmol) of a 1.27 M solution of *n*-butyllithium in hexane. After 15 min at −78 °C, a solution of 1.20 g (1.95 mmol) of 1,1-dimethylethyl [2*R*-[2α,3β(*R**)]]-2-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-6-oxo-3-[1-(phenylmethoxy)-ethyl]-1-piperidinecarboxylate in 12 mL of a 1:1 mixture of dry tetrahydrofuran and dry hexamethylphosphoramide was added via cannula to the solution of lithium diisopropylamide in tetrahydrofuran. After 30 min at −78 °C, the reaction was warmed to 0 °C and a solution of 468 mg (2.15 mmol) of diphenyl disulfide in 6.5 mL of dry tetrahydrofuran containing 3.5 mL of dry hexamethylphosphoramide was added. The reaction was immediately warmed to room temperature. The reaction was quenched after 30 min by pouring into 30 mL of a saturated ammonium chloride solution followed by the addition of 30 mL of brine. The product was isolated by extraction with ether (5 × 60 mL). The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography of the residue on 400 g of silica gel (elution with ether–hexane, 1:4) afforded 1.27 g of a mixture of sulfides as a pale yellow oil, which was used directly in the next reaction.

To a solution of the above sulfides in 55 mL of dry methylene chloride at −78 °C under argon was added 454 mg (2.64 mmol) of *m*-chloroperbenzoic acid in 40 mL of dry methylene chloride. After 2 h at −78 °C, the excess oxidant was destroyed by addition of 500 μL of dimethyl sulfide. After 15 min at −78 °C, the reaction was warmed to room temperature, diluted with 100 mL of ether, and washed with 50 mL of a saturated sodium bicarbonate solution. The aqueous phase was extracted with ether (3 × 50 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo affording 1.29 g of a mixture of sulfoxides as a white foam, which was used directly in the next reaction.

The above sulfoxides were dissolved in 19 mL of dry toluene and heated at 100 °C for 75 min. The reaction was cooled to room temperature and the solvent was removed in vacuo. Chromatography of the residue on 110 g of silica gel (elution with ether–hexane, 1:3) afforded 883 mg (74%) of unsaturated δ-lactam **11** as a faint yellow oil: $R_f$ 0.59 (ether–hexane, 3:2); IR ($CHCl_3$) 3055, 3015, 2985, 2945, 2920, 2850, 1755, 1710, 1630, 1590, 1460, 1450, 1425, 1390, 1365, 1290, 1240, 1210, 1150, 1140, 1105, 1025, 1005, 995, 940, 905, 845, 825, $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 7.72–7.25 (m, 15 H), 6.52 (dd, 1 H, $J$ = 6.0, 10.0 Hz), 6.00 (d, 1 H, $J$ = 10.0 Hz), 4.93 (br t, 1 H, $J$ = 6.0 Hz), 4.49 (AB q, 2 H, $J$ = 12.5 Hz, $\Delta\nu_{AB}$ = 32.7 Hz), 3.72 (t, 2 H, $J$ = 6.0 Hz), 3.51 (qd, 1 H, $J$ = 6.0, 8.0 Hz), 2.61 (br t, 1 H, $J$ = 8.0 Hz), 1.98 (m, 2 H), 1.43 (s, 9 H), 1.21 (d, 3 H, $J$ = 6.0 Hz), 1.03 (s, 9 H).

**(*R*)-2,3,4-Trideoxy-3-[[(1,1-dimethylethoxy)carbonyl]amino]-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2-[1-(phenylmethoxy)ethyl]-D-*erythro*-pentonic Acid (12).** To a solution of 375 mg (0.617 mmol) of unsaturated lactam **11** and 16 mL of *tert*-butyl alcohol was added a solution of 29 mg (0.184 mmol) of potassium permanganate, 785 mg (3.67 mmol) of sodium periodate, and 257 mg (3.06 mmol) of sodium bicarbonate in 16 mL of water. After 1.5 h at room temperature the excess oxidant was destroyed by addition of 2 mL of ethanol. The reaction was filtered through a pad of Celite. The Celite was washed with 40 mL of a 50% aqueous *tert*-butyl alcohol solution. The filtrate plus washing were concentrated in vacuo to ca. 25% of the original volume. The remaining heterogeneous mixture was dissolved in 30 mL of a 10% acetic acid solution, and the product was extracted with ethyl acetate (5 × 40 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Traces of acetic acid were removed azeotropically with benzene. There was obtained 381 mg of diacid **15** as a white amorphous solid, which was used directly in the next reaction.

A solution of the above diacid in 1.7 mL of dry methanol at 0 °C was treated with 1.7 mL (3.4 mmol) of a 2 M solution of sodium methoxide in methanol. After 1.5 h at 0 °C the reaction was quenched by addition of 25 mL of a 10% acetic acid solution. The product was extracted with ethyl acetate (5 × 25 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography of the residue on 40 g of silica gel (elution with chloroform–acetic acid, 99:1) afforded 240 mg (65%) of β-amino acid **12** as a crystalline material: $R_f$ 0.52 (ethyl acetate–hexane–acetic acid, 25:75:1); IR ($CHCl_3$) 3500–2400, 3395, 3055, 3040, 2950, 2925, 2885, 2850, 1705, 1590, 1500, 1475, 1465, 1455, 1430, 1390, 1370, 1245, 1160, 1110, 1090, 1020, 1010, 1000, 940, 825, 700 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 10.26 (br s, 1 H), 7.72–7.18 (m, 15 H), 5.54 (br d, 1 H, $J$ = 10 Hz), 4.63–4.32 (m, 3 H), 3.93–3.61 (m, 3 H), 2.80 (m, 1 H), 1.79 (m, 2 H), 1.40 (br s, 6 H), 1.31 (br s, 3 H), 1.26 (br d, 3 H, $J$ = 6.0 Hz), 1.01 (s, 9 H). Recrystallization from ether–pentane afforded analytically pure **12**, mp 146.0–149.0 °C. Anal. Calcd for $C_{35}H_{47}NO_6Si$: C, 69.22; H, 8.03. Found: C, 69.39; H, 7.82.

**(*R*)-3-Amino-2,3,4-trideoxy-5-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2-[1-(phenylmethoxy)ethyl]-D-*erythro*-pentonic Acid, β-Lactam (16).** A solution of 305 mg (0.504 mmol) of carboxylic acid **12** in 9.0 mL of freshly distilled trifluoroacetic acid was stirred for 20 min at 0 °C under argon. The trifluoroacetic acid was removed under vacuum leaving a

white solid, which was dissolved in 40 mL of dry acetonitrile to which was added 210 μL (1.51 mmol) of dry triethylamine. After the mixture was stirred for 5 min, 208 mg (1.01 mmol) of dicyclohexylcarbodiimide was added, and the reaction was stirred at 65 °C for 5 h. The reaction was cooled to room temperature and the solvent was removed in vacuo. Chromatography of the residue on 30 g of silica gel (elution with ether–hexane, 1:1) afforded 205 mg (84%) of β-lactam **16** as a viscous oil: $R_f$ 0.28 ($Et_2O$); IR ($CHCl_3$) 3400, 3055, 2990, 2920, 2880, 2845, 1747, 1650, 1585, 1490, 1485, 1455, 1450, 1425, 1390, 1375, 1360, 1325, 1260, 1235, 1185, 1165, 1140, 1110, 1090, 1060, 1025, 1005, 995, 970, 950, 905, 855, 820, 695 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 7.70–7.20 (m, 15 H), 5.95 (br s, 1 H), 4.55 (AB q, 2 H, $J$ = 12.5 Hz, $\Delta\nu_{AB}$ = 27.3 Hz), 3.86 (quintet, 1 H, $J$ = 6.0 Hz), 3.73 (m, 3 H), 2.85 (dd, 1 H, $J$ = 2.0, 7.0 Hz), 2.00–1.68 (m, 2 H), 1.27 (d, 3 H, $J$ = 6.0 Hz), 1.03 (s, 9 H); high-resolution MS, calcd for $C_{30}H_{37}NO_3Si$, 487.2543; found, 487.2551.

**Acknowledgment.** This investigation was supported by a Public Health Service Research Grant (CA 28865) from the National Cancer Institute. The 360-MHz NMR instrument (Nicolet) used in the above studies were purchased in part through funds provided by the National Science Foundation (Grant CHE-81-05004). We are grateful to S. Bongers and D. Zabrowski for experimental assistance during the early stages of this work. We thank Dr. D. G. Melillo for providing us with details for the transformation of **17** (R = H) into **2**.

**Registry No.** (±)-**1**, 65750-57-4; (±)-**2**, 77171-46-1; **3**, 91994-21-7; **4**, 91994-22-8; **5**, 92076-89-6; **6**, 91994-23-9; **7**, 91994-24-0; **8**, 91994-25-1; **9**, 91994-26-2; **10**, 91994-27-3; **11**, 91994-29-5; **12**, 91994-30-8; **13**, 91994-31-9; **14**, 92076-90-9; **15**, 91994-32-0; **16**, 91994-33-1; **17** (R = H), 78501-85-6; **17** (R = $CH_2Ph$), 91994-34-2; $p$-$NO_2C_6H_4CH_2OC(O)CH_2CO_2H$, 77359-11-6; 1,1-dimethylethyl [2*R*-[2α,3β(*R**)]]-2-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-6-oxo-3-[1-(phenylmethoxy)ethyl]-1-piperidinecarboxylate, 91994-28-4; 1,1-dimethylethyl [2*R*-[2α,3β(*R**),5α]]-2-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-ethyl]-6-oxo-5-(phenylthio)-3-[1-(phenylmethoxy)ethyl]-1-piperidinecarboxylate, 92009-74-0; 1,1-dimethylethyl [2*R*-[2α,3β(*R**),5β]]-2-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-6-oxo-5-(phenylthio)-3-[1-(phenylmethoxy)ethyl]-1-piperidinecarboxylate, 92009-80-8; 1,1-dimethylethyl 2-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-6-oxo-5-(phenylsulfinyl)-3-[1-(phenylmethoxy)ethyl]-1-piperidinecarboxylate, 92009-81-9.

# Palladium-Catalyzed Cross-Coupling of Vinyl Iodides with Organostannanes: Synthesis of Unsymmetrical Divinyl Ketones

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**Abstract:** The palladium-catalyzed cross-coupling reaction of vinyl iodides with trimethyl- or tributylvinylstannanes in the presence of carbon monoxide gives unsymmetrical divinyl ketones in good yields. The reaction conditions are neutral and mild enough (40–50 °C, 15–50 psig carbon monoxide) that other functional groups in either coupling partner can be brought unaltered into the coupled product. The *E* geometry in both partners is retained in the coupling product, and the *Z* geometry in the vinyltin reagent is maintained during the coupling reaction, but the coupled product undergoes slow *Z* to *E* isomerization under the usual reaction conditions. Isomerization of the divinyl ketone in the reaction medium is slowed in the dark. The reaction rate is especially sensitive to substituents on the vinyltin reagent, probably as a result of steric hindrance in the transmetalation step of the catalytic cycle. The sequence of reactions, including conversion of a cycloalkanone to a cycloakenyl iodide, the carbonylative coupling of the iodide to yield a cycloalkenyl vinyl ketone, and the acid-catalyzed cyclization of the divinyl ketone, presents a method of annelation of the parent ketone to a bicyclo[*n*.3.0] system.

Divinyl ketones, especially unsymmetrical divinyl ketones, are important intermediates in the synthesis of a wide variety of organic compounds. Not only are they Michael acceptors[1] for different nucleophiles, including organocopper reagents,[2] but they also undergo the Nazarov reaction[3] to provide, in some cases, an efficient route to cyclopentenones. This cyclization offers, therefore, an annelation procedure for five-membered rings and construction of the bicyclo[*n*.3.0] skeleton.

A number of methods of synthesis of divinyl ketones are available. Aldol-type condensations generally are efficient only in the synthesis of symmetrical divinyl ketones.[4] Unsymmetrical divinyl ketones are most often synthesized by the reaction of α,β-unsaturated acids or acid halides with various olefinic reagents. The direct acylation of alkenes with α,β-unsaturated acids in the presence of polyphosphoric acid or with acid halides in the presence of a aluminum chloride usually leads to mixtures of products and does not give particularly high yields of the divinyl ketone.[5] The reaction of α,β-unsaturated acid chlorides with vinylsilanes in the presence of Lewis acids is a cleaner reaction which gives moderate to excellent yields,[6] but the reaction does not work well with acryloyl chloride because of the accompanying polymerization.[6a,b] In certain examples, mixtures (double bond isomers) of α,β-unsaturated ketones are obtained, requiring a second isomerization reaction.[6b] The reaction of a vinyl mercurial with an α,β-unsaturated acid chloride in the presence of aluminum chloride gives an excellent yield of the unsymmetrical divinyl ketone, although under the reaction conditions, rearrangements are observed in some systems.[7] A similar reaction of acid chlorides with vinyl zirconium reagents takes place, although this procedure has not been adapted

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