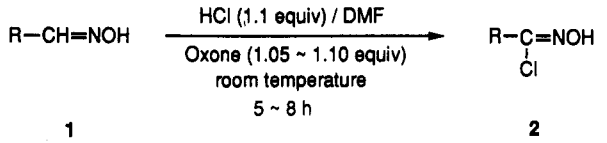
Scheme I



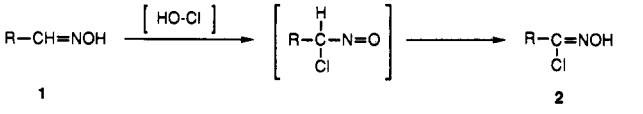
1 2

Table I. Preparation of Benzohydroximoyl Chlorides 2

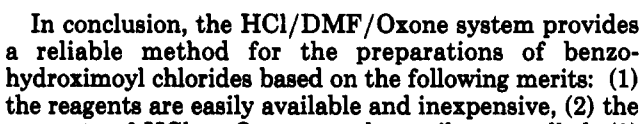
entry	R =	time (h)	yield[a] (%)	mp (°C) (lit. mp)
1	2-ClC_6H_4	8	95	56–58 (57–58)[7]
2	3-ClC_6H_4	8	99	65–67 (65–67)[4d]
3	4-ClC_6H_4	8	96	88–90 (87.5–89)[4d]
4	2,6-$Cl_2C_6H_3$	8	99	92–94 (93–94)[8]
5	3-$NO_2C_6H_4$	8	99	94–96 (94–96.5)[4d]
6	2-$CF_3C_6H_4$	8	99	81–82 (78–82)[4d]
7	4-$CF_3C_6H_4$	8	94	91–92 (89.5–91.5)[4d]
8	5-NO_2-2-furyl	8	80	143–145 (150)[9,b]
9	2-$CH_3OC_6H_4$	5	93	109–112 (112–112.5)[4d]
10	4-$CH_3OC_6H_4$	5	96	87–88 (87.5–88.5)[5]
11	3,4,5-$(CH_3O)_3C_6H_2$	5	91	128–130 (138–139)[4c,b]
12	2,4,6-$(CH_3)_3C_6H_2$	5	99	62–67 (61–69)[4d]
13	C_6H_5CO	8	94	130–132 (132–133)[10]
14	*tert*-butyl	5	92	oil (33)[11]

[a] Yields are of crude products which were pure by ^1H NMR and homogeneous by TLC. [b] Satisfactory elemental analysis (C, H, and N) was obtained.

and straightforward. Thus, a solution of benzaldoxime in 0.5 N anhydrous hydrogen chloride solution in DMF was treated with a slight excess of Oxone (1.05–1.10 equiv) at room temperature for 5–8 h. A small exotherm was noted. Cooling was more important in large-scale preparations. The reaction mixture was poured into cold water and extracted with ether to give products in the organic layers that were pure enough to be used directly in most cases. An excess (1.5–2.0 equiv) use of Oxone does not alter the yield or purity of products in the case of benzaldoximes having electron-withdrawing substituents but allows shortening of the reaction time. However, with a large excess of Oxone, benzaldoximes having electron-donating substituents give some ring chlorination. Thus, the use of only 1.05–1.10 equiv of Oxone is crucial here (entries 9–12). The present method can be applied to phenylglyoxaldoxime (2-isonitrosoacetophenone) as well as aliphatic aldoximes such as trimethylacetaldoxime. The results are summarized in Table I. A plausible mechanism for the chlorination of benzaldoximes is as follows: the hydrogen chloride is oxidized by Oxone to the positive chlorine species, hypochlorous acid. The reaction of the hypochlorous acid with the aldoximes 1 forms the nitroso intermediate,[4a] and this intermediate isomerizes to the hydroximoyl chlorides 2 as shown in eq 1.



(1)



1 2

In conclusion, the HCl/DMF/Oxone system provides a reliable method for the preparations of benzohydroximoyl chlorides based on the following merits: (1) the reagents are easily available and inexpensive, (2) the amounts of HCl or Oxone can be easily controlled, (3) initiation of the reaction and temperature control are not required, (4) workup procedures are convenient, and (5) regioselectively chlorinated pure products can be obtained in high yields.

Experimental Section

Melting points are uncorrected. All spectra were in accordance with the proposed structures.

Benzaldoximes were prepared according to the literature method from the corresponding aldehydes.[4c] Nifuroxime (*anti*-5-nitro-2-furaldoxime) and phenylglyoxaldoxime (2-isonitrosoacetophenone) were purchased from Aldrich and were used as received. Oxone was purchased from Aldrich. DMF was distilled from phosphorous pentoxide. Stock solution of anhydrous hydrogen chloride (0.5 N) in DMF was made by dissolving HCl gas in dry DMF.

General Procedure for the Synthesis of Benzohydroximoyl Chlorides 2. To a stirred solution of benzaldoxime (5 mmol) in a 0.5 N HCl stock solution in DMF (11 mL, 5.5 mmol of HCl) was added Oxone (1.62–1.69 g, 1.05–1.10 equiv of $KHSO_5$) at room temperature, and the reaction mixture was stirred at ambient temperature (a slight exotherm was noted) for 5–8 h. The reaction mixture was poured into cold water (100 mL) and extracted with ether (2 × 100 mL). The organic layers were washed with 0.5 N aqueous hydrochloric acid (100 mL) and brine (100 mL) and dried over anhydrous $MgSO_4$. Removal of ether gave the desired product. Analytically pure products were obtained by recrystallization from the reported solvents.[4c-d,5,7-11]

Acknowledgment. We thank the Korea Science and Engineering Foundation for financial support.

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Observations Concerning the Reactivity of Bicyclomycin and Bicyclomycin Derivatives with Organophosphorus Reagents

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Mechanistic proposals pertaining to the mode of action of the commercial antibiotic bicyclomycin[1,2] (1) have suggested that this agent alkylates the key protein(s) necessary for bacterial function.[3-6] To date chemical studies have demonstrated that the C(5)–C(5a) *exo*-methylene group in 1 is functionalized by sulfur[3,6] and nitrogen[7] nucleophiles under near neutral to basic conditions, while oxygen species[8] react at this site under acidic conditions. In this paper, we report the modification of the terminal double bond in bicyclomycin and 2[9-11] with

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(2) Williams, R. M.; Durham, C. A. *Chem. Rev.* **1988**, *88*, 511 and references cited therein.
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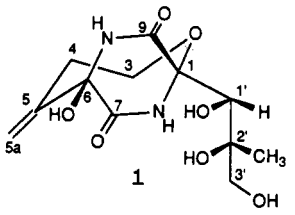
Table I. Key ^1H and ^{13}C NMR Spectral Properties for Phosphorus-Containing Compounds[a]

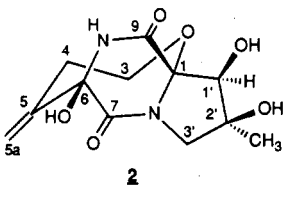
	^1H NMR			^{13}C NMR		
no.	$(RCH_2)_3PR'$	$(RCH_2)_3PCH_2$	$(RCH_2)_3PCH_2CH$	$(RCH_2)_3PR'$	$(RCH_2)_3PCH_2$	$(RCH_2)_3PCH_2CH$
3[b]	1.10–1.50[c] m			29.30[d] (d, J_{C-P} = 10.9 Hz)		
6[b]	2.20–2.80[c] m			19.50[d] (d, J_{C-P} = 47.6 Hz)		
4	2.15–2.45 m	2.15–2.45 m	1.82–1.96 m	19.73 (d, J_{C-P} = 48.7 Hz)	19.65, 20.28 (2 d, J_{C-P} = 48.1 Hz)	33.25, 33.36 (2 d, J_{C-P} = 8.3 Hz)
8	2.15–2.33 m	2.45–2.60 m 2.65–2.80 m	1.90–2.08 m	20.22 (d, J_{C-P} = 47.6 Hz)	20.20 (d, J_{C-P} = 45.4 Hz)	30.71 (d, J_{C-P} = 6.4 Hz)

[a] The number in each entry represents the chemical shift value (δ) observed in ppm relative to Me_4Si. ^1H NMR spectra were run at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz; the solvent was CD_3OD unless otherwise indicated. [b] The solvent was $CDCl_3$. [c] Reference 12. [d] Reference 13.

trialkylphosphines. The differential reactivity of 1 and 2 with sulfur and phosphorus nucleophiles has provided new evidence of the controlling factors for the critical C(5)–C(5a) chemical bonding step in the antibiotic.

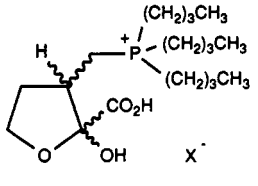


1

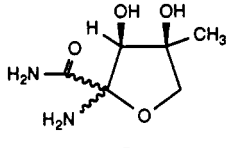


2

Treatment of bicyclomycin with $(nBu)_3P$ (3) in THF–H_2O (3:1, "pH" 7.8–9.0) mixtures gave 4 and 5.[7] Both compounds were obtained as diastereomeric mixtures (NMR analyses). Identification of 4 was aided by several spectral observations (Table I). First, the methylene protons adjacent to the phosphonium center in 4 resonated at δ 2.15–2.45 in the ^1H NMR spectrum. This value is consistent with the chemical shift reported for $nBu_4P^+I^-$[12] (6) (Table I). Second, the corresponding ^{13}C NMR chemical signals for these methylene units appeared at 19.65 and 20.28 ppm. Both the upfield shift of these resonances from 3 and the J_{C-P} coupling constants (i.e., J_{C-P} = 48.1–48.7 Hz) were in agreement with phosphonium salt production.[13] Third, a diagnostic signal for the hemiketal carbon in 4 was detected at 103.78 ppm.[14] Fourth, 4 gave a prominent peak in the mass spectrum that corresponded to the molecular ion for the phosphonium ion.

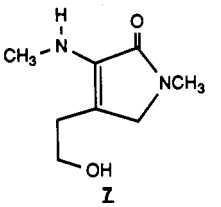


4



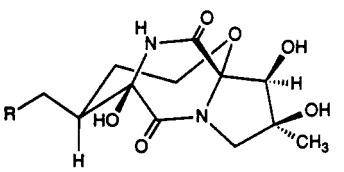
5

The conversion of 1 to 4 and 5 was reminiscent of the product profile observed for the reaction of bicyclomycin with methylamine at pH 12.5 in H_2O.[7] In this case both 5 and 7 were produced. We suspect that a pathway similar to that previously proposed[7] is operative in the $(nBu)_3P$-mediated transformation. The causative factors, however, for the remarkable facility of the full piperazinedione ring cleavage process at moderate "pH" values have not been determined. Attempts to isolate the product prior to ring scission by conducting the reaction at lower effective "pH" values at room temperature, (i.e., "pH" 2, 5) or at lower temperatures (i.e., 4 °C, 72 h) proved unsuccessful. Moreover, use of less nucleophilic organophosphorus reagents[15] (i.e., $P(CH_2Ph)_3$, PPh_3, $P(OCH_3)_3$; rt) in place of $(nBu)_3P$ (3) with 1 led to no reaction.



7

The efficiency of the $(nBu)_3P$-mediated transformation with 1 prompted us to explore the corresponding reaction with bicyclomycin derivative 2. Recently, we have shown that 2 underwent thiolate addition more rapidly than 1.[10] Treatment of 2 with $(nBu)_3P$ (3) in THF–H_2O (3:1, "pH" 8.0–9.1) mixtures led to the stereospecific production of 8 (^{13}C NMR analysis). Evidence in support of C(5a)-phosphonium salt 8 formation was provided by the characteristic upfield ^{13}C NMR shifts of the methylene carbons adjacent to the phosphorus center[13] (Table I) and the detection of a molecular ion peak in the mass spectrum.



8 R = $^+P((CH_2)_3CH_3)_3$ X^-
10 R = SCH_2CH_3

Information concerning the functionalization process in bicyclomycin-derived compounds has been attained by a series of competition experiments. Treatment of 2 (1 equiv) with equimolar amounts of $(nBu)_3P$ (3) and EtSNa (9) in a buffered THF–H_2O (3:1) mixture ("pH" 8.0) led to the formation of 10.[10] Correspondingly, treatment of 2 (1 equiv) with equimolar amounts of $(nBu)_3P$ (3) and Et_2S (11) provided only 8. Use of 1 in place of 2 in a

(11) The following uninverted Chemical Abstracts name for 2 modified by current IUPAC guidelines has been kindly provided by Dr. P. M. Giles (Chemical Abstract Services): (5*R*,9*R*,10*S*,10a*S*)-hexahydro-5,9,10-trihydroxy-9-methyl-4-methylene-8*H*-5,10a-(iminomethano)-6*H*-pyrrolo-[2,1-*b*][1,3]oxazocine-6,11-dione.

(12) Pouchert, C. J.; Campbell, J. R. *The Aldrich Library of NMR Spectra*; Aldrich: Milwaukee, WI, 1974; Vol. X, p 56.

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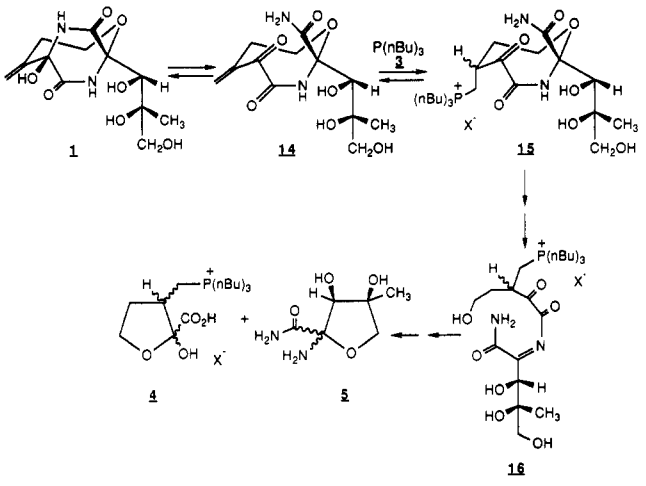
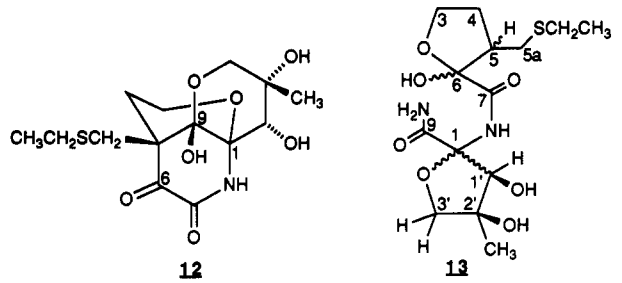
Scheme I. Proposed Pathway for the Formation of Compounds 4 and 5



similar protocol (THF–H_2O (3:1), "pH" 8.0 → 9.6) employing $(nBu)_3P$ (3) and EtSNa (9) led to a mixture of 12,[6a] 13,[16] unreacted 1, and an unidentified bicyclomycin–ethanethiolate adduct, while utilization of $(nBu)_3P$ (3) and Et_2S (11) gave only 4 and 5. These results are consistent



with a proposed reaction pathway in which C(6) hemiaminal bond cleavage of either 1 or 2 precedes the Michael addition of the nucleophile to the newly generated ring-opened enone,[17] and the expected relative nucleophilicities[15,18] of thiolate anions, trialkylphosphines, and sulfides. The proposed mechanism for 1 is depicted in Scheme I.

Experimental Section

General Procedures. The general procedures used in this study were identical to those employed in previous investigations.[6-8] Generous supplies of bicyclomycin (1) were obtained from the Fujisawa Pharmaceutical Co., Ltd., Japan. THF was distilled from Na^0 and benzophenone prior to use. H_2O refers to ultrapure water (18 MΩ-cm, MilliQ Water System). All products were purified to homogeneity by preparative TLC and were stable throughout the spectroscopic measurements.

Reaction of Bicyclomycin (1) with $(nBu)_3P$ (3). Bicyclomycin (1) (10.0 mg, 0.03 mmol) was dissolved in a THF–H_2O (3:1, "pH" 7.8–9.0) mixture (2.0 mL) under Ar, 3 (13.4 mg, 0.06 mmol) was syringed into the reaction vessel, and the solution was stirred at rt (48 h). TLC analysis prior to workup indicated that the reaction was complete, and no other significant 1-derived product was noted other than 4 and 5 that migrated beyond the origin. The solvents were removed in vacuo, and the residue was subjected to preparative TLC (25% MeOH–$CHCl_3$) to yield 4 as a semisolid, 2.8 mg (25%), and 5 (2.0 mg, 34%).

Compound 4: R_f 0.55 (25% MeOH–$CHCl_3$); FT-IR (KBr) 1682 cm^{-1}; ^1H NMR (CD_3OD) δ 0.85–1.05 (m, 9 H, P($CH_2CH_2CH_2CH_3$)$_3$), 1.40–1.65 (m, 14 H, P($CH_2CH_2CH_2CH_3$)$_3$, OCH_2CH_2CH), 1.82–1.96 (m, 1 H, CH), 2.14–2.45 (m, 8 H, P($CH_2CH_2CH_2CH_3$)$_3$, $CH_2P(nBu)_3$), 3.90–3.95 (m, 1 H, OCHH'), 4.01–4.06 (m, 1 H, OCHH') (the ^1H NMR assignments were confirmed by a COSY experiment); ^{13}C NMR (CD_3OD) 13.59 (P($CH_2CH_2CH_2CH_3$)$_3$), 19.73 (d, P($CH_2CH_2CH_2CH_3$)$_3$, J_{C-P} = 48.7 Hz), 19.65, 20.28 (2 d, $CH_2P(nBu)_3$, J_{C-P} = 48.1 Hz), 24.39 (d, P($CH_2CH_2CH_2CH_3$)$_3$, J_{C-P} = 5.2 Hz), 24.87 (d, P($CH_2CH_2CH_2CH_3$)$_3$, J_{C-P} = 14.6 Hz), 33.31 (2 d, $CHCH_2P(nBu)_3$, J_{C-P} = 8.5 Hz), 40.04 (br d, OCH_2CH_2, J_{C-P} = 4.0 Hz), 67.70 (CH_2O), 103.78 (d, C(COOH)(OH), J_{C-P} = 10.0 Hz), 175.89 (COOH) ppm. ^{13}C NMR analysis indicated that the product existed as a 1:1 diastereomeric mixture. MS (+FAB) 347 $[M]^+$; M_r (+FAB) 347.234 61 $[M]^+$ (calcd for $C_{18}H_{36}O_4P$ 347.235 12).

Compounds 5:[7] R_f 0.40 (25% MeOH–$CHCl_3$); ^1H NMR (CD_3OD) δ 1.28 (s, 3 H, CH_3), 3.75–3.92 (m, 3 H, CH_2, C(OH)H); ^{13}C NMR (CD_3OD) 22.52 (CH_3), 77.36, 77.46 (CH_2 or C(OH)CH_3 or C(OH)H), 77.55 (CH_2 or C(OH)CH_3 or C(OH)H), 79.62 (CH_2 or C(OH)CH_3 or C(OH)H), 93.47 ($H_2NC(O)CNH_2$), 177.63 (C(O)) ppm; M_r (+FAB) 177.087 87 $[M + 1]^+$ (calcd for $C_6H_{12}N_2O_4$ 177.087 53).

Reaction of [N(8)–C(3')] Cyclized Bicyclomycin 2 with $(nBu)_3P$ (3). Cyclized bicyclomycin 2[9,10] (10.0 mg, 0.035 mmol) was dissolved in a THF–H_2O (3:1, "pH" 8.0–9.1) mixture (2 mL), 3 (14.3 mg, 0.07 mmol) was syringed into the reaction vessel, and the solution was stirred at rt under Ar (24 h). TLC analysis prior to workup indicated that the reaction was complete, and no other significant 2-derived product was noted other than 8 that migrated beyond the origin. The solvents were removed in vacuo, and the residue was subjected to preparative TLC (20% MeOH–$CHCl_3$) to give 8 as a semisolid: 4.7 mg (28%); R_f 0.45 (20% MeOH–$CHCl_3$); FT-IR (KBr) 1660 cm^{-1}; ^1H NMR (CD_3OD) δ 0.95–1.05 (m, 9 H, P($CH_2CH_2CH_2CH_3$)$_3$), 1.45–1.65 (m, 15 H, P($CH_2CH_2CH_2CH_3$)$_3$, C(2')CH_3), 1.65–1.80 (m, 1 H, C(4)HH'), 1.90–2.08 (m, 2 H, C(4)HH', C(5)H), 2.15–2.33 (m, 6 H, P($CH_2CH_2CH_2CH_3$)$_3$), 2.45–2.60 (m, 1 H, C(5a)HH'), 2.65–2.80 (m, 1 H, C(5a)HH'), 3.53 (d, 1 H, C(3')HH', J = 12.0 Hz), 3.54–3.63 (m, 1 H, C(3)HH'), 3.70 (d, 1 H, C(3')HH', J = 12.0 Hz), 3.85 (s, 1 H, C(1')H), 3.90–4.00 (m, 1 H, C(3)HH'); ^{13}C NMR (CD_3OD) 13.66 (P($CH_2CH_2CH_2CH_3$)$_3$), 20.20 (d, C(5a)H_2P($CH_2CH_2CH_2CH_3$)$_3$), J_{C-P} = 45.4 Hz), 20.22 (d, P($CH_2CH_2CH_2CH_3$)$_3$, J_{C-P} = 47.6 Hz), 24.48 (d, P($CH_2CH_2CH_2CH_3$)$_3$, J_{C-P} = 4.0 Hz), 24.98 (d, P($CH_2CH_2CH_2CH_3$)$_3$, J_{C-P} = 15.0 Hz), 26.82 (C(2')CH_3), 30.71 (d, C(5), J_{C-P} = 6.4 Hz), 35.35 (d, C(4), J_{C-P} = 4.1 Hz), 58.31 (C(3')), 63.48 (C(3)), 75.19 (C(2')), 81.79 (C(1')), 93.95 (C(1)) ppm; the C(6) and carbonyl carbons were not detected; MS (+FAB) 487 $[M]^+$; M_r (+FAB) 487.292 87 (calcd for $C_{24}H_{44}N_2O_8P$ 487.293 70).

General Procedure for the Competition Experiments of Compound 2 with Phosphorus- and Sulfur-Containing Nucleophiles in THF–H_2O Mixtures. The reactions were performed in buffered THF–H_2O (3:1) mixtures (0.1 M Tris·HCl, 1.0 mL, "pH" = 8.0) containing 2 (5.0 mg, 0.02 mmol), 3 (4.0 mg, 0.02 mmol), and the sulfur-containing nucleophile 9 or 11 (0.02 mmol). The reaction was deaerated with Ar, capped, and stirred at rt (24 h). The solvents were removed in vacuo, and the residue was triturated with MeOH and filtered. The filtrate was concentrated and subjected to preparative TLC (20% MeOH–$CHCl_3$). The identities of the individual reaction components were confirmed by ^1H NMR analysis and the cospotting on TLC against authentic samples.

Reaction of 2, $(nBu)_3P$ (3), and EtSNa (9). Preparative TLC afforded 10:[10] 2.6 mg (38%); R_f 0.60 (20% MeOH–$CHCl_3$); ^1H NMR (CD_3OD) δ 1.25 (t, 3 H, CH_3CH_2S, J = 7.3 Hz), 1.53 (s, 3 H, C(2')CH_3), 1.95–2.05 (m, 2 H, C(4)H_2), 2.15–2.23 (m, 1 H, C(5)H), 2.35 (dd, 1 H, C(5a)HH', J = 11.3, 13.2 Hz), 2.45–2.58 (m, 2 H, CH_3CH_2S), 3.18 (dd, 1 H, C(5a)HH', J = 2.0, 13.2 Hz), 3.52 (d, 1 H, C(3')HH', J = 12.6 Hz), 3.67 (d, 1 H, C(3')HH', J = 12.6 Hz), 3.68–3.80 (m, 1 H, C(3)HH'), 3.82 (s, 1 H, C(1')H), 3.92–4.00 (m, 1 H, C(3)HH').

Reaction of 2, $(nBu)_3P$ (3), and Et_2S (11). Preparative TLC gave 8: 1.9 mg (20%); R_f 0.45 (20% MeOH–$CHCl_3$); ^1H NMR (CD_3OD) δ 0.95–1.05 (m, 9 H, P($CH_2CH_2CH_2CH_3$)$_3$), 1.45–1.65

(16) ^1H and ^{13}C NMR and mass spectral analyses of 13 indicated that this adduct was a member of a diastereomeric family of ring-opened bicyclomycin–ethanethiolate adducts previously reported by us.[6c] These specific adducts were not detected in noticeable amounts in the previous study.

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(m, 15 H, $P(CH_2CH_2CH_2CH_3)_3$, C(2′)CH_3), 1.70–1.80 (m, 1 H, C(4)*H*H′), 1.90–2.03 (m, 2 H, C(4)H*H*′, C(5)H), 2.12–2.32 (m, 6 H, $P(CH_2CH_2CH_2CH_3)_3$), 2.45–2.60 (m, 1 H, C(5a)*H*H′), 2.62–2.78 (m, 1 H, C(5a)H*H*′), 3.53 (d, 1 H, C(3′)*H*H′, J = 12.0 Hz), 3.52–3.62 (m, 1 H, C(3)*H*H′), 3.69 (d, 1 H, C(3′)H*H*′, J = 12.0 Hz), 3.86 (s, 1 H, C(1′)*H*), 3.90–4.00 (m, 1 H, C(3)H*H*′).

General Procedure for the Competition Experiments of 1 with Phosphorus- and Sulfur-Containing Nucleophiles in THF–H_2O (3:1) Mixtures. The reactions were carried out in THF–H_2O (3:1) mixtures (1.5 mL) containing **1**, **3**, and the sulfur-containing nucleophile (**9** or **11**). The "pH" of the solution was adjusted to 8 using aqueous dilute NaOH (or HCl) solutions. The solution was deaerated with Ar, capped, and stirred at rt. The solvents were removed in vacuo, and the residue was subjected to preparative TLC (20% MeOH–$CHCl_3$). The identities of these reaction products were verified by ^{1}H NMR analysis.

Reactions of 1, $(nBu)_3P$ (3), and EtSNa (9). Using **1** (10.0 mg, 0.03 mmol), **3** (30.3 mg, 0.15 mmol), and **9** (12.6 mg, 0.15 mmol) gave **12** (2.4 mg, 21%), **13** (1.6 mg, 14%), recovered **1** (2.8 mg, 28%), and an unidentified ethanethiolate–bicyclomycin adduct (1.2 mg) after 24 h. TLC analysis did not indicate the presence of **4** and **5**. The "pH" at the conclusion of the reaction was 9.6.

Bicyclomycin (1): R_f 0.40 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.35 (s, 3 H, C(2′)CH_3), 2.60–2.68 (m, 2 H, C(4)H_2), 3.52 (d, 1 H, C(3′)*H*H′, J = 12.0 Hz), 3.68 (d, 1 H, C(3′)H*H*′, J = 12.0 Hz), 3.82–3.96 (m, 2 H, C(3)H_2), 4.10 (s, 1 H, C(1′)H), 5.16 (s, 1 H, C(5a)*H*H′), 5.58 (s, 1 H, C(5a)H*H*′).

Compound 12:[6a] R_f 0.85 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.15 (s, 3 H, C(2′)CH_3), 1.24 (t, 3 H, CH_3CH_2S, J = 7.5 Hz), 1.91 (br d, 1 H, C(4)*H*H′, J = 14.1 Hz), 2.32 (dt, 1 H, C(4)H*H*′, J = 6.5, 14.1 Hz), 2.57 (q, 2 H, CH_3CH_2S, J = 7.5 Hz), 2.90 (d, 1 H, C(5a)*H*H′, J = 13.8 Hz), 3.02 (d, 1 H, C(5a)H*H*′, J = 13.8 Hz), 3.62 (d, 1 H, C(3′)*H*H′, J = 12.3 Hz), 3.72 (dt, 1 H, C(3)*H*H′, J = 2.1, 14.1 Hz), 3.90 (s, 1 H, C(1′)H), 3.97–4.10 (m, 2 H, C(3)H*H*′, C(3′)H*H*′).

Compound 13: R_f 0.55 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.20, 1.22 (2 t, 3 H, CH_3CH_2S, J = 7.0 Hz), 1.34 (s, 3 H, C(2′)CH_3), 1.80–1.92 (m, 1 H, C(4)*H*H′), 2.20–2.30 (m, 1 H, C(4)H*H*′), 2.45–2.60 (m, 4 H, CH_3CH_2S, C(5a)*H*H′, C(5)H), 2.80–2.85 (m, 1 H, C(5a)H*H*′), 3.90–4.00 (m, 2 H, C(3)*H*H′, C(3′)*H*H′), 4.02–4.12 (m, 1 H, C(3)H*H*′), 4.36 (d, 1 H, C(3′)H*H*′, J = 9.0 Hz), 4.62, 4.63 (2 s, 1 H, C(1′)H).

Reaction of 1, $(nBu)_3P$ (3), and Et_2S (11). Employing **1** (10.0 mg, 0.033 mmol), **3** (13.4 mg, 0.066 mmol), and **11** (5.9 mg, 0.066 mmol) afforded **4** (1.8 mg, 13%) and **5** (1.0 mg, 17%) after 48 h. No other products were observed by TLC analysis. The "pH" at the conclusion of the reaction was 9.8.

Compound 4: R_f 0.55 (25% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 0.90–1.11 (m, 9 H, $P(CH_2CH_2CH_2CH_3)_3$), 1.38–1.65 (m, 14 H, $P(CH_2CH_2CH_2CH_3)_3$, OCH_2CH_2CH), 1.82–1.95 (m, 1 H, CH), 2.13–2.45 (m, 8 H, $P(CH_2CH_2CH_2CH_3)_3$, $CH_2P(nBu)_3$), 3.88–3.94 (m, 1 H, OC*H*H′), 4.00–4.09 (m, 1 H, OCH*H*′).

Compound 5:[7] R_f 0.40 (25% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.28 (s, 3 H, CH_3), 3.78–3.88 (m, 3 H, CH_2, C(OH)*H*).

Reaction of Bicyclomycin (1) with EtSNa (9). Bicyclomycin (**1**) (20.0 mg, 0.066 mmol) and EtSNa (**9**) (11.1 mg, 0.132 mmol) were dissolved in a THF–H_2O (3:1) mixture (2.5 mL). The "pH" of this solution was adjusted to 10 using a dilute aqueous HCl solution, deaerated with Ar, capped, and stirred at rt (48 h). The solvents were removed in vacuo, and the residue was separated by preparative TLC (20% MeOH–$CHCl_3$) to give unreacted **1** (7.1 mg (36%), R_f 0.40 (20% MeOH–$CHCl_3$)), **12**, **13**, and an unidentified ethanethiolate–bicyclomycin adduct (1.0 mg).

Compound 12:[6a] 5.2 mg (23%); R_f 0.85 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.15 (s, 3 H, C(2′)CH_3), 1.24 (t, 3 H, CH_3CH_2S, J = 7.3 Hz), 1.90 (br d, 1 H, C(4)*H*H′, J = 14.0 Hz), 2.33 (dt, 1 H, C(4)H*H*′, J = 6.4, 14.0 Hz), 2.56 (q, 2 H, CH_3CH_2S, J = 7.3 Hz), 2.90 (d, 1 H, C(5a)*H*H′, J = 14.0 Hz), 3.01 (d, 1 H, C(5a)H*H*′, J = 14.0 Hz), 3.61 (d, 1 H, C(3′)*H*H′, J = 12.3 Hz), 3.76 (dt, 1 H, C(3)*H*H′, J = 2.0, 14.0 Hz), 3.90 (s, 1 H, C(1′)H), 4.03 (dd, 1 H, C(3)H*H*′, J = 6.4, 14.0 Hz), 4.05 (d, 1 H, C(3′)H*H*′, J = 12.3 Hz).

Compound 13: 2.8 mg (12%); R_f 0.55 (20% MeOH–$CHCl_3$); FT-IR (KBr) 1686 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.21, 1.22 (2 t, 3 H, CH_3CH_2S, J = 7.2 Hz), 1.32 (s, 3 H, C(2′)CH_3), 1.80–1.92 (m, 1 H, C(4)*H*H′), 2.20–2.32 (m, 1 H, C(4)H*H*′), 2.45–2.60 (m, 4 H, CH_3CH_2S, C(5a)*H*H′, C(5)H), 2.78–2.83 (m, 1 H, C(5a)H*H*′), 3.90–4.00 (m, 2 H, C(3)*H*H′, C(3′)*H*H′), 4.02–4.12 (m, 1 H, C(3)H*H*′), 4.35 (d, 1 H, C(3′)H*H*′, J = 9.0 Hz), 4.63 (s, 1 H, C(1′)H). ^{1}H NMR analysis indicated that the product existed as approximately a 1:1 diastereomeric mixture; the ^{1}H NMR assignments were verified by a COSY experiment: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 6 H, CH_3CH_2S, C(2′)CH_3), 1.80–1.95 (m, 1 H, C(4)*H*H′), 2.18–2.30 (m, 1 H, C(4)H*H*′), 2.50–2.65 (m, 4 H, CH_3CH_2S, C(5a)*H*H′, C(5)H), 2.70–2.80 (m, 1 H, C(5a)H*H*′), 3.80–3.95 (m, 2 H, C(3)*H*H′, C(3′)*H*H′), 4.00–4.10 (m, 1 H, C(3)H*H*′), 4.32 (d, 1 H, C(3′)H*H*′, J = 12.0 Hz), 4.55, 4.56 (2 s, 1 H, C(1′)H); ^{13}C NMR (CD_3OD) 15.06 (CH_3CH_2S), 21.15 (C(2′)CH_3), 26.96 (CH_3CH_2S), 31.46 (C(5a)), 68.73 (C(3)), 78.69 (C(1′)), 80.14 (C(2′)), 81.51 (C(3′)), 94.74 (C(1)), 103.38 (C(6)), 173.07 (C(7) or C(9)) ppm; the other carbonyl resonance was not observed, and the C(5) signal is believed to be beneath the solvent peak. Additional unassigned peaks detected at 31.53, 68.36, 78.08, 103.67, and 173.21 ppm may be attributable to the other diastereomer present in solution. ^{13}C NMR (DMSO-d_6) 14.58 (CH_3CH_2S), 20.86 (C(2′)CH_3), 25.32 (CH_3CH_2S), 29.97 (C(5a)), 45.93 (C(5)), 67.04 (C(3)), 77.20 (C(1′)), 78.74 (C(2′)), 78.99 (C(3′)), 92.40 (C(1)), 102.12 (C(6)), 169.65 (C(7) or C(9)), 170.46 (C(7) or C(9)) ppm. Additional unassigned peaks detected at 25.27, 30.07, 66.96, and 92.53 ppm may be attributable to the other diastereomer present in solution. MS (+FAB) 365 [M + 1]$^+$, 347 [M – H_2O + 1]$^+$; M_r (+FAB) 365.138 69 [M + 1]$^+$ (calcd for $C_{14}H_{25}N_2O_7S$ 365.138 25), 347.127 53 [M – H_2O + 1]$^+$ (calcd for $C_{14}H_{23}N_2O_6S$ 347.127 68). MS–MS (+FAB) indicated that the 347 ion emanated from the 365 ion.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds **4**, **8**, and **13** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

An Enantioselective Synthesis of Vicinal Diamines

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Chiral C_2-symmetric vicinal diamines and their derivatives, notably the bisaldimines, constitute an important class of bidentate ligands having broad application as chiral auxiliaries in metal-induced asymmetric synthesis.[1] Traditionally, enantiomerically pure vicinal diamines have

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