18. ^{1}H NMR: δ 3.93 (br s, 1 H) and 3.90 (br s, 1 H) (isoxazolidine CH_2), 2.68 (s, 3 H), 2.07–1.40 (m, 8 H), 1.15–0.90 (m, 1 H), 0.88–0.70 (m, 1 H), 0.68–0.52 (m, 1 H), 0.50–0.35 (m, 1 H). ^{13}C NMR (only detected signals): δ 77.44 t, 31.31 t, 27.43 t, 25.66 t, 25.05 t. MS: *m/z* (relative intensity) 167 ($M^{\bullet+}$, 18), 138 (100), 121 (17), 108 (22), 93 (51), 79 (55), 68 (71), 67 (50), 55 (76).

Cycloaddition of *N*-Methylcyclohexylideneamine *N*-Oxide (16) to 1: 5-Methyl-4-oxa-5-azadispiro[2.2.5.1]dodecane (19) and 6-Methyl-5-oxa-6-azadispiro[2.3.5.0]dodecane (20). A solution of nitrone **16**[14] (470 mg, 3.07 mmol) and methylenecyclopropane (**1**) in excess in dry benzene (0.5 mL) was heated in a sealed tube at 80 °C for 1 day. The oil obtained after concentration contained the two regioisomers **19** and **20** in 6:1 ratio (from the ^{1}H NMR). The crude mixture was chromatographed on silica gel (eluant, ethyl acetate/petroleum ether (1:3)) to give fractions only enriched in either regioisomers **19** and **20** (362 mg, 64% yield, R_f = 0.46) as oils. Mixture of regioisomers. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 73.16; H, 10.88; N, 7.58.

19. ^{1}H NMR: δ 2.66 (s, 3 H), 2.18 (s, 2 H), 1.68–1.27 (m, 10 H), 0.90 (s, 2 H), 0.57 (s, 2 H). ^{13}C NMR: δ 68.52 s, 61.42 s, 43.53 t, 38.60 q, 36.34 t (br), 31.47 t (br), 25.64 t, 23.39 t (2 C), 11.83 s (br), 9.22 s (br). IR ($CDCl_3$): 2938, 2861, 1447, 1346, 1093 cm^{-1}. MS: *m/z* (relative intensity) 181 ($M^{\bullet+}$, 6), 155 (25), 138 (45), 125 (12), 92 (37), 91 (100), 67 (22), 65 (52).

20. ^{1}H NMR: δ 3.96 (d, *J* = 6.5 Hz, 1 H) and 3.87 (d, *J* = 6.5 Hz, 1 H) (AB system), 1.97–0.35 (m, 14 H). MS: *m/z* (relative intensity) 181 ($M^{\bullet+}$, 12), 138 (100), 125 (15), 91 (14), 79 (31), 68 (30), 67 (28), 55 (49). IR ($CDCl_3$): 3075, 2998, 2936, 2859, 1441, 1356, 1156, 1063 cm^{-1}.

Thermal Rearrangement of 17: 6-Methyl-6-azaspiro[4.5]decan-9-one (21). The spiroisoxazolidine **17** (142 mg, 0.85 mmol) was subjected to FVT (400 °C (10^{-3} mmHg)) by vaporization at room temperature. The crude reaction product (80 mg) was chromatographed on a short pad of silica gel (eluant, ethyl acetate/petroleum ether (1:2) first, and then ethyl acetate/methanol (1:4)) to give **21** (60 mg, 42%) as a volatile oil.

21. R_f = 0.40 (EtOAc–MeOH (1:4)). ^{1}H NMR: δ 2.96 (t, *J* = 6.1 Hz, 2 H), 2.43 (s, 3 H), 2.39 (t, *J* = 6.2 Hz, 2 H), 2.35 (s, 2 H), 1.74–1.40 (m, 8 H). ^{13}C NMR: δ 209.58 s, 69.77 s, 51.70 t, 49.78 t, 38.95 t, 37.23 q, 35.21 t, 24.59 t. IR ($CDCl_3$): 1707 cm^{-1}. MS: *m/z* (relative intensity) 167 ($M^{\bullet+}$, 16), 138 (42), 125 (83), 110 (29), 97 (66), 96 (58), 82 (35), 69 (49), 68 (82), 55 (100). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 72.02; H, 10.41; N, 8.86.

Thermal Rearrangement of 19: 1-Methyl-1-azaspiro[5.5]undecan-4-one (22). The spiroisoxazolidine **19** (233 mg, 1.28 mmol) was subjected to FVT (400 °C (10^{-3} mmHg)) by vaporization at 50 °C. The collected crude mixture (204 mg) was chromatographed on a short pad of silica gel (eluant ethyl acetate/petroleum ether (1:4) first, and then ethyl acetate) to give **22** (92 mg, 40%) as a volatile oil.

22. R_f = 0.37 (MeOH/EtOAc/petroleum ether (1:1:2)) ^{1}H NMR: δ 3.09 (t, *J* = 6.2 Hz, 2 H), 2.45 (s, 3 H), 2.34 (t, *J* = 6.1 Hz, 2 H), 2.30 (s, 2 H), 1.61–1.35 (m, 10 H). ^{13}C NMR: δ 209.82 s, 60.34 s, 49.49 t, 47.38 t, 38.11 t, 35.59 q, 33.71 t, 25.62 t, 21.38 t. IR 1703 cm^{-1}. MS: *m/z* (relative intensity) 181 ($M^{\bullet+}$, 12), 139 (11), 138 (100), 125 (52), 97 (24), 96 (52), 69 (31), 68 (46), 55 (75). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.56; H, 10.77; N, 7.46.

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C-Aryl Glycosides: Electrophile Initiated Cyclizations of 6-Aryl-5-hexen-2-ols

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An approach to the synthesis of C-aryl glycosides is described. Treatment of β-lactam **9** with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) afforded *trans*-2,6-disubstituted pyrans **11a** and **11b**. Treatment of **9** with phenylselenenyl chloride (PhSeCl) or *N*-(phenylselenenyl)phthalimide (N-PSP) gave **11c** and cis-2,6-disubstituted pyran **12c** in different ratios depending on the reaction conditions. Treatment of β-lactam **10** with NBS, NIS, PhSeCl, or N-PSP gave mixtures of pyrans **16** and **17**. Treatment of unsaturated alcohol **24a** with PhSeCl gave pyran **23a**. Conversion of **23a** to virenose analog **22**, a C-aryl glycoside related to the chrysomycins, was accomplished using a selenoxide elimination–osmium tetraoxide oxidation sequence.

Introduction

C-Aryl glycosides are a family of natural products of interest because of their structural complexity and biological properties.[1] A number of methods for the preparation of C-aryl glycosides have been reported. These can be placed in either of two broad categories: (1) grafting of an aryl group onto an available carbohydrate and (2) de novo synthesis of the aryl-containing carbohydrates. Methods belonging to the first category involve reactions between carbohydrate C-1 carbocation equivalents and aromatic nucleophiles,[2] addition of carbohydrate C-1 carbanions to aryl cation equivalents,[3] palladium-mediated coupling of glycals with aryl halides and stannanes,[4] and

(1) Hacksell, U.; Daves, G. D. *Prog. Med. Chem.* **1985**, *38*, 1280.

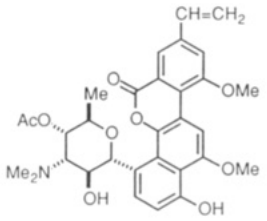
(2) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289. Bellosta, V.; Czernecki, S. *Carbohydr. Res.* **1987**, *171*, 279. Schmidt, R. R.; Effenberger, G. *Carbohydr. Res.* **1987**, *171*, 59. Suzuki, K.; Katsuki, M.; Matsumoto, T. *Tetrahedron Lett.* **1988**, 6935. Casiraghi, G.; Cornia, M.; Rassu, G.; Zetta, L.; Fava, G. G.; Bellichi, M. S. *Tetrahedron Lett.* **1988**, 3323. Bihovsky, R.; Selick, C.; Giusti, I. *J. Org. Chem.* **1988**, *53*, 4026. Czernecki, S.; Bellosta, V. *J. Chem. Soc., Chem. Commun.* **1989**, 199. Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293. Cai, M.-S.; Qiu, D.-X. *Synth. Commun.* **1989**, *19*, 851. Cai, M.-S.; Qiu, D.-X. *Carbohydr. Res.* **1989**, *191*, 125.

(3) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752. Parker, K. A.; Coburn, C. A. *J. Am. Chem. Soc.* **1991**, *113*, 8516.

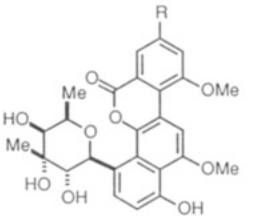
0022-3263/92/1957-5670$03.00/0

elaboration of C-alkyl glycosides.[5] Cycloaddition reactions between aromatic aldehydes and α,β-unsaturated carbonyl compounds and applications of the Achmatowicz reaction constitute two starting points for general de novo syntheses of C-aryl glycosides.[6]

Our interest in C-aryl glycoside synthesis was derived from our previously reported use of β-lactams as intermediates in aminosaccharide synthesis and the appearance of ravidomycin (**1**) as one member of a small family of



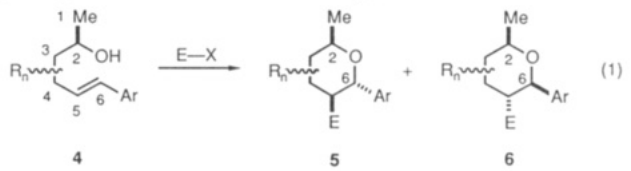
1 (Ravidomycin)



2 R = $CH=CH_2$ (Chrysomycin A)
3 R = Me (Chrysomycin B)

C-aryl glycoside antitumor agents.[7-9] This article describes an approach to the de novo synthesis of C-aryl glycosides within the context of model studies directed toward ravidomycin and the related C-aryl glycosides chrysomycin A (**2**) and chrysomycin B (**3**).[10-12]

Our approach to C-aryl glycosides is outlined in eq 1. We imagined that treatment of substituted 6-aryl-5-hexen-2-ols **4** with electrophiles (E–X) would afford tetrahydropyrans (**5** and **6**) which might be converted to the

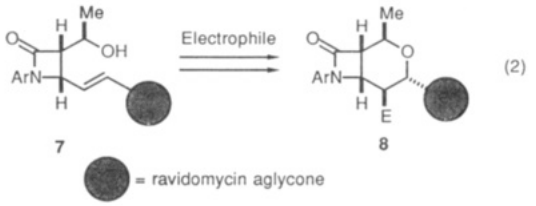


4 **5** **6**

(R_n = substituents at C–3 and C–4 and E—X = PhSe—Br, Br—Br, I—I)

desired C-aryl glycosides.[13d] Substituent patterns at C-3 and C-4 of **4**, olefin geometry, and perhaps the choice of electrophile were variables expected to influence the stereochemical course of cyclizations (**4** → **5** + **6**). It was hoped that adjustment of these variables would afford pyrans with either 2,6-trans (**1**) or 2,6-cis (**2** and **3**) substitution.[13,14]

Ravidomycin Model Studies. We imagined application of this strategy to ravidomycin (**1**) as shown in eq 2.



We hoped that an electrophile-initiated cyclization of a compound of type **7** would afford pyran **8** which might be converted to **1** using, in part, a β-lactam to vicinal amino alcohol transformation.[7] As a point of departure, electrophile-initiated cyclizations of **9** and **10** were investigated. Thus, β-lactam **9** was prepared by a known method and converted to **10** in 82% yield using a Mitsunobu reaction (Figure 1).[15,16]

The results of cyclization reactions performed with unsaturated alcohol **9** are summarized in Table I. Thus, treatment of **9** with NBS in dichloromethane at room temperature (entry 1) gave pyran **11a** in 92% yield. Only trace amounts of material that might be **12a** were detected. The stereochemistry of **11a** was initially assigned on the basis of ^1H NMR spectroscopy. It was possible to identify all of the pyran protons through a series of decoupling and COSY experiments. A large coupling constant of 11 Hz established the trans relationship between H-5 and H-6, and a 7% NOE was observed at H-5 upon irradiation of H-2. Assuming no change in relative stereochemistry at C-2, C-3, and C-4 during the reaction, these experiments are consistent with structure **11a** provided it adopts a pseudo-boat conformation to establish the proximal relationship between H-2 and H-5.[17] The structure **11a** was

(4) Czernecki, S.; Dechavanne, V. *Can. J. Chem.* **1983**, *61*, 533. Dunkerton, L. V.; Eusbe, J. M.; Serino, A. *J. Carbohydr. Res.* **1987**, *171*, 89. Outten, R. A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 5064. Kwok, D. I.; Outten, R. A.; Huhn, R.; Daves, G. D., Jr. *J. Org. Chem.* **1988**, *53*, 5359. Outten, R. A.; Daves, G. D., Jr. *J. Org. Chem.* **1989**, *54*, 4496. Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201. Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 2572. Tius, M. A.; Gu, X.; Gomez-Galeno, J. *J. Am. Chem. Soc.* **1990**, *112*, 8188.

(5) Hoffmann, M. G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 2403. Kozikowski, A. P.; Cheng, X. M. *J. Chem. Soc., Chem. Commun.* **1987**, 680. Kraus, G. A.; Shi, J. M. *J. Org. Chem.* **1990**, *55*, 4922.

(6) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285. Danishefsky, S. J.; Phillips, G.; Ciufolini, M. *Carbohydr. Res.* **1987**, *171*, 317. Bates, M. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1983**, 896.

(7) Ha, D.-C.; Hart, D. J. *Tetrahedron* **1989**, *45*, 1283.

(8) For the structure of ravidomycin see: Findlay, J. A.; Liu, J.-S.; Radics, L.; Rakhit, S. *Can. J. Chem.* **1981**, *59*, 3018. Findlay, J. A.; Liu, J.-S.; Radics, L. *Can. J. Chem.* **1983**, *61*, 323.

(9) For a synthesis of the carbohydrate portion of ravidomycin see: Knapp, S.; Lal, G. S.; Sahai, D. *J. Org. Chem.* **1986**, *51*, 380.

(10) For the structure of the chrysomycins see: Weiss, U.; Yoshihara, K.; Highet, R. J.; White, R. J.; Wei, T. T. *J. Antibiot.* **1982**, *35*, 1194. Matson, J.; Myllymaki, R.; Doyle, T.; Bush, J. U.S. Patent 4,461,831.

(11) For synthetic work on the aglycons of ravidomycin and the chrysomycins see: Findlay, J. A.; Daljeet, A.; Murray, P.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427. McKenzie, T. C.; Hassen, W. *Tetrahedron Lett.* **1987**, 2563. McKenzie, T. C.; Hassen, W.; MacDonald, S. J. F. *Tetrahedron Lett.* **1987**, 5453. MacDonald, S. J. F.; McKenzie, T. C.; Hassen, W. O. *J. Chem. Soc., Chem. Commun.* **1987**, 1528. McGee, L. R.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695. Patten, A. D.; Hguyen, N. H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1003. Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, 2517. Hart, D. J.; Merriman, G. H. *Tetrahedron Lett.* **1989**, 5093. Hua, D. H.; Saha, S.; Maeng, J. C.; Bensoussan, D. *Synlett* **1990**, 233. Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, 6313. Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1991**, 1666. For an elegant total synthesis of a related C-aryl glycoside, gilvocarcin M, see: Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568.

(12) This work is abstracted in part from the Ph.D. Thesis of G. Merriman (1990) and the MS Thesis of D. G. J. Young (1991), The Ohio State University.

(13) For a discussion of electrophile-initiated etherifications see: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 411–454. (b) Most electrophile-initiated cyclizations of hex-5-en-1-ols afford tetrahydrofurans. For one detailed study see: Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III. *J. Org. Chem.* **1987**, *52*, 4191. (c) For cyclizations of hex-5-en-1-ols to afford tetrahydropyrans see: Bresson, A.; Dauphin, G.; Geneste, J.-M.; Kergourard, A.; Lacount, A. *Bull. Soc. Chim. Fr.* **1971**, 1080. Kato, T.; Ichinose, I.; Hosogai, T.; Kitahara, Y. *Chem. Lett.* **1976**, 1187. Gonzalez, A. B.; Martin, J. D.; Perez, C.; Ramierez, M. A.; Kardo, F. *Tetrahedron Lett.* **1981**, 5071. (d) For a bromine-initiated cyclization of a 1-substituted D-*arabino*-hex-1-enitol 3,4,6-triacetate that gives a hexose-containing C-glycoside see: Arai, I.; Lee, T. D.; Hanna, R.; Daves, G. D., Jr. *Organometallics* **1982**, *1*, 742. We thank a reviewer for bringing this article to our attention. (e) For examples involving *O*-glycopyranoside synthesis see: Suzuki, R.; Mukaiyama, T. *Chem. Lett.* **1982**, 683. Gonzalez, A. G.; Betancor, C.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1977**, 2959. (f) For alkoxyselenations of 3,4-dihydropyrans, see: Kozikowski, A. P.; Sorgi, K. L.; Schmiesing, R. J. *J. Chem. Soc., Chem. Commun.* **1980**, 477.

(14) One example of an electrophile-initiated cyclization of a substituted 6-aryl-6-hepten-2-ol has been reported (RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458). The regiochemical and stereochemical aspects of this reaction differ from the examples reported herein.

(15) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. Compounds described in Tables I and II and eqs 3, 5, 7, and 8 have the indicated absolute configurations. Compounds described in Schemes I and II were prepared as racemic mixtures.

(16) Mitsunobu, O.; Kato, K.; Kimura, J. *J. Am. Chem. Soc.* **1969**, *1*, 6510. Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, *Tetrahedron Lett.* **1973**, 1619.

(17) Other NOE's for **11a** (proton irradiated → NOE observed): H_2 → CH_3 (5%), H_3 (8%), H_5 (7%); H_3 → H_2 (7%), H_4 (8%); H_4 → H_3 (8%), H_5 (8%).

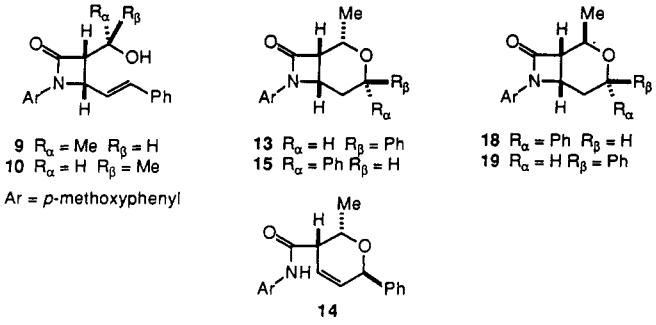
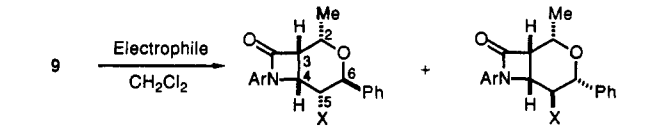


Figure 1.

Table I. Electrophile-Initiated Cyclizations of Compound 9



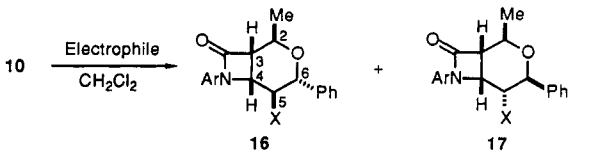
entry	condns	X	% 11	% 12
1	NBS, 0 → 25 °C, 24 h	Br	92	
2	NIS, 0 → 25 °C, 72 h	I	60	
3	PhSeCl, −78 → 25 °C, 24 h	SePh		72
4	PhSeCl, −78 °C, 2.5 h	SePh	87	
5	PhSeCl, Et_3N, 25 °C, 24 h	SePh	59	6
6	N-PSP, p-TsOH, 0 → 25 °C, 15 h	SePh	51	46

ultimately established by X-ray crystallography.[18] It is notable that (1) the stereochemical course of this cyclization (**9** → **11a**) is consistent with a related bromoetherification[7] and (2) compound **11a** crystallizes in the boatlike conformation suggested by the aforementioned NMR studies.[18]

Treatment of **9** with NIS at room temperature gave similar results as pyran **11b** was obtained in 60% yield. The structure of **11b** was established by chemical correlation with **11a**. Thus, pyrans **11a** and **11b** both gave reduction product **13** upon treatment with tri-*n*-butyltin hydride (Figure 1).[19] It is notable that radical fragmentation product **14** was also obtained from **11a** when the reduction was conducted under high dilution conditions.

The stereochemical course of PhSeCl-initiated cyclizations of **9** depended on reaction conditions.[20] Thus, treatment of **9** with PhSeCl at room temperature gave **12c** (72%) and only a trace of **11c** (entry 3). The stereochemistry of **12c** was assigned on the basis of ^1H NMR experiments. As with **11a**, it was possible to identify all of the pyran protons of **12c** using a series of decoupling and COSY experiments. A large coupling constant of 8 Hz indicated a trans relationship between H-5 and H-6 and a 13% NOE was observed at H-2 upon irradiation of H-6, establishing the cis relationship between these stereogenic centers.[21] These experiments are consistent with structure

Table II. Electrophile-Initiated Cyclizations of Compound 10



entry	condns	X	% 16	% 17
1	NBS, 0 °C, 2.5 h	Br	80	17
2	NIS, 0 → 25 °C, 24 h	I	53	23
3	PhSeCl, −78 → 25 °C, 4 h	SePh	68	21
4	PhSeCl, −78 °C, 2.5 h	SePh	64	18
5	PhSeCl, Et_3N, −78 → 25 °C, 24 h	SePh	70	18
6	N-PSP, p-TsOH, 0 → 25 °C, 15 h	SePh	47	33

12c provided it adopts a half-chair conformation. The stereochemistry of **11c** was proven by conversion to **13** upon treatment with tri-*n*-butyltin hydride, while reduction of **12c** gave isomeric pyran **15** (Figure 1).

It was surprising that the stereochemical course of the selenoetherification (**9** → **12c**) differed from the haloetherifications. Thus, an important observation was the appearance and disappearance of **11c** during the course of the selenoetherification. In fact, when the selenoetherification was conducted at low temperature (entry 4) or at room temperature in the presence of triethylamine (entry 5), pyran **11c** was once again the major product. This suggested that trans-2,6-disubstituted pyrans **11** were products of kinetic control while cis-2,6-disubstituted pyrans **12** were products of thermodynamic control.[22] In addition, treatment of a 1:1 mixture of **9** and **11c** with PhSeCl using the conditions described in entry 3 gave only **12c**. We suspect that hydrochloric acid, at least in part, is responsible for the isomerization of **11c** to **12c**.[23]

To provide a selenium electrophile under conditions that better mimic the NBS and NIS cyclizations, **9** was also treated with *N*-(phenylselenenyl)phthalimide (N-PSP) and a catalytic amount of *p*-toluenesulfonic acid.[24] These conditions gave a 97% yield of a nearly equal mixture of **11c** and **12c** (entry 6). The reason for the reduced selectivity of this reaction relative to entries 1 and 2 remains unclear.

The results of cyclizations performed with alcohol **10** are summarized in Table II. Thus, treatment of **10** with NBS (entry 1), NIS (entry 2), PhSeCl (entries 3–5), and *N*-(phenylselenenyl)phthalimide (entry 6) gave trans-2,6-disubstituted pyrans **16a–16c** as the major products. All

(18) We thank Dr. Judith Gallucci (The Ohio State University) for performing the X-ray crystallographic analyses of **11a** and **33a**. Crystallographic details are given in the supplementary material. For **11a** in the crystalline state, the H(2)–C(2)–C(5)–H(5) dihedral angle is 2.4°, the C(4)–C(3)–O–C(6) dihedral angle is 5.8°, and the H(3)–C(3)–C(4)–H(4) dihedral angle is 0.3°. These values indicate that (a) the boat is only slightly twisted, (b) the "base" of the boat deviates little from planarity, and (c) eclipsing is severe, as expected, along the C(3)–C(4) bond. Substituents on the C(2)–C(3), C(4)–C(5), and C(5)–C(6) bonds are staggered.

(19) For reviews of tin hydride chemistry see: Neumann, W. P. *Synthesis* **1987**, 665. Kuivila, H. F. *Synthesis* **1970**, 499. Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.

(20) For a review of organoselenium-based ring closure reactions see: Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. In *Organoselenium Chemistry*; Liotta, D., Ed.; John Wiley: New York, 1987; pp 127–162.

(21) Other NOE's for 12c (proton irradiated → NOE observed): CH_3 → H_2 (8%), H_3 (4%); H_2 → CH_3 (4%), H_3 (4%), H_6 (13%); H_3 → CH_3 (2%) H_2 (9%), H_4 (10%); H_4 → H_3 (10%), H_5 (5%); H_5 → H_4 (5%), H_6 (3%); H_6 → H_2 (13%), H_5 (3%).

(22) The issue of reversibility in phenylselenenyl halide addition reactions has been addressed by several studies: Raucher, S. *J. Org. Chem.* **1977**, *42*, 2951. Garratt, E. G.; Kabo, A. *Can. J. Chem.* **1980**, *58*, 1030. For a recent publication describing examples of "reagent-based stereocontrol" in electrophile-initiated cyclizations of 4-hexen-2-ols see: Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084. Further examples of electrophile-initiated cyclizations whose stereocyhemistry is electrophile-dependent have been reported by the Liotta group.[13b]

(23) On several occasions we experienced difficulty repeating the result described in entry 3. We eventually traced this problem to the low solubility of HCl in dichloromethane. When these reactions were performed in tightly stoppered flasks under a static atmosphere of argon, reproducible results were obtained. On one occasion, 11c was treated with HCl in dichloromethane for 24 h at room temperature to provide a 62:38 mixture of 11c and 12c, respectively, along with small amounts of alcohol 9 and phenylselenenyl chloride. This establishes that hydrochloric acid is, at least in part, responsible for isomerization of 11c to 12c. The incomplete conversion of 11c to 12c in this experiment may have been due to the aforementioned solubility problem.

(24) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

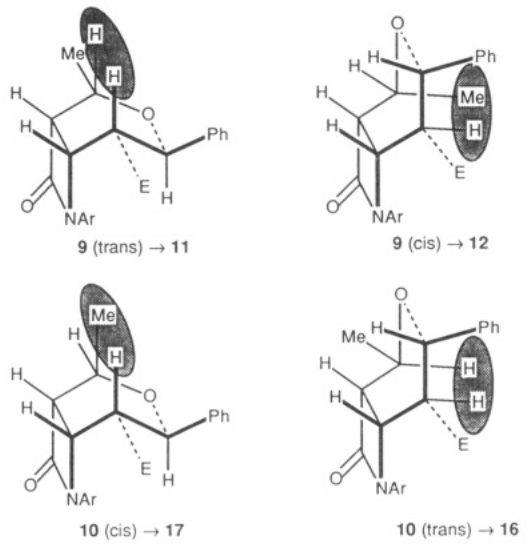


Figure 2.

reactions gave **17a–17c** as minor products. The stereochemical assignment for **16a** was based in part on a large coupling constant (10 Hz) between H-5 and H-6 and a 10% NOE observed at the C-2 methyl group upon irradiation of H-6. These experiments are consistent with structure **16a** and suggest that it prefers a half-chair conformation. Treatment of **16a–16c** with tri-*n*-butyltin hydride gave pyran **18**, establishing the common trans-2,6-substitution pattern in the major cyclization products (Figure 1). The stereochemical assignment for **17a** was based on a large coupling constant (9 Hz) between H-5 and H-6 and a 3% NOE observed at H-6 upon irradiation of H-2. Treatment of **17a–17c** with tri-*n*-butyltin hydride gave the same reduction product (**19**), establishing the common cis-2,6-disubstitution pattern for these compounds (Figure 1).

One explanation for the stereochemical results presented in Tables I and II is shown in Figure 2. If one assumes that (1) the cyclizations of **9** and **10** involve antiperiplanar addition of oxygen and electrophile across the double bond and (2) cyclizations take place through transition states in which the resulting pyran (**11**/**12** or **16**/**17**) is born in a boatlike conformation (perhaps due to conformational constraints imposed by the β-lactam), it appears that transannular Me–H interactions might make transition states **9** (cis) and **10** (cis) higher in energy than transition states **9** (trans) and **10** (trans), respectively.[25] This would explain the kinetic preference for trans-2,6-disubstituted pyrans (**11** and **16**) in the cyclizations of both **9** and **10**. Under conditions of thermodynamic control, the most stable pyrans would predominate. Although the results in entries 3–5 of Table I indicate that **11** is thermodynamically less stable than **12**, we have no evidence that indicates the relative thermodynamic stability of **16** and **17**.

To provide one test of the explanation offered in Figure 2, we examined the NBS-initiated cyclization of β-lactam **20**.[26] This substrate lacks the C(2)-methyl group of either

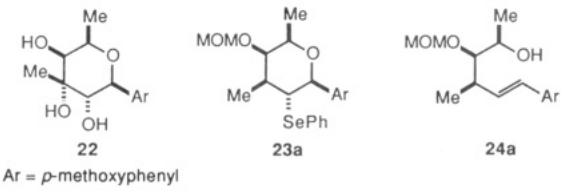
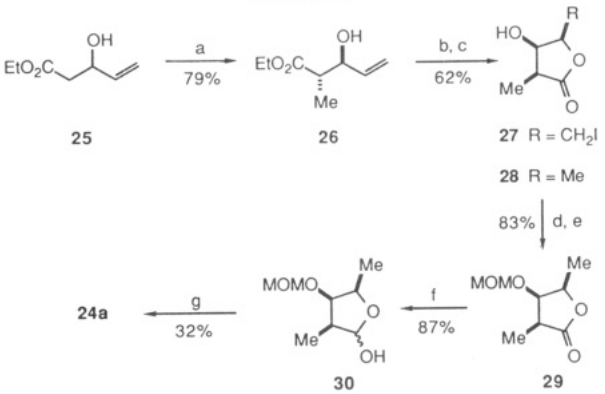


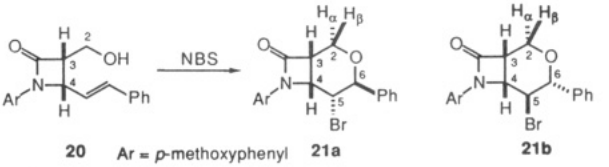
Figure 3.

Scheme I[a]



[a] Key: (a) LDA, MeI, HMPA; (b) KOH, EtOH; (c) I_2, $NaHCO_3$; (d) n-Bu_3SnH, AIBN, PhH, Δ; (e) CH_3OCH_2Cl, EtN (i-Pr)$_2$, CH_2Cl_2; (f) i-Bu_2AlH, PhMe, −78 °C; (g) p-$MeOC_6H_4CH_2P(O)(OEt)_2$, n-BuLi, DME; NaH, PhH, Δ.

9 or **10** and the corresponding boatlike transition states; for example, **9** (trans) and **9** (cis), where Me→H, both lack the aforementioned transannular Me–H interaction. Thus, one would expect **20** to show less selectivity than **9** or **10** in kinetically controlled electrophile-initiated cyclizations. Treatment of **20** with NBS in dichloromethane using the conditions described for entry 1 of Table I gave **21a** (64%) and **21b** (19%) (eq 3).[27] The structures of **21a** and **21b**



(3)

were assigned on the basis of spectroscopic data and NOE experiments. For example, large coupling constants (10 Hz) established the trans relationship between H-5 and H-6 in each isomer. In **21a**, NOE's between H_5 and $H_{2\beta}$ (3%) and H_6 and $H_{2\alpha}$ (2%) helped establish stereochemistry at C-6 and suggest that boatlike and half-chair conformations are close in energy. In **21b**, an NOE between H_6 and $H_{2\beta}$ (8–12%) helped establish stereochemistry at C-6 and suggest that it adopts a half-chair conformation. The result of this experiment is consistent with the model proposed in Figure 2.

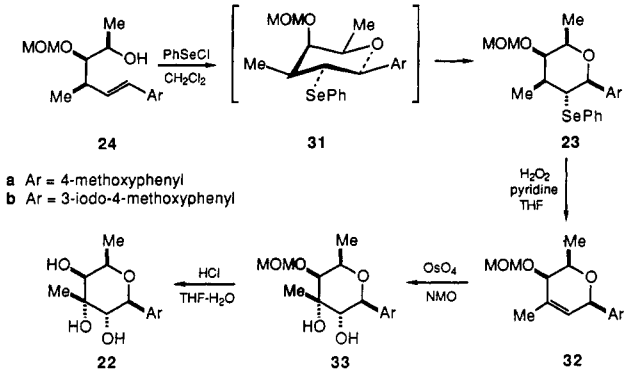
Although the conversions of **10** to **16a–16c** (Table II) suggested that this procedure might be used to establish stereochemistry in the carbohydrate portion of ravidomycin (**1**), this approach was abandoned due to our failure to improve the aforementioned method for converting β-lactams into vicinal amino alcohols. Application of the approach delineated in eq 1 to the synthesis of C-aryl glycosides related to the chrysomycins (**2** and **3**) is described in the following section.

(25) The structures shown in Figure 2 represent an extreme. We realize that intermediate bridged ions are likely to be involved. We thank a reviewer for pointing out a related bromoetherification that does not proceed with strict anti addition of electrophile and nucleophile.[13d]

(26) Lactam **20** was prepared in low yield by treating the dianion of ethyl β-hydroxypropanoate with *N*-(*p*-methoxyphenyl)cinnamylideneaniline. This gave a 4:1 mixture of the trans isomer of **20** (J_{34} = 2 Hz) and **20** (J_{34} = 6 Hz) in 39% yield. A sample of **20** that was about 80% pure (20% trans isomer and other trace contaminants) was obtained after repeated chromatography. Cyclizations were conducted using this material. Treatment of the trans isomer of **20** with NBS returned the starting β-lactam.

(27) Reduction of **21a** with tri-*n*-butyltin hydride gave a product (**21a** where Br → H) with coupling patterns consistent with a tetrahydropyran and inconsistent with a tetrahydrofuran.

Scheme II



Chrysomycin Model Studies. One total synthesis of methyl D-virenopyranoside, a glycoside derived from the 6-deoxyhexose substructure of the chrysomycins, has been described.[28] The initial target of our model studies was C-aryl glycoside **22** (Figure 3). We planned to prepare **22** from pyran **23a**, which was to be prepared using an electrophile-initiated cyclization of 6-aryl-5-hexen-2-ol **24a**.

Cyclization substrate **24a** was prepared as outlined in Scheme I. The known iodolactone **27** was obtained in three steps (46% overall) from racemic β-hydroxy ester **25** using a procedure reported by Chamberlin.[29] Reduction of the iodide with tri-*n*-butyltin hydride gave lactone **28** (88%), and protection of the hydroxy group afforded MOM ether **29** (94%). Treatment of **29** with diisobutylaluminum hydride gave lactol **30** (87%), and a Horner–Wadsworth–Emmons reaction completed the synthesis of **24a** (32%).[30]

Treatment of **24a** with PhSeCl in dichloromethane at low temperature gave cis-2,6-disubstituted pyran **23a** as the only detected stereoisomer in 74% yield (Scheme II). The observed stereochemistry was anticipated based on the expectation that the lowest energy cyclization transition state would lead directly to a chair conformation of the pyran in which steric interactions were minimized (**31a**).

The synthesis of **22a** was completed as follows. Oxidation of selenide **23a** was accompanied by elimination to afford olefin **32a** in 80% yield.[31] Treatment of **32a** with catalytic osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide gave diol **33a** (88%).[32] The structure of **33a** was confirmed by X-ray crystallography.[18] Removal of the MOM-protecting group using hydrochloric acid in aqueous tetrahydrofuran completed the synthesis of **22a** (69%).

This reaction sequence was also applied to the synthesis of aryl iodide **33b**, a substrate that might serve as an intermediate in a chromium carbene–aryne annulation route to chrysomycin B.[33] Thus, a Horner–Wadsworth–Emmons reaction between lactol **30** and diethyl (3-iodo-4-methoxybenzyl)phosphonate (**34**) gave **24b** in 27% yield. Selenoetherification of **24b** gave **23b** in 75% yield, and oxidation–elimination gave olefin **32b** in 69% yield. Treatment of **32b** with the aforementioned vicinal hydroxylation conditions completed the synthesis of **33b** (93%).

Conclusions

A procedure for preparing C-aryl glycopyranosides related to ravidomycin (**1**) and the chrysomycins (**2** and **3**) has been evaluated. Both studies indicate that the aryl group directs the regiochemical course of electrophile-initiated cyclizations of substituted 6-aryl-5-hexen-2-ols. The studies directed toward ravidomycin (Tables I and II) show that reaction conditions and choice of electrophile can influence the stereochemical course of such cyclizations. In addition, an example of acid-catalyzed reversal of a selenoetherification has been documented. A model that explains the stereochemistry observed in these studies has also been proposed. The chrysomycin model studies suggest that the stereochemical course of cyclizations of the type shown in eq 1, where C-3 and C-4 substituents do not represent a small ring, might be predicted by conformational arguments frequently used to explain the stereochemical course of other reactions involving 6-membered ring transition states. Improved methods for preparing olefins of type **24** will have to be developed before application of this strategy to the chrysomycins will be possible.

Experimental Section

All melting points are uncorrected. ^{13}C NMR multiplicities were determined using DEPT or INEPT spectra. Mass spectra were obtained at an ionization energy of 70ev. Compounds for which exact masses are reported exhibited no significant peaks at *m/e* greater than that of the parent. Reactions were conducted under a blanket of Ar or N_2, and solvents were dried when deemed necessary. Specific rotations [α] were recorded at the sodium D-line at room temperature.

[3*S*,4*S*(*E*)]-3-[1(*R*)-Hydroxyethyl]-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (10). To a solution of 500 mg (1.55 mmol) of β-lactam **9**, 818 mg (3.12 mmol) of Ph_3P, and 120 μL (3.12 mmol) of formic acid (95%) in 17 mL of THF at 0 °C was added a solution of 515 μL (3.12 mmol) of diethyl azodicarboxylate as a solution in 6.5 mL of THF over a 1-h period. The cold bath was removed, and the mixture was stirred at rt for 1 h. The solution was concentrated in vacuo and chromatographed over 100 g of silica gel (eluted with EtOAc–hexane (1:5)) to afford 500 mg of a formate ester.

To a solution of 500 mg (1.42 mmol) of the formate ester in 14 mL of ethanol was added 2.0 mL of 1.0 N aqueous NaOH. The mixture was stirred for 2 h during which time the starting material slowly dissolved. A solution of 2.0 mL of 1 N aqueous HCl in 20 mL of ethanol was added. The mixture was concentrated in vacuo, dissolved in CH_2Cl_2, and washed with 20 mL of water. The aqueous phase was extracted with two 15-mL portions of CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with EtOAc–hexane (1:2)) to afford 412 mg (82%) of β-lactam **10** as a white solid: mp 124–127 °C; [α] = 168° (*c*, 0.16); IR (CH_2Cl_2) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.42 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.95 (br s, 1 H, OH), 3.46 (dd, *J* = 9.1, 5.6 Hz, 1 H, CHCO), 3.76 (s, 3 H, OCH_3), 4.25 (m, 1 H, CHOH), 4.8 (dd, *J* = 7.4, 5.8 Hz, 1 H, CHN), 6.5 (dd, *J* = 16, 7.8 Hz, 1 H, CH=CHPh), 6.85 (m, 3 H, CH=CHPh, ArH), 7.2–7.5 (m, 7 H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.66 (q), 55.43 (q), 56.82 (d), 61.63 (d), 64.41 (d), 114.31 (d), 118.27 (d), 124.55 (d), 126.67 (d), 128.41 (d), 128.73 (d), 131.56 (s), 135.26 (d), 135.56 (s), 156.06 (s), 164.10 (s); exact mass calcd for $C_{20}H_{21}O_3N$ *m/e* 323.1521, found *m/e* 323.1514.

[1*S*-(1α,2β,4α,5β,6α)]-5-Bromo-7-(*p*-methoxyphenyl)-2-methyl-4-phenyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (11a). To a solution of 100 mg (0.31 mmol) of β-lactam **9** in 2.5 mL of CH_2Cl_2 cooled to 0 °C in an ice bath was added 58 mg (0.33 mmol) of NBS in one portion. The mixture was stirred at 0 °C for 30 min and then allowed to warm to rt and stir for 24 h. The mixture

(28) Yoshimura, J.; Hong, N.; Sato, K. I. *Chem. Lett.* **1980**, 1131.
(29) Chamberlin, R. A.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. It is notable that we observed only one diastereomer in the conversion of **26** to **27** (79%; mp 85–86 °C).
(30) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
(31) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(32) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(33) Parker, K. A.; Coburn, C. *J. Org. Chem.* **1991**, *56*, 1666. McKinney, J. A. Ph.D. Thesis, The Ohio State University, 1989.

was concentrated in vacuo and chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:4)) to afford 113 mg (91%) of bromide **11a** as a white solid (mp 202–204 °C). A portion of this material was recrystallized from CH_2Cl_2–hexane to afford material for X-ray crystallographic analysis: mp 202–204 °C; $[\alpha] = 29.6°$ ($CHCl_3$, *c*, 1.06); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 (d, J = 6.3 Hz, 3 H, CH_3), 3.55 (dd, J = 6, 2.3 Hz, 1 H, C(1)H), 3.80 (s, 3 H, OCH_3), 4.50 (dq, J = 6.3, 2.3 Hz, 1 H, C(2)H), 4.60 (dd, J = 11, 2.4 Hz, 1 H, C(5)H), 4.88 (dd, J = 5.9, 2.4 Hz, 1 H, C(6)H), 5.17 (d, J = 11 Hz, 1 H, C(4)H), 6.9 (d, J = 10.5 Hz, 2 H, ArH), 7.4 (m, 5 H, ArH), 7.6 (d, J = 10 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.84 (q), 48.73 (d), 54.77 (d), 55.41 (q), 56.62 (d), 66.29 (d), 77.46 (d), 113.93 (d), 122.07 (d), 127.04 (d), 128.41 (d), 130.07 (s), 140.40 (s), 156.98 (s), 165.00 (s) (one doublet not located); exact mass calcd for $C_{20}H_{20}BrNO_3$ m/e 401.627, found m/e 401.0611. Anal. Calcd for $C_{20}H_{20}BrNO_3$: C, 59.71; H, 5.01; Found: C, 59.33; H, 4.95.

[1*S*-(1α,2β,4α,5β,6α)]-5-Iodo-7-(*p*-methoxyphenyl)-2-methyl-3-oxa-4-phenyl-7-azabicyclo[4.2.0]octan-8-one (11b). To a solution of 100 mg (0.31 mmol) of β-lactam **9** in 2.0 mL of CH_2Cl_2 cooled to 0 °C in an ice bath was added 250 mg (1.11 mmol) of NIS in one portion. The mixture was stirred in the dark for 1 h at 0 °C, allowed to warm to rt, and stirred for an additional 72 h. The solution was diluted with 20 mL of CH_2Cl_2 and washed with 15 mL of saturated sodium thiosulfate. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 139 mg of crude residue. The residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:3)) to afford 84 mg (60%) of iodide **11b** as a white solid: mp 190–193 °C dec; $[\alpha] = 33.0°$ ($CHCl_3$, *c*, 1.01); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.5 (d, J = 6.3 Hz, 3 H, CH_3), 3.48 (dd, J = 6.0, 2.3 Hz, 1 H, C(1)H), 3.8 (s, 3 H, OCH_3), 4.5 (qd, J = 6.3, 2.2 Hz, 1 H, C(2)H), 4.7 (dd, J = 11.4, 2.2 Hz, 1 H, C(5)H), 4.9 (dd, J = 5.9, 2.2 Hz, 1 H, C(6)H), 5.3 (d, J = 11.4 Hz, 1 H, C(4)H), 6.9 (d, J = 9.0 Hz, 2 H, ArH), 7.3 (s, 5 H, ArH), 7.5 (d, J = 8.9 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.96, 24.35, 55.46, 56.18, 56.87, 65.82, 78.83, 113.99, 123.47, 127.18, 128.48, 128.59, 129.05, 140.88, 157.43, 165.34; exact mass calcd for $C_{20}H_{20}INO_3$ m/e 449.0445, found m/e 449.0466.

[1*S*-(1α,2β,4α,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-4-phenyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (13) and [2*S*-(2α,3α,6β)]-3,6-Dihydro-3-(4-methoxyacetanilido)-2-methyl-6-phenyl-2*H*-pyran (14). From **11a**. To a solution of 100 mg (0.25 mmol) of bromide **11a** in 2 mL of benzene was added 0.05 mL (0.26 mmol) of n-Bu_3SnH in one portion, followed by a catalytic amount (4 mg) of AIBN. The mixture was warmed under reflux with stirring for 1.5 h, concentrated in vacuo, diluted with 50 mL of diethyl ether, and washed with 50 mL of saturated aqueous potassium fluoride. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:6)) to afford 17.2 mg (21%) dihydropyran **14** as a white solid: mp 161–165 °C; $[\alpha] = 284°$ (*c*, 0.29); IR ($CHCl_3$) 3350, 2950, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.28 (d, J = 6.6 Hz, 3 H, CH_3), 2.93 (t, J = 3.5 Hz, 1 H, C(5)H), 3.79 (s, 3 H, OCH_3), 3.88 (qd, J = 6.4, 3.0 Hz, 1 H, C(6)H), 5.48 (s, 1 H, C(2)H), 6.32 (d, J = 2.5 Hz, 2 H, CH=CH), 6.85 (d, J = 9.0 Hz, 2 H, ArH), 7.2–7.5 (m, 7 H, ArH), 8.13 (s, 1 H, NH); exact mass calcd for $C_{20}H_{21}NO_3$ m/e 323.1521, found m/e 323.1539. Further elution afforded 30 mg (37%) of β-lactam **13** as a white solid: mp 104–106 °C; $[\alpha] = 50.64°$ ($CHCl_3$, *c*, 0.31); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.4 Hz, 3 H, CH_3), 2.13 (ddd, J = 15, 12.2, 2.5 Hz, 1 H, C(5)H), 2.6 (ddd, J = 15, 5.1, 2.7 Hz, 1 H, C(5)H), 3.35 (dd, J = 6.0, 2.4 Hz, 1 H, C(1)H), 3.8 (s, 3 H, OCH_3), 4.3–4.5 (m, 2 H, C(2)H, C(6)H), 5.0 (dd, J = 12.1, 5.0 Hz, 1 H, C(4)H), 6.9 (d, J = 9.0 Hz, 2 H, ArH), 7.2–7.4 (m, 5 H, ArH), 7.45 (d, J = 9 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.13 (q), 29.86 (t), 48.93 (d), 53.22 (d), 55.50 (q), 65.88 (d), 70.92 (d), 114.65 (d), 118.13 (d), 125.10 (d), 127.27 (s), 128.46 (d), 131.38 (s), 143.77 (s), 156.15 (s), 164.44 (s); exact mass calcd for $C_{20}H_{21}NO_3$ m/e 323.1522, found m/e 323.1530.

From **11b**. To a slurry of 42 mg (0.1 mmol) of iodide **11b** in 0.5 mL of neat n-Bu_3SnH was added 2 mg of AIBN. The mixture was warmed to 60 °C for 2.5 h, allowed to cool to rt, diluted with 20 mL of diethyl ether, and washed with two 10-mL portions of aqueous saturated aqueous NaF. The organic phase was dried ($MgSO_4$) and concentrated in vacuo, and the residue was washed several times with hexane (to remove excess n-Bu_3SnH) to afford 8.5 mg (26%) of pyran **13** as a white solid (mp 104–106 °C).

From **11c**. To 50 mg (0.10 mmol) of selenide **11c** was added 0.5 mL of neat n-Bu_3SnH and 4 mg of AIBN. The mixture was stirred for 2.5 h at 70 °C. The mixture was diluted with 20 mL of diethyl ether and washed with 10 mL of saturated aqueous NaF. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was washed with copious amounts of hexane to afford 23.4 mg (70%) of pyran **13**, identical to material prepared from **11a** (mp 105–106 °C).

[1*S*-(1α,2β,4β,5α,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-3-oxa-4-phenyl-5-(phenylselenenyl)-7-azabicyclo[4.2.0]octan-8-one (12c) and [1*S*-(1α,2β,4α,5β,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-3-oxa-4-phenyl-5-(phenylselenenyl)-7-azabicyclo[4.2.0]octan-8-one (11c). Method A. To a solution of 100 mg (0.31 mmol) of β-lactam **9** in 2.5 mL of CH_2Cl_2 cooled to −78 °C in a dry ice–acetone bath was added 65 mg (0.34 mmol) of PhSeCl in one portion. The mixture was stirred at −78 °C for 4 h and allowed to warm to rt and stir an additional 20 h. Solvent was removed in vacuo, and the residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:4)) to afford 107 mg (72%) of selenide **12c** as a white solid: mp 164–165 °C; $[\alpha] = -86.7°$ ($CHCl_3$, *c*, 0.84); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.6 (d, J = 6.5 Hz, 3 H, CH_3), 3.4 (dd, J = 5.7, 3.8 Hz, 1 H, C(1)H), 3.56 (dd, J = 7.7, 1.9 Hz, 1 H, C(5)H), 3.74 (s, 3 H, OCH_3), 4.0 (qd, J = 6.5, 3.9 Hz, 1 H, C(2)H), 4.63 (dd, J = 5.7, 1.9 Hz, 1 H, C(6)H), 4.67 (d, J = 7.7 Hz, 1 H, C(4)H), 6.7 (d, J = 10 Hz, 2 H, ArH), 7.0–8.0 (m, 12 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.57 (q), 43.06 (d), 51.38 (d), 55.07 (d), 55.41 (q), 71.20 (d), 83.61 (d), 114.40 (d), 118.66 (d), 126.81 (d), 127.76 (s), 127.93 (d), 128.37 (d), 128.76 (d), 129.38 (d), 129.90 (s), 135.83 (d), 141.30 (s), 156.06 (s), 163.20 (s); exact mass calcd for $C_{26}H_{25}SeNO_3$ m/e 479.0999, found m/e 479.0967. **Method B.** To a solution of 100 mg (0.31 mmol) of β-lactam **9** in 2.0 mL of CH_2Cl_2 cooled to −78 °C in a dry ice–acetone bath was added 200 mg (1.04 mmol) of PhSeCl in one portion. The mixture was allowed to stir for 2.5 h at −78 °C. The mixture was concentrated in vacuo, and the residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:4)) to afford 130 mg (87%) of selenide **11c** as a white solid: mp 123–125 °C; $[\alpha] = -22.9°$ ($CHCl_3$, *c*, 0.99); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.2 Hz, 3 H, CH_3), 3.5 (dd, J = 6.3, 2.5 Hz, 1 H, C(1)H), 3.8 (dd, J = 12.5, 2.5 Hz, 1 H, C(5)H), 3.85 (s, 3 H, OCH_3), 4.55 (qd, J = 6.3, 2.5 Hz, 1 H, C(2)H), 4.95 (dd, J = 6.3, 2.5 Hz, 1 H, C(6)H), 5.10 (d, J = 12.5 Hz, 1 H, C(4)H), 6.59–7.4 (m, 12 H, ArH), 7.51 (d, J = 8 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.91 (q), 46.64 (d), 55.29 (d), 55.40 (q), 56.34 (d), 65.95 (d), 78.10 (d), 114.06 (d), 122.36 (d), 127.42 (d), 127.67 (d), 128.02 (d), 128.11 (d), 128.83 (d), 129.86 (s), 130.01 (s), 134.02 (d), 141.29 (s), 157.17 (s), 165.25 (s); exact mass calcd for $C_{26}H_{25}SeNO_3$ m/e 479.1000, found m/e 479.0986. **Method C.** To a solution of 100 mg (0.31 mmol) of β-lactam **9** and 61 mg (0.6 mmol) of triethylamine in 2.5 mL of CH_2Cl_2 at −78 °C was added 65 mg (0.34 mmol) of PhSeCl. The cold bath was removed, and the mixture was allowed to stir for 16 h. The mixture was diluted with 30 mL of CH_2Cl_2 and washed with 20 mL of water. The aqueous layer was extracted with two 13-mL portions of CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over a Lobar size A silica gel column (EtOAc–hexane (1:7)) to give 10 mg (6%) of selenide **12c** (mp 164–165 °C) and 79 mg (54%) of selenide **11c** (mp 123–124 °C). **Method D.** To a solution of 101 mg (0.31 mmol) of β-lactam **9** in 2 mL of CH_2Cl_2 cooled to 0 °C in an ice bath was added 122 mg (0.40 mmol) of N-PSP and 7 mg of *p*-TsOH in one portion. The mixture was stirred at 0 °C for 1.5 h and allowed to warm to rt and stir an additional 18 h. The solution was filtered through alumina (activity II), solvent was removed in vacuo, and the residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:3)) to afford 68 mg (46%) of selenide **11c** and 76 mg (51%) of selenide **12c**.

[1*S*-(1α,2β,4β,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-4-phenyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (15). To 75 mg (0.16 mmol) of selenide **12c** was added 0.5 mL of neat n-Bu_3SnH and 4 mg of AIBN. The mixture was heated to 80 °C for 2 h. The mixture was diluted with 1 mL of benzene and heated for an additional hour at 80 °C. The mixture was cooled, and 4 mL

of saturated aqueous NaF was added in one portion. The mixture stirred for 12 h, diluted with 30 mL of diethyl ether, and washed with 20 mL of water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The white residue was washed with copious amounts of hexane and chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:5)) to afford 30 mg (59%) of pyran **15** as a white solid: mp 168 °C; $[\alpha]$ = 11.9° ($CHCl_3$, *c*, 0.42); IR ($CHCl_3$), 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.6 (d, J = 6.5 Hz, 3 H, CH_3), 2.05 (ddd, J = 14.2, 10.0, 4.1 Hz, 1 H, C(5)H), 2.45 (ddd, J = 14.6, 7.6, 4.8 Hz, 1 H, C(5)H), 3.3 (m, 1 H, C(1)H), 3.7 (s, 3 H, OCH_3), 4.1 (qu, J = 6.5 Hz, 1 H, C(2)H), 4.4 (m, 1 H, C(6)H), 4.5 (dd, J = 10.0, 4.8 Hz, 1 H, C(4)H), 6.8 (d, J = 9.0 Hz, 2 H, ArH), 7.1–7.4 (m, 7 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.85 (q), 33.31 (t), 48.00 (d), 50.12 (d), 55.46 (q), 72.01 (d), 76.57 (d), 114.39 (d), 117.97 (d), 125.58 (d), 127.38 (s), 128.32 (d), 130.80 (s), 142.42 (s), 155.88 (s), 163.66 (s); exact mass calcd for $C_{20}H_{21}NO_3$ m/e 323.1522, found m/e 323.1509. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.55. Found: C, 74.22; H, 6.64.

[1*S*-(1α,2α,4β,5α,6α)]-5-Bromo-7-(*p*-methoxyphenyl)-2-methyl-3-oxa-4-phenyl-7-azabicyclo[4.2.0]octan-8-one (16a) and [1*S*-(1α,2α,4α,5β,6α)]-5-Bromo-7-(*p*-methoxyphenyl)-2-methyl-3-oxa-4-phenyl-7-azabicyclo[4.2.0]octan-8-one (17a). To a solution of 100 mg (0.31 mmol) of β-lactam **10** in 2.5 mL of CH_2Cl_2 cooled to 0 °C in an ice bath was added 66 mg (0.372 mmol) of NBS in one portion. The mixture was stirred for 2.5 h and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc–hexane (1:6)) to afford 103 mg (83%) of α-bromo ether **16a** as a white solid: mp 107–108 °C; $[\alpha]$ = −79.1° ($CHCl_3$, *c*, 0.23); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.8 Hz, 3 H, CH_3), 3.35 (dd, J = 5.9, 2.9 Hz, 1 H, C(1)H), 3.8 (s, 3 H, OCH_3), 4.25 (dd, J = 10.0, 3.9 Hz, 1 H, C(5)H), 4.7–4.9 (m, 3 H, C(4)H), C(2)H and C(6)H), 6.9 (d, J = 9 Hz, 2 H, ArH), 7.45 (s, 5 H, ArH), 7.5 (d, J = 9 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.89 (q), 49.78 (d), 52.72 (d), 55.48 (q), 57.51 (d), 67.57 (d), 75.06 (d), 114.60 (d), 119.17 (d), 127.26 (d), 128.46 (d), 128.66 (d), 129.84 (s), 139.13 (s), 156.57 (s), 163.80 (s); exact mass calcd for $C_{20}H_{20}BrNO_3$ m/e 401.0626, found m/e 401.0654. Further elution afforded 22 mg (17%) of β-bromo ether **17a** as a white solid: mp 138–139 °C; $[\alpha]$ = 78.6° ($CHCl_3$, *c*, 5.35); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.3 Hz, 3 H, CH_3), 3.35 (dd, J = 7.3, 5.7 Hz, 1 H, C(1)H), 3.78 (s, 3 H, OCH_3), 4.4 (dd, J = 8.9, 5.3 Hz, 1 H, C(5)H), 4.55 (qu, J = 6.3 Hz, 1 H, C(2)H), 4.7 (t, J = 5.6 Hz, 1 H, C(6)H), 4.8 (d, J = 8.9 Hz, 1 H, C(4)H), 6.8 (d, J = 9.0 Hz, 2 H, ArH), 7.35 (m, 7 H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.12 (q), 50.26 (d), 52.20 (d), 54.03 (d), 55.44 (q), 70.54 (d), 79.57 (d), 113.97 (d), 121.79 (d), 127.12 (d), 128.45 (d), 128.66 (d), 130.48 (s), 138.94 (s), 157.03 (s), 166.49 (s); exact mass calcd for $C_{20}H_{20}BrNO_3$ m/e 401.0627, found m/e 401.0638.

[1*S*-(1α,2α,4β,5α,6α)]-5-Iodo-7-(*p*-methoxyphenyl)-2-methyl-3-oxa-4-phenyl-7-azabicyclo[4.2.0]octan-8-one (16b) and [1*S*-(1α,2α,4α,5β,6α)]-5-Iodo-7-(*p*-methoxyphenyl)-2-methyl-3-oxa-4-phenyl-7-azabicyclo[4.2.0]octan-8-one (17b). To a solution of 100 mg (0.31 mmol) of β-lactam **10** in 2.5 mL of dry CH_2Cl_2 cooled to 0 °C in an ice bath was added 90.3 mg (0.40 mmol) of NIS in one portion. The mixture was stirred in the dark for 2 h at 0 °C and was allowed to warm to rt and stir for an additional 24 h. An additional 70 mg (0.31 mmol) of NIS was added, and the solution was allowed to stir for another 24-h period. The mixture was diluted with 20 mL of CH_2Cl_2 and washed with 15 mL of saturated sodium thiosulfate. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc–hexane (1:6)) to afford 74 mg (53%) of the β-iodo ether **16b** as a white solid: mp 115–117 °C; $[\alpha]$ = −105.7° ($CHCl_3$, *c*, 0.26); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.8 Hz, 3 H, CH_3), 3.3 (dd, J = 5.8, 2.7 Hz, 1 H, C(1)H), 3.8 (s, 3 H, OCH_3), 4.35 (dd, J = 10.1, 3.8 Hz, 1 H, C(5)H), 4.8 (qd, J = 6.8, 2.7 Hz, 1 H, C(2)H), 4.9 (d, J = 10.1 Hz, 1 H, C(4)H), 5.0 (dd, J = 5.8, 3.8 Hz, 1 H, C(6)H), 6.9 (d, J = 9 Hz, 2 H, ArH), 7.3 (s, 5 H, ArH), 7.5 (d, J = 9 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.80 (q), 28.53 (d), 52.36 (d), 55.47 (q), 58.73 (d), 67.61 (d), 76.48 (d), 114.59 (d), 119.16 (s), 119.68 (d), 127.31 (d), 128.48 (d), 128.67 (d), 129.54 (s), 139.62 (s), 156.60 (s), 163.95 (s); exact mass calcd for $C_{20}H_{20}INO_3$ m/e 449.0488, found m/e 449.0453. Further elution afforded 32.3 mg (23%) of the β-iodo ether **17b** as a white solid: mp 162–164 °C; $[\alpha]$ = 100.4° ($CHCl_3$, *c*, 0.235); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.2 Hz, 3 H, CH_3), 3.3 (dd, J = 7.4, 5.7 Hz, 1 H, C(1)H), 3.80 (s, 3 H, OCH_3), 4.4 (dd, J = 9.5, 5.3 Hz, 1 H, C(5)H), 4.5 (qu, J = 6.3 Hz, 1 H, C(2)H), 4.65 (t, J = 5.6 Hz, 1 H, C(6)H), 4.85 (d, J = 9.4 Hz, 1 H, C(4)H), 6.9 (d, J = 9.0, 2 H, ArH), 7.3 (d, J = 9.0 Hz, 2 H, ArH), 7.34 (s, 5 H, ArH); exact mass calcd for $C_{20}H_{20}INO_3$ m/e 449.0488, found m/e 449.0522.

[1*S*-(1α,2α,4β,5α,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-3-oxa-4-phenyl-5-(phenylselenenyl)-7-azabicyclo[4.2.0]octan-8-one (16c) and [1*S*-(1α,2α,4α,5β,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-3-oxa-4-phenyl-5-(phenylselenenyl)-7-azabicyclo[4.2.0]octan-8-one (17c). Method A. To a solution of 107 mg (0.33 mmol) of β-lactam **10** in 2.6 mL of CH_2Cl_2 cooled to −78 °C in a dry ice–actone bath was added 70 mg (0.37 mmol) of PhSeCl in one portion. The mixture stirred for 3 h at −78 °C and allowed to warm to rt and stir an additional 21 h. The mixture was concentrated in vacuo, and the residue was chromatographed over 50 g of silica gel (eluted with ethyl acetate–petroleum ether (2:5)) to afford 142 mg (89%) of a 77:23 mixture of selenides **16c** and **17c**, respectively. Recrystallization from CH_2Cl_2–hexane (1:3) gave 86 mg of pure **16c** as a white solid: mp 138–140 °C; $[\alpha]$ = 65.7° ($CHCl_3$, *c*, 0.23); IR ($CHCl_3$) 3000, 1750 cm^{-1}; ^1H NMR (C_6D_6, 250 MHz) δ 1.0 (d, J = 6.7 Hz, 3 H, CH_3), 2.7 (dd, J = 5.9, 3.5 Hz, 1 H, C(1)H), 3.2 (s, 3 H, OCH_3), 3.6 (dd, J = 9.4, 4.0 Hz, 1 H, C(5)H), 4.2 (dd, J = 5.9, 3.9 Hz, 1 H, C(6)H), 4.55 (qd, J = 6.7, 3.5 Hz, 1 H, C(2)H), 4.6 (d, J = 9.4 Hz, 1 H, C(4)H), 6.6–7.6 (m, 14 H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.71 (q), 43.92 (d), 51.54 (d), 54.56 (d), 55.45 (q), 66.80 (d), 74.58 (d), 114.40 (d), 119.56 (d), 127.31 (d), 127.68 (s), 128.08 (d), 128.34 (d), 128.67 (d), 129.22 (d), 129.63 (s), 135.92 (d), 140.77 (s), 156.37 (s), 164.54 (s); exact mass calcd for $C_{26}H_{25}SeNO_3$ m/e 477.1008, found m/e 477.0998. A pure sample of **17c** was not obtained. Its presence in the mixture was inferred from signals in the ^1H-NMR spectrum of the mixture ($CDCl_3$): δ 1.50 (d, J = 7 Hz, CH_3), 3.30 (dd, C(1)H), 3.80 (s, OCH_3). The structure assignment of **19c** was supported by conversion of a mixture of **16c** + **17c** to **18** + **19** (vide infra). **Method B.** To a solution of 100 mg (0.31 mmol) of β-lactam **10** in 2.0 mL of CH_2Cl_2 cooled to −78 °C in a dry ice–actone bath was added 200 mg (1.04 mmol) of PhSeCl in one portion. The mixture stirred for 2.5 h at −78 °C, solvent was removed in vacuo, and the residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:4)) to afford 120 mg (81%) of an 80:20 mixture of selenides **16c** and **17c**, respectively (by NMR). Recrystallization from CH_2Cl_2–hexane (1:3) gave 73 mg of pure **16c** as a white solid. **Method C.** To a solution of 96 mg (0.30 mmol) of β-lactam **10** and 40 mg (0.39 mmol) of triethylamine in 2.6 mL of CH_2Cl_2 cooled to −78 °C in a dry ice–actone bath was added 63 mg (0.33 mmol) of PhSeCl in one portion. The mixture stirred for 3 h at −78 °C and allowed to warm to rt and stir an additional 2 h. Thin-layer chromatography indicated that the reaction was incomplete, and thus an additional 53 mg of PhSeCl was added. Stirring was continued for 19 h, and an additional 52 mg of PhSeCl was added. The mixture was stirred for 5 h and diluted with 30 mL of CH_2Cl_2. The mixture was washed with 20 mL of water, and the aqueous layer was extracted with two 30-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexanes (1:4)) to afford 126 mg (88%) of an 80:20 mixture of selenides **16c** and **17c**, respectively (by NMR). **Method D.** To a solution of 101 mg (0.31 mmol) of β-lactam **10** in 2 mL of CH_2Cl_2 cooled to 0 °C in an ice bath was added 123 mg (0.41 mmol) of N-PSP and 7 mg of *p*-TsOH in one portion. The mixture was stirred at 0 °C for 1.5 h and allowed to warm to rt and stir an additional 15 h. The mixture was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:5)) to afford material contaminated with phthalimide. This material was filtered through alumina (activity II) to give 128 mg (86%) of a 58:42 mixture of selenides **16c** and **17c**, respectively (by NMR).

[1*S*-(1α,2α,4β,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-4-phenyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (18). From **16a**. To a slurry of 48 mg (0.2 mmol) of bromide **16a** in 0.5 mL of n-Bu_3SnH was added 1 mg of AIBN. The mixture was warmed to 80 °C with stirring for 1 h. The mixture was diluted with 10 mL of diethyl ether and washed with 10 mL of aqueous saturated

NaF. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:4)) to afford 22 mg (57%) of pyran **18** as a white solid: mp 118–121 °C; [α] = 49.4° ($CHCl_3$, c, 0.75); IR 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.2 Hz, 3 H, CH_3), 2.0 (ddd, J = 14, 12.5, 9.5 Hz, 1 H, C(5)H), 2.55 (ddd, J = 14, 6.7, 4.1 Hz, 1 H, C(5)H), 3.25 (dd, J = 9.5, 5.7 Hz, 1 H, C(1)H), 3.76 (s, 3 H, OCH_3), 4.35 (m, 1 H, C(2)H), 4.45 (m, 1 H, C(6)H), 4.8 (dd, J = 12.5, 4.1 Hz, 1 H, C(4)H), 6.8 (d, J = 8 Hz, 2 H, ArH), 7.2–7.4 (m, 7 H, ArH); ^{13}C ($CDCl_3$) δ 20.96 (q), 34.03 (t), 48.33 (d), 53.78 (d), 55.50 (q), 66.66 (d), 72.24 (d), 114.52 (d), 117.93 (d), 125.27 (d), 127.64 (d), 128.60 (d), 131.18 (s), 143.24 (s), 156.13 (s), 164.04 (s); exact mass calcd for $C_{20}H_{21}O_3N$ m/e 323.1521; found m/e 323.1487.

From **16b**. To a slurry of 46 mg (0.10 mmol) of iodide **16b** in 0.3 mL of n-Bu_3SnH was added 0.5 mg of AIBN. The mixture was warmed to 70 °C for 20 min, allowed to cool to rt, diluted with 2 mL of CH_2Cl_2, and directly chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:3)) to give 13 mg (40%) of pyran **18** as a white solid (mp 115–118 °C).

From **16c**. To a slurry of 20 mg (0.04 mmol) selenide **16c** in 0.5 mL of n-Bu_3SnH was added 0.5 mg of AIBN. The mixture was warmed to 70 °C and stirred for 2 h. The mixture was diluted with 10 mL of diethyl ether and washed with 10 mL of saturated aqueous NaF. The aqueous phase was extracted with two 10-mL portions of diethyl ether. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was washed with copious amounts of hexane to afford 8 mg (59%) of pyran **18** as a white solid (mp 115–118 °C).

[1*S*-(1α,2α,4α,6α)]-7-(*p*-Methoxyphenyl)-2-methyl-4-phenyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (19). From **17a**. To a slurry of 20 mg (0.05 mmol) of bromide **17a** in 0.3 mL of neat n-Bu_3SnH was added 0.5 mg of AIBN. The mixture was warmed to 100 °C for 2 h, allowed to cool to rt, and directly chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:3)) to afford 7 mg (48%) of pyran **19** as a white solid: mp 134–136 °C; [α] = 80.6° ($CHCl_3$, c, 0.33); IR (CCl_4), 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (d, J = 6.3 Hz, 3 H, CH_3), 2.0 (ddd, J = 14.8, 10.8, 5.8 Hz, 1 H, C(5)H), 2.4 (ddd, J = 14.8, 3.2, 2 Hz, 1 H, C(5)H), 3.14 (t, J = 5.7 Hz, 1 H, C(1)H), 3.80 (s, 3 H, OCH_3), 4.3 (qu, J = 6.4 Hz, 1 H, C(2)H), 4.4 (td, J = 5.7, 2 Hz, 1 H, C(6)H), 4.58 (dd, J = 10.8, 3.1 Hz, 1 H, C(4)H), 6.9 (d, J = 8 Hz, 2 H, ArH), 7.2–7.45 (m, 7 H, ArH); ^{13}C ($CDCl_3$) δ 23.57 (q), 32.25 (t), 48.59 (d), 50.93 (d), 55.53 (q), 71.22 (d), 73.74 (d), 114.64 (d), 118.45 (d), 125.74 (d), 127.68 (d), 128.48 (d), 130.57 (s), 141.86 (s), 156.28 (s), 165.73 (s); exact mass calcd for $C_{20}H_{21}O_3N$ m/e 323.1522, found m/e 323.1537.

From **17b**. To a slurry of 27 mg (0.06 mmol) of iodide **17b** in 0.5 mL of n-Bu_3SnH was added 0.5 mg of AIBN. The mixture was warmed to 70 °C and stirred for 20 min. The solution was allowed to cool to rt and directly chromatographed over 20 g of silica gel (eluted with EtOAc–hexane (1:4)) to afford 10.5 mg (54%) of pyran **19** as a white solid (mp 134–136 °C).

From **16c** + **17c**. To a slurry of 53 mg (0.11 mmol) of a 3:1 mixture of **16c** and **17c**, respectively, was added 0.5 mL of n-Bu_3SnH and 0.5 mg of AIBN. The mixture was warmed to 80 °C for 2.8 h. The solution was allowed to cool to rt, diluted with 20 mL of ether, and washed with 10 mL of saturated aqueous NaF. The aqueous phase was extracted with two 10-mL portions of ether, and the combined ether layers were dried ($MgSO_4$). Solvent was removed in vacuo, and the residue was chromatographed over 10 g of silica gel (eluted with EtOAc–hexane (1:3)) to afford 12 mg (33%) of a 3:1 mixture of **18** and **19**, respectively (by NMR).

***rel*-[3*S*,4*S*(*E*)]-3-(Hydroxymethyl)-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (20) and *rel*-[3*R*,4*S*(*E*)]-3-(Hydroxymethyl)-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (3-*epi*-20).** To a solution of 2.70 g (26.7 mmol) of diisopropylamine in 45 mL of dry THF cooled to −78 °C was added 17.3 mL (26.0 mmol) of 1.5 M n-BuLi in hexanes. The mixture was stirred 1 h, and 1.5 g (12.7 mmol) of ethyl 3-hydroxypropanoate in 25 mL of THF was added dropwise over a period of 1 h. The solution was stirred for 1 h, and 3.31 g (14.0 mmol) of N-(p-methoxyphenyl)cinnamaldimine was added in one portion. The solution was stirred at −78 °C for 1 h and at rt for 18 h. The black mixture was diluted with 170 mL of CH_2Cl_2 and washed with two 150-mL portions of 1 M aqueous HCl. The aqueous washes were extracted with two 150-mL portions of CH_2Cl_2. The organic phases were dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed over 250 g of silica gel (EtOAc–hexane (1:1)) to give 1.54 g (39%) of a 4:1 mixture (NMR) of trans and cis β-lactams, respectively. Extensive chromatography of this material, followed by recrystallization of appropriate fractions from ether, gave 3-*epi*-**20** as a white solid: mp 121.5–122.5 °C; IR ($CHCl_3$) 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.4 (broad s, 1 H, OH), 3.3 (m, 1 H, CHCO), 3.75 (s, 3 H, OCH_3), 3.95 (dd, J = 12, 4 Hz, 1 H, CHOH), 4.1 (dd, J = 12, 4.6 Hz, 1 H, CHOH), 4.7 (dd, J = 8.4, 2 Hz, 1 H, NCH), 6.3 (dd, J = 16, 8 Hz, 1 H, CH=), 6.7–6.9 (m, 3 H, =CHPh and ArH), 7.2–7.4 (m, 7 H, ArH); ^{13}C NMR ($CDCl_3$) δ 55.4 (q), 56.7 (d), 58.6 (t), 59.5 (d), 114.3 (d), 118.4 (d), 126.6 (d), 126.7 (d), 128.3 (d), 128.7 (d), 131.5 (s), 134.3 (d), 135.7 (s), 156.1 (s), 164.9 (s). Extensive chromatography also gave 58 mg of impure **20** (20% 3-*epi*-**20** by NMR) that was used in subsequent reactions. Recrystallization of a small portion of this material from ether gave pure **20** as a white solid: mp 125–126 °C; IR ($CHCl_3$, mixture) 1736 cm^{-1}; ^1H NMR ($CHCl_3$, pure) δ 1.75 (broad s, 1 H, OH), 3.7 (m, 1 H, CHCO), 3.8 (s, 3 H, OCH_3), 4.05 (m, 2 H, CH_2O), 4.8 (dd, J = 8, 6 Hz, 1 H, NCH), 6.5 (dd, J = 16, 8 Hz, 1 H, CH=), 6.8 (m, 3 H, =CHPh and ArH), 7.2–7.5 (m, 7 H, ArH); ^{13}C ($CDCl_3$, 62.9 MHz, signals due to **20** in mixture) δ 55.4 (q), 56.6 (d), 57.0 (d), 57.8 (t), 114.3 (d), 118.3 (d), 124.3 (d), 126.6 (d), 128.3 (d), 128.7 (d), 131.6 (s), 135.6 (d), 135.8 (s), 156.1 (s), 164.8 (s).

***rel*-(1α,4β,5α,6α)-5-Bromo-7-(*p*-methoxyphenyl)-4-phenyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (21b) and *rel*-(1α,4α,5β,6α)-5-Bromo-7-(*p*-methoxyphenyl)-4-phenyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (21a).** To a solution of 20 mg (0.065 mmol) of β-lactam **20** (20% 3-*epi*-**20** by NMR) in 0.7 mL of CH_2Cl_2 at 0 °C was added 12 mg (0.068 mmol) of N-bromosuccinimide in one portion. The solution was stirred for 30 min, warmed to rt, and stirred an additional 17 h. Solvent was removed in vacuo and the residue was chromatographed over 20 g of silica gel (EtOAc–hexane (1:3 followed by 1:2)) to afford 4.8 mg (19%) of slightly impure **21b** as a yellow oil: IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.6 (t, J = 5.5 Hz, 1 H, C(1)H), 3.8 (s, 3 H, OCH_3), 4.05 (dd, J = 13, 5 Hz, 1 H, $C(2)_\beta H$), 4.2 (dd, J = 9.5, 2.3 Hz, 1 H, C(5)H), 4.5 (d, J = 9.5 Hz, 1 H, C(4)H), 4.7 (d, J = 13 Hz, 1 H, $C(2)_\alpha H$), 4.8 (dd, J = 5.8, 2.3 Hz, 1 H, C(6)H), 6.9 (bd, J = 9 Hz, 2 H, ArH), 7.3 (s, 5 H, ArH), 7.5 (d, J = 9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.8 (d), 49.4 (d), 55.5 (q), 57.3 (d), 65.2 (t), 83.8 (d), 114.7 (d), 118.6 (d), 127.0 (d), 128.4 (d), 128.7 (d), 130.0 (s), 138.8 (s), 156.5 (s), 163.5 (s); relevant NOE data for **21b** (proton irradiated → NOE observed): $H_1 \rightarrow H_{2\beta}$ (6%), $H_{2\alpha}$ (2%), H_6 (9%); $H_{2\alpha} \rightarrow H_{2\beta}$ (24%), H_1 (3%); $H_{2\beta} \rightarrow H_{2\alpha}$ (28%), H_1 (8%), H_4 (12%); $H_4 \rightarrow H_{2\beta}$ (7%), H_5 (2%), H_6 (2%); $H_5 \rightarrow H_4$ (2%), H_6 (3%); $H_6 \rightarrow H_1$ (8%), H_5 (3%), H_4 (1%). Further elution afforded 16.2 mg (64%) of slightly impure **21a** as a white solid. A small portion was recrystallized from diethyl ether to provide a pure sample: mp 154 °C; IR ($CHCl_3$) 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.7 (m, 1 H, C(1)H), 3.8 (s, 3 H, OCH_3), 4.3 (dd, J = 13, 5 Hz, 1 H, $C(2)_\beta H$), 4.35 (dd, J = 13, 3.4 Hz, 1 H, $C(2)_\alpha H$), 4.6 (dd, J = 10.6, 3.2 Hz), 1 H, C(5)H), 4.9 (dd, J = 6, 3.2 Hz, 1 H, C(6)H), 5.0 (d, J = 10.5 Hz, 1 H, C(4)H), 6.9 (d, J = 9 Hz, 2 H, ArH), 7.35 (s, 5 H, ArH), 7.5 (d, J = 9 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 49.0 (d), 50.8 (d), 53.8 (d), 55.4 (q), 60.8 (t), 77.5 (d), 114.0 (d), 122.0 (d), 127.1 (d), 128.5 (d), 128.7 (d), 130.2 (s), 139.5 (s), 157.1 (s), 166.1 (s); relevant NOE data for **21a** (proton irradiated → NOE observed): $H_1 \rightarrow H_{2\alpha} + H_{2\beta}$ (7%), H_5 (2%), H_6 (4%); $H_{2\alpha} + H_{2\beta} \rightarrow H_1$ (8%), H_4 (2%), H_5 (3%); $H_4 \rightarrow H_{2\alpha}$ (2%), H_5 (1%); $H_5 \rightarrow H_{2\beta}$ (2%), H_5 (3%), H_6 (5%); $H_6 \rightarrow H_1$ (10%), H_5 (12%).

***rel*-(3*S*,4*R*,5*S*)-Dihydro-4-hydroxy-3,5-dimethyl-2-(3*H*)-furanone (28).** To a solution of 1.00 g (3.92 mmol) of iodolactone **27** in 10 mL of benzene was added 1.11 mL (6.24 mmol) of n-Bu_3SnH and 5 mg of AIBN. The solution was warmed under reflux for 6 h followed by addition of 10 mL of CCl_4 and additional stirring for 12 h. The solution was concentrated in vacuo, and the residue was chromatographed over 100 g of silica gel (eluted with EtOAc–petroleum ether (1:2)) to afford 450 mg (88%) of furanone **28** as a white solid: mp 54–55 °C; IR (CH_2Cl_2) 3600–3500 (br), 2920, 1770 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.2 (d, J = 7.4 Hz, 3 H, CH_3), 1.45 (d, J = 7.4 Hz, 3 H, CH_3), 2.7 (m, 2 H, C(3)H and OH), 4.25 (m, 1 H, C(4)H), 4.5 (m, 1 H, C(5)H);

^{13}C NMR ($CDCl_3$) δ 7.95 (q), 13.58 (q), 42.24 (d), 72.10 (d), 79.33 (d), 179.07 (s); exact mass calcd for $C_6H_{10}O_3$ *m/e* 130.0630, found *m/e* 130.0671. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.29; H, 7.78.

***rel*-(3*S*,4*R*,5*S*)-Dihydro-4-(methoxymethoxy)-3,5-dimethyl-2-(3*H*)-furanone (29).** To a solution of 474 mg (3.65 mmol) of furanone **28** in 6 mL of CH_2Cl_2 at 0 °C was added 0.58 mL (7.3 mmol) of chloromethyl methyl ether followed by 1.35 mL (7.3 mmol) of diisopropylethylamine. The solution was allowed to warm to rt and stir for 72 h. The mixture was diluted with 100 mL of CH_2Cl_2 and washed with 50 mL of water. The aqueous phase was extracted with three 50-mL portions of CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc–hexane (1:2)) to afford 600 mg (94%) of **29** as a clear colorless liquid: IR (CH_2Cl_2) 2950, 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.42 (d, *J* = 6.5 Hz, 3 H, CH_3), 2.75 (dq, *J* = 7.2, 5.3 Hz, 1 H, C(3)H), 3.42 (s, 3 H, OCH_3), 4.22 (dd, *J* = 5.3, 3.4 Hz, 1 H, C(4)H), 4.5 (dq, *J* = 6.5, 3.4 Hz, 1 H, C(5)H), 4.65 (s, 2 H, OCH2O); ^{13}C NMR ($CDCl_3$) δ 8.47 (q), 14.09 (q), 41.29 (d), 55.98 (q), 77.70 (d), 78.21 (d), 96.82 (t); exact mass calcd for $C_8H_{14}O_4$ *m/e* 174.0892, found *m/e* 174.0880.

***rel*-(3*S*,4*R*,5*R*)-Tetrahydro-4-(methoxymethoxy)-3,5-dimethyl-2-furanol (30).** To a solution of 511 mg (2.94 mmol) of lactone **29** in 10 mL of toluene at −78 °C was added 2.35 mL (3.5 mmol) of DIBAH (1.5 M in toluene) over a 5-min period via syringe. The mixture was stirred for 10 min at −78 °C and quenched with 1 mL of 3 N aqueous NaOH. The solution was filtered through a cake of Celite, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc–petroleum ether (1:1)) to afford 420 mg (81%) of a roughly 2:1 (^1H NMR) mixture of anomers **30** as a clear colorless oil: IR (CH_2Cl_2) 3585, 3400 cm^{-1}; ^1H NMR (C_6D_6, 250 MHz) peaks due to major diastereomer: δ 1.05 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.20 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.19 (m, 1 H, C(3)H), 3.10 (s, 3 H, OCH_3), 3.68 (m, 1 H, C(4)H), 4.25 (dq, *J* = 6.4, 3.4 Hz, 1 H, C(5)H), 4.33 (q AB, *J* = 6.8 Hz, 2 H, OCH_2O), 4.43 (d, *J* = 3.9 Hz, 1 H, OH), 5.29 (dd, *J* = 5.2, 3.9 Hz, 1 H, C(2)H); peaks due to minor diastereomer: δ 0.95 (d, *J* = 7.1 Hz, 3 H, CH_3), (d, *J* = 6.4 Hz, 3 H, CH_3), 1.65 (m, 1 H, C(3)H), 3.03 (s, 3 H, OCH_3), 3.3 (d, *J* = 11.8 Hz, 1 H, OH), 3.38 (t, *J* = 3.8 Hz, 1 H, C(4)H), 3.68 (m, 1 H, C(5)H), 4.18 (q AB, *J* = 3 Hz, 2 H, OCH_2O), 5.1 (dd, *J* = 11.7, 4.9 Hz, 1 H, C(2)H); ^{13}C NMR (C_6D_6) peaks due to major diastereomer: δ 11.15 (q), 15.48 (q), 46.90 (d), 55.58 (q), 77.32 (d), 81.55 (d), 97.09 (t), 103.91 (d); peaks due to minor diastereomer: δ 8.95 (q), 16.66 (q), 43.52 (d), 55.72 (q), 78.59 (d), 80.86 (d), 96.92 (t), 100.41 (d).

***rel*-(2*R*,3*R*,4*R*)-*trans*-5-(*p*-Methoxyphenyl)-3-(methoxymethoxy)-4-methyl-1-hex-5-en-1-ol (24a).** To a solution of 1.5 g (6.4 mmol) of diethyl (4-methoxybenzyl)phosphonate in 15 mL of DME at −78 °C was added 4.1 mL (6.4 mmol) of *n*-BuLi (1.55 M in hexanes) slowly via syringe. The solution was stirred for 1 h, and a solution of 377 mg (2.14 mmol) of lactol **30** in 5 mL of DME was added. The mixture was warmed to rt, stirred for 30 min, diluted with 100 mL of EtOAc, and washed with 50 mL of water. The aqueous layer was extracted with five 50-mL portions of EtOAc. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc–petroleum ether (2:1), followed by EtOAc) to afford 630 mg (68%) of a β-hydroxy phosphonate ester as a yellowish oil.

To a solution of 630 mg (1.45 mmol) of the β-hydroxy phosphonate in 5 mL of benzene at 5 °C was added 108 mg (4.5 mmol) of NaH in one portion. The mixture was heated to reflux for 30 min, cooled to rt, diluted with 100 mL of CH_2Cl_2, and washed with 75 mL of water. The aqueous phase was extracted with three 50-mL portions of CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc–petroleum ether (1:2)) to afford 193 mg (32% from **30**) of olefin **24a** as an oil: IR (CH_2Cl_2) 3680, 3600, 3460, 2950 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.55 (m, 1 H, ═CCH), 3.17 (dd, *J* = 7.0, 3.3 Hz, 1 H, C(3)H), 3.44 (s, 3 H, OCH3), 3.7 (qu, *J* = 6.5 Hz, 1 H, C(2)H), 3.79 (s, 3 H, $ArOCH_3$), 4.67 (d, *J* = 6.6 Hz, 1 H, OCH_2O), 4.81 (d, *J* = 6.6 Hz, 1 H, OCH_2O), 6.07 (dd, *J* = 16, 8.6 Hz, 1 H, C(5)H), 6.28 (d, *J* = 16 Hz, 1 H, C(6)H), 6.8 (d, *J* = 9 Hz, 2 H, ArH), 7.26 (d, *J* = 9 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.37 (q), 18.90 (q), 39.50 (d), 55.23 (q), 55.92 (q), 68.38 (d), 90.91 (d), 99.00 (t), 113.87 (d), 127.15 (d), 128.76 (d), 129.69 (d), 130.28 (s), 158.83 (s); exact mass calcd for $C_{16}H_{24}O_4$ *m/e* 280.1674, found *m/e* 280.1692.

***rel*-(2*R*,3*R*,4*S*,5*R*,6*S*)-Tetrahydro-3-(methoxymethoxy)-6-(*p*-methoxyphenyl)-2,4-dimethyl-5-(phenylselenenyl)-2*H*-pyran (23a).** To a solution of 193 mg (0.69 mmol) of enol **24a** in 6 mL of CH_2Cl_2 at −78 °C was added 263 mg (1.38 mmol) of PhSeCl in one portion. The mixture was stirred for 30 min, diluted with 100 mL of CH_2Cl_2, and washed with 50 mL of saturated $NaHCO_3$. The aqueous phase was extracted with two 50-mL portions of CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with EtOAc–petroleum ether (1:5)) to afford 221 mg (74%) of selenide **23a** as a yellow oil: IR (CH_2Cl_2) 3000 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.39 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.88 (m, 1 H, C(4)H), 3.16 (t, *J* = 11.8 Hz, 1 H, C(5)H), 3.43 (dd, *J* = 11.2, 8.5 Hz, 1 H, C(3)H), 3.47 (s, 3 H, OCH_3), 3.63 (q, *J* = 6.5 Hz, 1 H, C(2)H), 3.77 (s, 3 H, OCH_3), 4.74 (d, *J* = 10.8 Hz, 1 H, C(6)H), 4.75 (dd, *J* = 9.5, 6.8 Hz, 2 H, OCH_2O), 6.75 (d, *J* = 8.6 Hz, 2 H, ArH), 7.15 (m, 5 H, ArH), 7.3 (d, *J* = 8.6 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.08 (q), 18.18 (q), 41.11 (d), 52.48 (d), 55.23 (q), 56.39 (q), 76.06 (d), 80.58 (d), 84.68 (d), 98.79 (t), 113.35 (d), 127.37 (d), 128.40 (s), 128.47 (d), 129.38 (d), 133.17 (s), 135.48 (d), 159.21 (s); exact mass calcd for $C_{22}H_{28}O_4$ *m/3* 436.1152, found *m/e* 436.1127.

***rel*-(2*R*,3*R*,6*R*)-3,6-Dihydro-3-(methoxymethoxy)-6-(*p*-methoxyphenyl)-2,4-dimethyl-2*H*-pyran (32a).** To a solution of 90 mg (0.21 mmol) of selenide **23a** in 2 mL of THF at 0 °C was added 0.20 mL (2.0 mmol) of 30% of H_2O_2, followed by 33 μL (0.41 mmol) of pyridine. The solution was stirred for 30 min at 0 °C and allowed to warm to rt with 8 h of additional stirring. The solution was diluted with 40 mL of CH_2Cl_2 and washed with 20 mL of water. The aqueous phase was extracted with two 30-mL portions of CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with EtOAc–petroleum ether (1:5)) to afford 45 mg (79%) of olefin **32a** as a clear colorless oil: IR (CH_2Cl_2) 2940, 1615, 1520 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.35 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.88 (t, *J* = 2 Hz, CH_3), 3.46 (s, 3 H, OCH_3), 3.61 (t, *J* = 1.9 Hz, 1 H, C(3)H), 3.8 (s, 3 H, $ArOCH_3$), 3.80 (m, 1 H, C(2)H), 4.75 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.89 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.97 (d, *J* = 2.0 Hz, 1 H, C(5)H), 5.65 (t, *J* = 1.5 Hz, 1 H, C(6)H), 6.88 (d, *J* = 8.7 Hz, 2 H, ArH), 7.28 (d, *J* = 8.7 Hz, 2 H, ArH); ^{13}C NMR (C_6D_6) δ 17.44 (q), 21.04 (q), 54.73 (q), 55.63 (q), 73.94 (d), 75.61 (d), 77.85 (d), 97.06 (t), 114.03 (d), 128.94 (d), 129.63 (d), 132.11 (s), 134.38 (s), 159.78 (s); exact mass calcd for $C_{16}H_{22}O_4$ *m/e* 278.1491, found *m/e* 278.1521.

***rel*-(2*S*,3*S*,4*S*,5*S*,6*R*)-Tetrahydro-5-(methoxymethoxy)-2-(*p*-methoxyphenyl)-4,6-dimethyl-2*H*-pyran-3,4-diol (33a).** To a solution of **30** mg (0.11 mmol) of olefin **32a** in 4 mL of acetone was added 14 mg (0.12 mmol) of *N*-methylmorpholine *N*-oxide, followed by 0.28 mL (0.01 mmol) of 1% wt OsO_4 in water. The mixture was stirred for 48 h, and 250 mg of solid sodium thiosulfate was added followed by 5 mL of water and 500 mg of Celite. The slurry was allowed to stir for 3 h and filtered, and the filter cake was rinsed with 150 mL of EtOAc. The filtrate was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with EtOAc–petroleum ether (2:1)) to afford 30 mg (88%) of C-aryl glycoside **33a** as a clear colorless oil. A portion of the oil was crystallized from CH_2Cl_2–hexane to afford a white solid suitable for X-ray crystallographic analysis: mp 110–111 °C; IR (CH_2Cl_2) 3580, 2900 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.7 (br s, 1 H, OH), 2.4 (br s, 1 H, OH), 3.31 (s, 1 H, C(5)H), 3.46 (s, 3 H, OCh_3), 3.58 (d, *J* = 9.5 Hz, 1 H, C(3)H), 3.7 (s, 3 H, $ArOCH_3$), 4.21 (q, *J* = 6.5 Hz, 1 H, C(6)H), 4.33 (d, *J* = 9.5 Hz, 1 H, C(2)H), 4.7 (d, *J* = 6.8 Hz, 1 H, OCH_2O), 4.75 (d, *J* = 6.8 Hz, 1 H, OCH_2O), 6.87 (d, *J* = 8.7 Hz, 2 H, ArH), 7.35 (d, *J* = 8.7 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.12 (q), 23.70 (q), 55.27 (q), 56.67 (q), 71.22 (d), 72.77 (s), 73.46 (d), 78.75 (d), 83.23 (d), 99.03 (t), 113.98 (d), 128.99 (d), 131.45 (s), 159.60 (s);

exact mass calcd for $C_{16}H_{24}O_6$ *m/e* 312.1519, found *m/e* 312.1579. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.51; H, 7.75. Found: C, 61.27; H, 7.69.

***rel*-(2*S*,3*S*,4*S*,5*S*,6*R*)-Tetrahydro-2-(*p*-methoxyphenyl)-4,6-dimethyl-2*H*-pyran-3,4,5-triol (22).** To a solution of 6 mg (0.02 mmol) of ether **33a** in 1 mL of THF was added 10 drops of aqueous 2 N HCl. The mixture was warmed under reflux for 2 h, allowed to cool to rt, diluted with 30 mL of CH_2Cl_2, and washed with 10 mL of saturated $NaHCO_3$. The aqueous phase was extracted with two 20-mL portions of CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was chromatographed over 1 g of silica gel (eluted with EtOAc–hexane (1:1)) to give 3.5 mg (69%) of C-aryl glycoside **22a** as a white oily solid: IR (CH_2Cl_2) 3700, 3000 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (d, J = 6.6 Hz, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.55 (br s, 1 H, OH), 1.92 (br d, J = 8.3 Hz, 1 H, OH), 2.25 (br s, 1 H, OH), 3.36 (br d, J = 7 Hz, 1 H, C(5)H), 3.6 (br d, J = 9.5 Hz, 1 H, C(3)H), 3.8 (s, 3 H, OCH_3), 4.29–4.40 (m, 2 H, C(2)H and C(6)H), 6.9 (d, J = 8.8 Hz, 2 H, ArH), 7.3 (d, J = 8.8 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 16.61 (q), 23.76 (q), 55.33 (q), 71.46 (d), 72.68 (s), 73.16 (d), 76.12 (d), 79.46 (d), 114.17 (d), 128.74 (d), 131.16 (s), 159.80 (s); exact mass calcd for $C_{14}H_{20}O_5$ *m/e* 268.1311, found *m/e* 268.1289.

Diethyl (3-Iodo-4-methoxybenzyl)phosphonate (34). A solution of 28.2 g (100 mmol) of 3-iodo-4-methoxybenzyl chloride in 100 mL of triethylphosphite was heated at 160 °C for an 8-h period. The resulting solution was cooled to rt, and the lower boiling materials were removed via Kugelrohr distillation at 120 °C (1.5 mmHg) to afford 37.2 g (97%) of **34** as a residual yellow-green oil. The resulting material was used in subsequent reactions without further purification. Crystallization from THF–pentane, however, afforded pure **34** as a colorless solid: mp 42–44 °C; IR ($CHCl_3$) 2981, 1494, 1392, cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.12 (t, J = 7 Hz, 6 H, CH_3), 3.04 (d, J = 22 Hz, 2 H, PCH_2), 3.85 (s, 3 H, OCH_3), 4.01 (m, 4 H, OCH_2), 6.75 (d, J = 9.5 Hz, 1 H, Ar(5)-H), 7.25 (dt, J = 6.4, 2.3 Hz, 1 H, Ar(6)-H), 7.68 (t, J = 1.1 Hz, 1 H, Ar(2)-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 15.99 (dq, $J_{C,P}$ = 6.0 Hz), 31.71 (dt, $J_{C,P}$ = 139 Hz), 55.96 (q), 61.70 (dt, $J_{C,P}$ = 6.9 Hz), 85.36 (ds, $J_{C,P}$ = 3.5 Hz), 110.45 (d), 125.29 (ds, $J_{C,P}$ = 8.8 Hz), 130.39 (dd, $J_{C,P}$ = 6.3 Hz), 140.96 (dd, $J_{C,P}$ = 6.3 Hz), 156.71 (s); exact mass calcd for $C_{12}H_{16}IO_4$ *m/e* 383.9990, found *m/e* 383.9977. Anal. Calcd for $C_{12}H_{16}IO_4$: C, 37.52; H, 4.71. Found: C, 37.61; H, 4.72.

***rel*-(2*R*,3*R*,4*S*)-*trans*-6-(*m*-Iodo-*p*-methoxyphenyl)-3-(methoxymethoxy)-4-methyl-5-hexen-2-ol (24b).** To a solution of 0.38 mL (273 mg, 2.7 mmol) of diisopropylamine in 12 mL of THF at −78 °C was added 1.69 mL (2.5 mmol) of *n*-BuLi (1.48 M solution in hexanes) in two portions via syringe. The resulting solution was stirred for 20 min at −78 °C, warmed to −20 °C over a 1-h period, and held at that temperature for 1 h before being recooled to −78 °C. To the resulting solution of lithium diisopropylamide was added a solution of phosphonate **34** in 10 mL of THF such that the temperature of the resulting solution did not exceed −75 °C. This solution was stirred at −75 °C or below for 45 min and then cooled to −85 °C, and a solution of 176 mg (1.0 mmol) of lactol **30** in 4 mL of THF was added dropwise over 10 min. The resulting solution was stirred at −80 °C or below for 30 min and then warmed to rt and stirred overnight. The reaction mixture was diluted with 200 mL of EtOAc and washed with 30 mL of water. The aqueous layer was extracted with three 200-mL portions of EtOAc, and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether–EtOAc (7:1)) to afford 106 mg (27%) of enol **24b** as a yellow oil which crystallized on standing to give a white solid: mp 67–68 °C; IR ($CHCl_3$) 3458 (broad), 3010, 2964, 2934, 1594, 1490, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15 (m, 6 H, CH_3), 2.57 (m, 1 H, C(4)-H), 3.18 (dd, J = 7.1, 3.3 Hz, 1 H, C(3)-H), 3.29 (bs, 1 H, OH), 3.45 (s, 3 H, OCH_3), 3.69 (qu, J = 6.6 Hz, 1 H, C(2)-H), 3.87 (s, 3 H, $ArOCH_3$), 4.69 (d, J = 6.6 Hz, 1 H, OCH_2O), 4.83 (d, J = 6.6 Hz, 1 H, OCH_2O), 6.08 (dd, J = 16, 8.5 Hz, 1 H, C(5)-H), 6.23 (d, J = 16 Hz, 1 H, C(6)-H), 6.74 (d, J = 8.5 Hz, 1 H, Ar(5)-H), 7.26 (dd, J = 8.5, 2.1 Hz, 1 H, Ar(6)-H), 7.80 (d, J = 2.1 Hz, 1 H, Ar(2)-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 18.38 (q), 18.93 (q), 39.51 (d), 56.02 (q), 56.42 (q), 68.40 (d), 86.25 (s), 90.91 (d), 99.10 (t), 110.73 (d), 127.37 (d), 128.33 (d), 130.19 (d), 132.37 (s), 136.80 (d), 157.27 (s); exact mass calcd for $C_{16}H_{23}IO_4$ *m/e* 406.0641, found *m/e* 406.0641. Anal. Calcd for $C_{16}H_{23}IO_4$: C, 47.30; H, 5.71. Found: C, 47.26; H, 5.71.

***rel*-(2*R*,3*R*,4*S*,5*R*,6*S*)-Tetrahydro-6-(*m*-iodo-*p*-methoxyphenyl)-3-(methoxymethoxy)-2,4-dimethyl-5-(phenylselenenyl)-2*H*-pyran (23b).** To a solution of 30 mg (74 μmol) of enol **24b**, in 0.80 mL of CH_2Cl_2 at −78 °C, was added 27 mg (0.14 mmol) of PhSeCl in a single portion. The resulting solution was stirred 1.5 h at −78 °C, diluted with 3 mL of CH_2Cl_2, and washed with 1.5 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with three 7-mL portions of CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with petroleum ether–EtOAc (5:1)) to afford 29.6 mg (75%) of selenide **23b** as a colorless oil. Upon exposure to methanol the oil solidified giving selenide **83** as a white solid: mp 116–122 °C. Although this material was used without further purification, an analytically pure sample was prepared by recrystallization from methanol: mp 126–127 °C; IR ($CHCl_3$) 3006, 2959 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.22 (d, J = 6.5 Hz, 3 H, CH_3), 1.41 (d, J = 6.7 Hz, 3 H, CH_3), 1.82–1.90 (m, 1 H, C(4)-H), 3.14 (dd, J = 11.9, 10.8 Hz, 1 H, C(5)-H), 3.43 (m, 1 H, C(3)-H), 3.48 (s, 3 H, OCH_3), 3.64 (dq, J = 6.5, 0.9 Hz, 1 H, OCH_2), 4.76 (d, J = 6.9 Hz, 1 H, CH_2), 6.60 (d, J = 8.5 Hz, 1 H, Ar(5)-H), 7.05–7.20 (m, 5 H, SeAr-H), 7.24 (dd, J = 8.5, 2.1 Hz, 1 H, Ar(6)-H), 7.68 (d, J = 2.1 Hz, 1 H, Ar(2)-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 17.98 (q), 18.17 (q), 40.85 (d), 52.22 (d), 56.32 (q), 56.41 (q), 76.21 (d), 80.38 (d), 84.39 (d), 85.59 (s), 98.79 (t), 110.11 (d), 127.35 (d), 128.45 (d), 129.61 (s), 134.98 (d), 135.07 (d), 138.99 (d), 157.59 (s), one aromatic singlet was not observed; exact mass calcd for $C_{22}H_{27}IO_4{}^{80}Se$ *m/e* 562.0087, found *m/e* 562.0103. Anal. Calcd for $C_{22}H_{27}IO_4Se$: C, 47.08; H, 4.85. Found: C, 46.96; H, 4.90.

***rel*-(2*R*,3*R*,6*R*)-3,6-Dihydro-6-(*m*-iodo-*p*-methoxyphenyl)-3-(methoxymethoxy)-2,4-dimethyl-2*H*-pyran (32b).** To a solution of 70 mg (0.13 mmol) of selenide **23b** in 2.0 mL of THF at 0 °C was added 123 μL (1.25 mmol) of 30% aqueous H_2O_2 followed by 19.6 μL (0.25 mmol) of pyridine. The resulting solution was stirred at 0 °C for 30 min and then warmed to rt and stirred for 8 h. The reaction mixture was diluted with 45 mL of CH_2Cl_2 and washed with 25 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with three 50-mL portions of CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether–EtOAc (5:1)) to afford 35 mg (69%) of olefin **32b** as a light brown oil that foamed under vacuum: IR (neat) 3010, 2953 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.33 (d, J = 6.5 Hz, 3 H, CH_3), 1.80 (m, 3 H, $=CCH_3$), 3.46 (s, 3 H, OCH_3), 3.59 (d, J = 1.6 Hz, 1 H, C(3)-H), 3.70–3.82 (m, 1 H, C(2)-H), 3.85 (s, 3 H, $ArOCH_3$), 4.75 (d, J = 6.7 Hz, 1 H, OCH_2), 4.85 (d, J = 6.7 Hz, 1 H, OCH_2), 4.93 (d, J = 1.8 Hz, 1 H, C(6)-H), 5.60 (m, 1 H, =CH), 6.80 (d, J = 2.1 Hz, 1 H, Ar(5)-H), 7.32 (dd, J = 8.5, 2.1 Hz, 1 H, Ar(6)-H), 7.78 (d, J = 2.1 Hz, 1 H, Ar(2)-H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 17.19 (q), 20.98 (q), 56.06 (q), 56.46 (q), 73.87 (d), 75.33 (d), 76.73 (d), 85.99 (s), 97.12 (t), 110.85 (d), 128.09 (d), 128.79 (d), 132.98 (s), 135.53 (s), 138.54 (d), 157.84 (s); exact mass calcd for $C_{16}H_{21}O_4I$ *m/e* 404.0485, found *m/e* 404.0487.

***rel*-(2*S*,3*S*,4*S*,5*S*,6*R*)-Tetrahydro-2-(*m*-iodo-*p*-methoxyphenyl)-5-(methoxymethoxy)-4,6-dimethyl-2*H*-pyran-3,4-diol (33b).** To a solution of 8.0 mg (20 μmol) of olefin **32b** in 0.91 mL of acetone was added 29 mg (70 μmol) of *N*-methylmorpholine *N*-oxide and 67 μL of a 1% weight solution of OsO_4. The resulting solution was stirred 80 h, and 50 mg of sodium bisulfite was added followed by 100 mg of Celite and 0.5 mL of water. The resulting slurry was stirred for 6 h and filtered, and the filter cake was rinsed with three 15-mL portions of EtOAc. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (eluted with EtOAc–petroleum ether (1:10); followed by the same solvents (1:5); followed by EtOAc) to afford 8.2 mg (93%) of diol **33b** as a colorless oil: IR (neat) 3500, 2900 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (m, 4 H, CH_3, OH), 1.42 (s, 3 H, CH_3), 2.10 (bs, 1 H, OH), 3.34 (d, J = 1 Hz, 1 H, C(5)-H), 3.48 (s, 3 H, OCH_3), 3.58 (dd, J = 9.6, 4.1 Hz, 1 H, C(3)-H), 3.87 (s, 3 H, $ArOCH_3$), 4.24 (dq, J = 6.5, 1.3 Hz, 1 H, C(6)-H), 4.34 (d, J = 9.6 Hz, 1 H, C(2)-H), 4.73 (d, J = 6.8 Hz, 1 H, OCH_2), 4.80 (d, J = 6.8 Hz, 1 H, OCH_2), 6.80

(d, J = 8.4 Hz, 1 H, Ar(5)-H), 7.38 (dd, J = 8.4, 2.1 Hz, 1 H, Ar(6)-H), 7.87 (d, J = 2.1 Hz, 1 H, Ar(2)-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ 17.10 (q), 23.75 (q), 56.46 (q), 56.75 (q), 71.37 (d), 72.88 (s), 73.43 (d), 78.12 (d), 83.22 (d), 86.34 (s), 99.12 (t), 110.71 (d), 129.21 (d), 133.81 (s), 138.57 (d), 158.13 (s); exact mass calcd for $C_{16}H_{23}IO_6$ m/e 438.0539, found m/e 438.0555.

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Registry No. **9**, 101977-77-9; **9** formate derivative, 143288-86-2; **10**, 101977-78-0; **11a**, 143191-27-9; **11b**, 143191-28-0; **11c**, 143288-87-3; **12c**, 143191-31-5; **13**, 143191-30-4; **14**, 143191-29-1; **15**, 143288-88-4; **16a**, 143288-89-5; **16b**, 143288-91-9; **16c**, 143288-94-2; **17a**, 143288-90-8; **17b**, 143288-92-0; **17c**, 143288-93-1; **18**, 143288-95-3; **19**, 143288-96-4; **20**, 143288-97-5; 3-*epi*-**20**, 143191-32-6; **21a**, 143288-98-6; **21b**, 143191-33-7; **22a**, 143191-42-8; **23a**, 143191-39-3; **23b**, 143191-46-2; **24a**, 143191-38-2; **24b**, 143191-45-1; **27**, 83569-29-3; **28**, 116696-37-8; **29**, 143191-34-8; **30** diethyl (*p*-methoxybenzyl)phosphonate adduct, 143191-37-1; α-**30**, 143191-35-9; β-**30**, 143191-36-0; **32a**, 143191-40-6; **32b**, 143191-47-3; **33a**, 143191-41-7; **33b**, 143191-48-4; **34**, 143191-44-0; ethyl 3-hydroxypropionate, 623-72-3; *N*-(*p*-methoxyphenyl)cinnamaldimine, 80542-40-1; diethyl (4-methoxybenzyl)phosphonate, 1145-93-3.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for selected compounds, crystallographic data for compounds **11a** and **33a**, and tabular NMR data for compounds **11a–11c**, **12c**, **16a–16c**, and **17a–17c** (82 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.

Cyclocondensation of Alkylhydrazines and β-Substituted Acetylenic Esters: Synthesis of 3-Hydroxypyrazoles[1]

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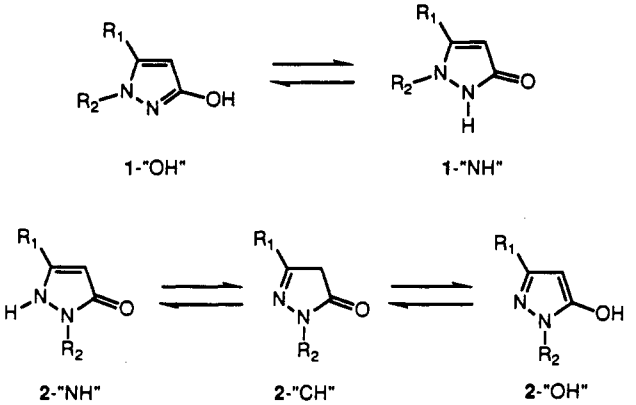
Addition of monosubstituted alkylhydrazines to acetylenic esters with either electron-withdrawing or sterically bulky β-substituents afforded 1-alkyl-3-hydroxy-5-substituted-pyrazoles **1** as the major regioisomeric product. By comparison, the classical cyclocondensation of alkylhydrazines with β-keto esters gives the regioisomeric pyrazol-5-ones **2**. The reaction solvent employed in these cyclocondensations can have a profound effect on regioisomeric product ratios. Addition of methylhydrazine to **5g** in methylene chloride gave regiospecific formation of pyrazolinone **2o**, whereas addition in water–methanol mixtures afforded hydroxypyrazole **1o** as the major product. Structural assignment of regioisomers **1** and **2** are based on ^{13}C NMR chemical shifts, long-range heteronuclear coupling constants, and comparisons with regiochemically known hydroxypyrazoles and/or pyrazolinones. Additions of acetylene **5b** to 1,1-dimethylhydrazine afforded either acyclic enehydrazone **12** or pyrazolium betaine **13** depending on the reaction conditions.

Introduction

Reactions of acetylenes and substituted hydrazines have been extensively studied as a means to prepare enehydrazines, hydrazones, and various cyclocondensation products.[2] Typically, cyclocondensations of either β-alkylacetylenic esters[3] or β-keto esters with alkylhydrazines[4] afford 1-substituted-pyrazolin-5-ones, **2**, as the major regioisomeric product. Surprisingly few reports have appeared describing the regioselective preparation of 3-hydroxypyrazoles, 1-"OH", or the tautomeric 3-pyrazolinones, 1-"NH", from acetylenic esters and alkylhydrazines.[5,6] Such reports have been limited to phenylhydrazine additions in the presence of base[7] and addition of alkylhydrazines to acetylene dicarboxylates.[8] A regiospecific synthesis of 3-hydroxy-5-arylpyrazoles from addition of methylhydrazine to arylglycidates followed by dehydration of the intermediate hydroxypyrazolinone has been reported.[9]



In view of the biological activity associated with a variety of pyrazole derivatives, the ability to prepare 1-alkyl-3-hydroxypyrazoles **1** seemed particularly attractive. De-

(1) Hamper, B. C.; Kurtzweil, M.; Beck, J.; Murray, T. Presented in part at the 13th International Congress of Heterocyclic Chemistry; Corvallis, OR, August 11–16, 1991.
(2) For a recent review, see: Sucrow, W. *Org. Prep. Proced. Int.* **1982**, *14*, 91–155.
(3) Butler, D. E.; DeWalt, H. A. *J. Org. Chem.* **1971**, *36*, 2542–2547.
(4) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, pp 167–344.
(5) Hamper, B. C. *J. Fluorine Chem.* **1990**, *48*, 123–131.
(6) A manuscript for the preparation of perfluoroalkyl-substituted pyrazoles **1** (e.g., R_1 = CF_3) from haloalkyl-substituted α,β-unsaturated esters is in preparation; Gaede, B. J., personal communication.
(7) (a) Nakamura, N.; Kishida, Y.; Ishida, N. *Chem. Pharm. Bull.* **1971**, *19*, 1389–1394. (b) Bouchet, P.; Elguero, J.; Pereillo, J.-M. *Bull. Soc. Chim. Fr.* **1973**, 2482–2485. (c) Al-Jallo, H. N. *Tetrahedron Lett.* **1970**, 875–876. (d) Badder, F. G.; El-Newaihy, M. F.; Salem, M. R. *J. Chem. Soc. C* **1969**, 836–838.
(8) (a) Sucrow, W.; Bredthauer, G. *Chem. Ber.* **1983**, *116*, 1520–1524. (b) Sucrow, W.; Mentzel, C.; Slopianka, M. *Chem. Ber.* **1974**, *107*, 1318–1328. (c) Fehlauer, A.; Grosz, K.; Slopianka, M.; Sucrow, W.; Lockley, W. J. S.; Lwowski, W. *Chem. Ber.* **1976**, *109*, 253–260.
(9) Sabaté-Alduy, C.; Bastide, J.; Bercot, P.; Lematre, J. *Bull. Soc. Chim. Fr.* **1974**, 1942–48.

0022-3263/92/1957-5680$03.00/0