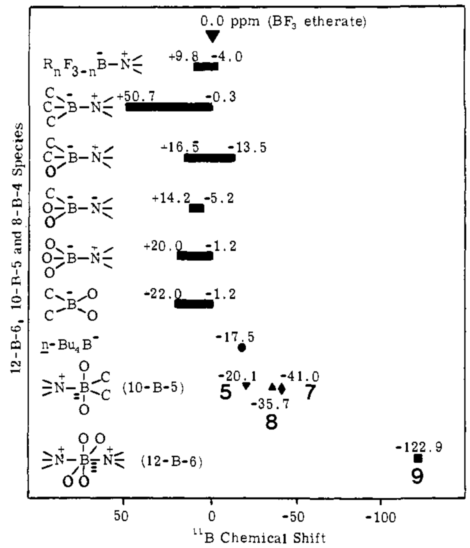
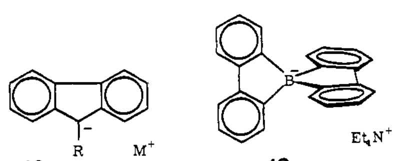



**Figure 1.** Ranges of $^{11}B$ NMR chemical shifts reported[18] for 8-B-4 borates, with first-row elements C, N, O, and F attached to boron, compared with the chemical shifts of 10-B-5 species **5**, **7**, and **8** and 12-B-6 species **9**.

inversion,[13] with nonequivalent geminal $CF_3$ groups, if the interaction between the nitrogen and boron were repulsive. The 8-B-4 borate anion o **10c** acts as a Lewis acid toward the transannular pyridine nitrogen to give the more stable ring-closed product **5**.[14]

The electronic spectrum of yellow 10-B-5 species **5** ($\lambda_{max}$ = 397 nm, $\epsilon$ 1650)[15] is consistent with delocalization of electrons of the hypervalent three-center, four-electron O-B-O bond into $\pi$-acceptor diequatorial five-membered ring, making it a bis-ipso aromatic[3a] 6-$\pi$ Hückel aromatic system analogous to yellow fluorenyl anion **12**.[16] Spirobicyclic borate **13**,[17] is, in contrast, colorless.




**12** **13**

The reported $^{11}B$ NMR chemical shifts for 8-B-4 species with only first-row elements (F, O, N, C) attached to the quaternary borons are downfield of -17.5 ppm.[18] The observed $^{11}B$ NMR chemical shifts for **5**, **7**, and **8** are upfield of this, at -20.1, -41.0, and -35.7 ppm, respectively. That for 12-B-6 species **9** is -122.9 ppm, about 80 ppm upfield of 10-B-5 species **5**, **7**, and **8** and ca. 130 ppm[18] upfield of ordinary 8-B-4 compounds. This strongly supports the postulated, unprecedented 12-B-6 structure for **9**.

Compounds **5**, **7**, and **9** react with triflic acid (TfOH) to give colorless solutions whose $^{11}B$ NMR spectra show signals in the range associated with 8-B-4 species such as **5a** and **7a** in Figure 1. Both **5a** and **7a** show $^{19}F$ NMR peaks for nonequivalent $CF_3$ groups at room temperature. The monoprotonation of **9** gives **9a**, a 10-B-5 species with a chemical shift (-70.1 ppm) near those of the other 10-B-5 species **5**, **7**, and **8**.

The above evidence strongly supports our conclusion that these are the first hypervalent boron compounds, 10-B-5 and 12-B-6 species.[19-21]

(14) The conversion of **10c** to **5** is expected[2e] to result in negative charge delocalization onto both oxygens.

(15) Follows Beer's law—extinction coefficient constant after three recrystallizations.

(16) Streitwieser, A.; Brauman, J. I. *J. Am. Chem. Soc.* **1963**, *85*, 2633.

(17) (a) Köster, R. *Angew. Chem.* **1961**, *73*, 66. (b) Köster, R.; Benedikt, G. *Ibid.* **1963**, *75*, 419.

(18) Nöth, H.; Wrackmeyer, B. "Nuclear Magnetic Resonance Spectroscopy of Boron Compounds"; Springer-Verlag: New York, 1978. The $^{11}B$ chemical shift for $(n\text{-}Bu)_4B^-$ is -17.5 ppm (Ganem, Bruce private communication.)

**Acknowledgment.** This research was supported by a grant from the National Science Foundation (NSF CHE 81-13142) and a fellowship from Lubrizol Corporation. The NMR spectra were provided by the University of Illinois Midwest NSF Regional NMR Facility (CHE 79-16100). Mass spectra were obtained from facilities provided under grants from the National Institutes of Health (CA 11388 and GM 16864).

(19) Compounds **3**, **5**, **7**, **8**, and **9** showed molecular ions in their mass spectra. All except **8** gave satisfactory elemental analyses.

(20) The 8-B-5 and 8-B-6 borons in carboranes[21] are electron deficient and only superficially similar to the 10-B-5 and 10-B-6 species reported here.

(21) Muetterties, E. L. "Boron Hydride Chemistry"; Academic Press: New York, 1973; pp 300-430.

## Syntheses of Heme *d* Models

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*Received April 6, 1984*

A gradually increasing number of biological redox systems have recently been shown to possess hydroporphyrin hemes (iron chlorins) as their prosthetic groups. Examples include siroheme,[1] probably the heme in hemoglobin[2] and the prosthetic group in myeloperoxidase,[3] as well as the green hemes (originally called heme $a_2$, now called heme *d*),[4] from *Escherichia coli* and other bacteria, various cd-type nitrite reductases,[5-9] and the catalase from *Neurospora crassa*.[10,11] Barrett[4] showed the heme *d* from *Aerobacter aerogenes* and *Escherichia coli* to be related to protoporphyrin IX and, as a result of various classical chemical and spectroscopic studies, suggested several structures similar to **1** for heme *d*; all had vinyl, ethyl, or hydroxyethyl groups at C-2 and C-4, and though the site of subunit reduction was not defined, it has since been generally assumed to be ring D;[12] this assumption presumably arose because all known chlorophyll derivatives are reduced in that ring. The green heme from the *Neurospora crassa* catalase appears[11] to have four (rather than two) carboxylate groups and cannot be reoxidized to a porphyrin using high-potential quinones.

In this paper we describe a route, from chlorophyll *a*, for the synthesis of the heme *d* model **2**, which is structurally analogous to Barrett's heme *d*, and then develop a procedure for synthesis and separation of all possible ring-reduced isomers of this compound. A logical synthetic approach to a pigment such as **2** would be from natural chlorophyll derivatives, and the problem resolves itself into the "retro-biosynthetic"[13] conversion of the isocyclic (ring

(1) Murphy, M. J.; Siegel, L. M.; Tove, S. R.; Kamin, H. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 612-616.

(2) Berzofsky, J. A.; Peisach, J.; Blumberg, W. E. *J. Biol. Chem.* **1971**, *246*, 3367-3377.

(3) Bakkenist, A. R. J.; Wever, R.; Vulsma, T.; Plat, H.; van Gelder, B. F. *Biochim. Biophys. Acta* **1978**, *524*, 45-54. Davis, J. C.; Averill, B. A. *J. Biol. Chem.* **1981**, *256*, 5992-5996. Sibbett, S. S.; Hurst, J. K. *Biochemistry*, in press.

(4) Barrett, J. *Biochem. J.* **1956**, *64*, 626-639.

(5) Kuronen, T.; Ellfolk, N. *Biochim. Biophys. Acta* **1972**, *275*, 308-318.

(6) Newton, N. *Biochim. Biophys. Acta* **1969**, *185*, 316-331.

(7) Le Gall, J.; Payne, W. J.; Morgan, T. V.; DerVartanian, D. V. *Biochem. Biophys. Res. Commun.* **1979**, *87*, 355-362.

(8) Iwasaki, H.; Matsubara, T. *J. Biochem.* **1971**, *69*, 847-857.

(9) Cox, C. D.; Payne, W. J.; DerVartanian, D. V. *Biochim. Biophys. Acta* **1971**, *253*, 290-294.

(10) Jacob, G. S.; Orme-Johnson, W. H. *Biochemistry* **1979**, *18*, 2967-2975.

(11) Jacob, G. S.; Orme-Johnson, W. H. *Biochemistry* **1979**, *18*, 2975-2980.

(12) For example: Chang, C. K. *NATO Adv. Study Inst. Ser., Ser. C* **1982**; *89*, 313-334.

(13) The five-membered isocyclic ring of the chlorophylls is biosynthesized from the corresponding propionic acid group in protoprophyrin IX: e.g., Battersby, A. R.; McDonald, E. In "Porphyrins and Metalloporphyrins", Smith, K. M., Ed.; Elsevier: Amsterdam, 1975; pp 107-112.

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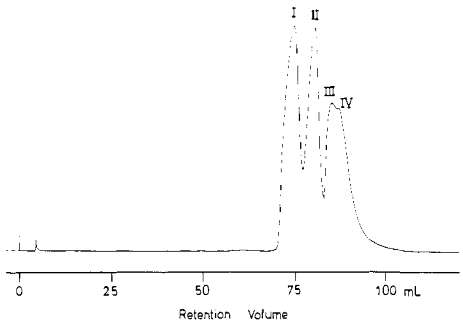
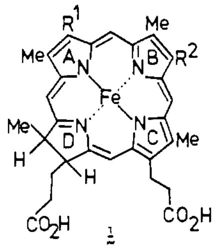



**Figure 1.** High-pressure liquid chromatogram of the mixture of chlorin dimethyl esters **12–15**.[19]

E) ring of chlorophyll *a* into a propionate.

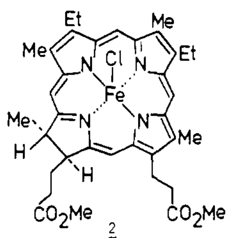
Thus, methyl pheophorbide *a* (**3**), obtained by methanolysis of chlorophyll *a* extracted from the alga *Spirulina maxima*, was degraded into 2-vinylrhodochlorin XV dimethyl ester (**4**);[14] sa-



1

$R^1/R^2$ = Et, V, or CH(OH)CH$_3$

V = CH=CH$_2$



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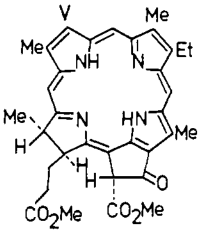

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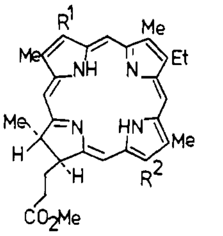
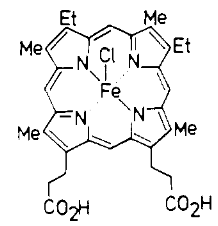


4: $R^1$ = V; $R^2$ = CO$_2$Me
5: $R^1$ = V; $R^2$ = CO$_2$H
6: $R^1$ = V; $R^2$ = CO.(imidazolyl)
7: $R^1$ = V; $R^2$ = CO.CH$_2$.CO$_2$Me
8: $R^1$ = V; $R^2$ = CH(OH).CH$_2$.CO$_2$Me
9: $R^1$ = V; $R^2$ = CH=CH.CO$_2$Me
10: $R^1$ = Et; $R^2$ = CH$_2$.CH$_2$.CO$_2$Me

ponification and partial reesterification (MeOH/$H_2SO_4$) gave the monomethyl ester **5**, which was transformed, in 44% yield, into the $\beta$-keto ester **7** by way of the imidazolide **6**.[15] Sodium borohydride reduction of **7** gave a 65% yield of the hydroxypropionate **8** obtained as two HPLC separable diastereomers, and these were converted into the acrylate **9**, by phosphoryl chloride treatment (90% yield). Finally, catalytic hydrogenation gave a 71% yield of the chlorin **10** and iron insertion[16] afforded the heme *d* analogue **2**. Electronic absorption spectra of the chlorin and its iron complex were very similar to those published by Barrett.[4]

With the knowledge that some recently characterized hydroporphyrins are, unlike chlorophylls, not reduced in ring D (e.g., siroheme, originally postulated to be reduced in rings C and D,[1] is actually reduced in rings A and B), the basic assumption that heme *d* is reduced in ring D should be regarded as untested. Though Fischer[17] studied chlorin formation from several unsymmetrically substituted porphyrins, so far as we are aware, no studies of isomeric purity were carried out, apart from his report[18] that reduction of $\gamma$-phylloporphyrin XV gives uniquely the ring-D reduced chlorin. Reduction of mesohemin **11** with sodium in isoamyl alcohol[19] gave a mixture, after esterification and removal of iron, of four isomers **12–15** (52%, 74% yield based on recovered



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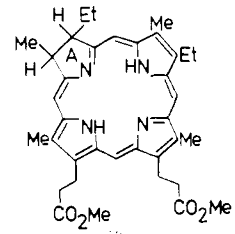

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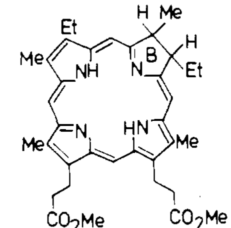

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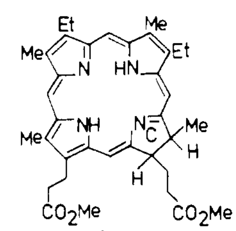

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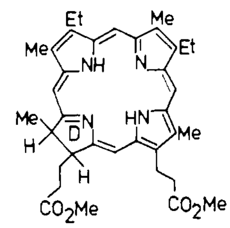

15

All chlorins are trans-reduced

mesoporphyrin), which were separable by HPLC (Figure 1).[20] Coinjection of the above synthetic chlorin identified peak III as the ring-D reduced isomer. Preparative quantities of all four isomers were isolated, and 360-MHz proton NMR spectra showed peaks III and IV to contain compounds reduced in propionate rings (i.e., **14**, **15**), while the compounds from peaks I and II were reduced in rings A and B (i.e., **12**, **13**).[21] Structures of compounds from peaks I and II were differentiated in a nuclear Overhauser enhancement (NOE) study in which the compound from peak I was irradiated at the methylene appearing at 3.99 ppm; an enhancement of the meso proton at 9.71 ppm (and not a meso proton adjacent to the reduced ring, at 8.86 or 8.87 ppm) identified this compound as **12**. Similarly, irradiation of the methylene at 3.90 ppm in the compound from band II gave a strong enhancement at 8.86 ppm, confirming its structure as **13**. Thus, complete HPLC assignments are I (**12**), II (**13**), III (**15**), and IV (**14**).

Insertion of iron and hydrolysis[16] of the four isomers **12–15** gave electronic absorption spectra that were very similar, indicating

(14) Smith, K. M.; Lewis, W. M. *Tetrahedron* **1981**, *37*, *Suppl. 1*, 339–403.
(15) Cox, M. T.; Jackson, A. H.; Kenner, G. W.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 516–527.
(16) Smith, K. M.; Fujinari, E. M.; Langry, K. C.; Parish, D. W.; Tabba, H. D. *J. Am. Chem. Soc.* **1983**, *105*, 6638–6646.
(17) Fischer, H.; Stern, A. "Die Chemie des Pyrrols"; Akademische Verlag: Leipzig, 1940; Vol. II, part 2, pp 144–154.
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(19) Whitlock, H. W.; Hanauer, R.; Oester, M. Y.; Bower, B. K. *J. Am. Chem. Soc.* **1969**, *91*, 7485–7489. Eisner, U.; Lichtarowicz, A.; Linstead, R. P. *J. Chem. Soc.* **1957**, 733–739.
(20) A Waters Associates HPLC system was used, with a Model 6000A pump, U6K injector, UV detector set at 405 nm, and a microporasil (250 × 4.6 mm i.d.) column eluted with a hexane/toluene/isopropyl alcohol mixture (100:3:0.3), at 1.3 mL/min.
(21) Approximate relative proportions of the four bands (I–IV) are 2:2:1:1. At the present time it is not clear whether the reduction of ethyl-substituted rings is prefered over propionate, or whether the propionate rings are preferentially reoxidized during workup; some mesoporphyrin IX is indeed recovered from the reduction procedure. Similar reductions of other unsymmetrically substituted hemins are currently being investigated.

that spectrophotometry cannot be used for identification of the site of reduction in these synthetic chlorins and in those from natural sources.

Finally, it should be mentioned that this procedure offers access to a number of isomeric tetrapyrrole compounds suitable for spectroscopic study of model biological systems containing green hemes. Moreover, previous total syntheses of 2-vinylrhodoporphyrin XV[22] and 2,4-divinylrhodoporphyrin XV,[15] coupled with the published transformation of 2-vinylrhodochlorin into chlorophyll *a*,[14] open up a viable route for the efficient total synthesis of both chlorophyll *a* and 2,4-divinylchlorophyll *a*, the latter having been the topic of considerable attention in recent times.[23] This work is currently in progress.

**Acknowledgment.** This research was supported by grants from the National Science Foundation (CHE-81-20891) and the National Institutes of Health (HL 22252). We thank Frank Bobe for carrying out the NOE study.

**Supplementary Material Available:** Proton NMR spectra (360 MHz), melting points, and electronic absorption spectra of compounds **10** and **12–15** and the electronic absorption spectrum of the iron(III) chloride complex of **12** (typical example) (2 pages). Ordering information is given on any current masthead page.

(22) Howarth, T. T.; Jackson, A. H.; Kenner, G. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 502–511.

(23) Rebeiz, C. A. *Chem Tech*, **1982**, *12*, 52–63. Castelfranco, P. A.; Beale, S. *Annu. Rev. Plant Physiol.* **1983**, *34*, 241–278.

## Stereocontrolled Total Synthesis of (±)- and (+)-Bicyclomycin: New Carbon–Carbon Bond-Forming Reactions on Electrophilic Glycine Anhydride Derivatives†

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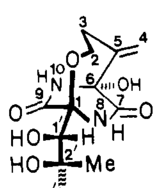
Bicyclomycin[1] (**1**) is a novel antibiotic that is biosynthetically derived[2] by the oxidative cyclodimerization of the amino acids leucine and isoleucine. Bicyclomycin has recently achieved



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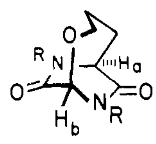

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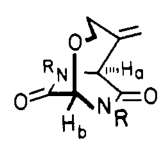

3

commerical stature[3] on a worldwide basis as a clinically useful antibiotic and is now produced on large scale from cultures of *Streptomyces sapporonensis*.

We have recently reported[4] the synthesis and regiocontrolled bridgehead carbanion elaboration of the 4-demethylene nucleus **2**. In order to reduce this efficient model study[5] to a total synthesis[6] of **1**, two difficult problems had to be addressed: (1) introduction of the C4–C5 *exo*-methylene moiety via a suitably oxidized isoleucine precursor and (2) selection of a suitable blocking group for the amides. In this paper, we wish to report a completely regio- and stereocontrolled total synthesis of bicyclomycin from the nucleus **3** that features a fundamentally new and generally useful C–C bond-forming reaction via *electrophilic* coupling to a glycine anhydride derivative.

As shown in Scheme I, 1,4-bis(*p*-methoxybenzyl)- and 1,4-dibenzyl-2,5-piperazinedione were brominated[7] and condensed with the sodium salt of 2-mercaptopyridine (THF, 25 °C, 30 min) to afford the crystalline *syn*-bis(sulfide) **5**. Precomplexation of **5** with 1 equiv of silver (I) triflate in THF at 25 °C for 10 min followed by addition of 1 equiv of butyrolactone trimethylsilyl enol ether (2 h, 25 °C) furnished the lactones **6** (1.3:1, syn:anti; 1.8:1 ratio, epimeric at the lactone $\alpha$-carbon) in 71% yield.[8] It turned out to be critical to *precomplex* **5** with the silver salt before addition of the nucleophile to effect coupling. We were quite surprised to find that the silver complex of **5** is *indefinitely stable in solution* (THF, $CH_2Cl_2$, $CHCl_3$) and cleanly reacts, producing **6** upon addition of the trimethylsilyl ketene acetal. Additionally, the reaction proceeds predominantly with overall *retention* of stereochemistry with respect to the departing thiopyridyl residue and the newly attached lactone moiety. An X-ray crystallographic analysis[9] of the major syn diastereomer **6a** established the relative configuration (shown). Most importantly, we found that the *product* **6** *completely resists further C–C substitution at the remaining thiopyridyl residue* (excess AgOTf/ketene silyl acetal) at C-3 so that absolutely no 3,6-biscoupled products are observed. This remarkable chemoselectivity is highly significant since a major competing side reaction observed in the *nucleophilic* C-functionalization of N-substituted glycine anhydride enolates (i.e., of **4**) is 3,6-disubstitution.[4a]

Reduction of the major syn and anti lactones **6** afforded the diol **7**, which was cleanly cyclized[10] to the desired bicyclic alcohol **8** in the presence of silver(I) triflate in THF at 25 °C. Dehydration of **8** to the bicyclic olefin **9** was readily accomplished in three steps (Scheme I, steps e, f, g).

† Dedicated to the memory of the late Professor Kunio Sakan.

‡ NIH Research Career Development Awardee 1984–1989.

(1) Miyoshi, T.; Miyairi, N.; Aoki, H.; Kohsaka, M.; Sakai, H.; Imanaka, H. *J. Antibiot.* **1972**, *25*, 569. See ref 4 for additional citations for isolation, structure determination, and isolation from *Streptomyces aizunensis*.

(2) (a) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 480. (b) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *Ibid.* **1980**, *33*, 488.

(3) "Merck Index", 10th Ed.; Merck: Rahway, NJ, 1983; no. 1213. Bicozamycin is the commercial synonym (Fujisawa Pharmaceutical Company, Ltd., Japan) for bicyclomycin (aizumycin).

(4) (a) Williams, R. M.; Anderson, O. P.; Armstrong, R. W.; Joey, J.; Meyers, H.; Eriksson, C. *J. Am. Chem. Soc.* **1982**, *104*, 6092. (b) Williams, R. M.; Dung, J.-S.; Josey, J.; Armstrong, R. W.; Meyers, H. *Ibid.* **1983**, *105*, 3214. (c) Armstrong, R. W.; Dung, J.-S.; Williams, R. M. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, WA, March 1983; American Chemical Society: Washington, DC, 1983; ORGN 10.

(5) For other synthetic approaches to **1**, see the references cited in ref 4; see also: (a) Yates, P.; Hoare, J. H. *Can. J. Chem.* **1983**, *61*, 519. (b) Yates, P.; Hoare, J. H. *Ibid.* **1983**, *61*, 1397. (c) Dirlam, J. P.; James, R. B.; Shoop, E. V. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, WA, March 1983; American Chemical Society: Washington, DC, 1983; ORGN 9.

(6) For a recent total synthesis, see: (a) Nakatsuka, S.; Yamada, K.; Yoshida, K.; Asano, O.; Murakami, Y.; Goto, T. *Tetrahedron Lett.* **1983**, *24*, 5627. (b) Nakatsuka, S.; Goto, T. *Heterocycles* **1984**, *21*, 61.

(7) Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 402.

(8) The coupling reaction of **5a** to afford **6a** proceeded to give a 2:1 ratio of syn lactones. The major syn diastereomer was directly converted to **8a** by $LiAlH_4$ reduction and cyclization. The minor syn lactone could either be epimerized to the major syn diastereomer or converted to **9a** as described in ref 10.

(9) Williams, R. M.; Armstrong, R. W.; Maruyama, L. K.; Dung, J.-S.; Anderson, O. P., unpublished results.

(10) The minor syn lactone **6b** could be epimerized to a 1:1 mixture of the two syn diastereomers (0.1 N NaOH, THF, 25 °C) or reduced to the corresponding diol ($LiAlH_4$). This diol was converted to the desired bicyclic system through (1) selective silylation at the 3″-hydroxyl ($Me_2Bu^tSiCl$, DMAP, $Et_3N$, $CH_2Cl_2$), (2) mesylation (MsCl, $Et_3N$, THF), and (3) cyclization with $Cu(ClO_4)_2$/THF, 25 °C, to afford the bicyclo[4.2.2] mesylate (epimeric at C-5, cf. structure **8**) which was directly converted to olefin **9** (Scheme I, steps f and g).

 