In this paper we report a highly concise chemical route to differentially functionalized congeners of the Lewis X antigen, including the critical sialyl-Lewis X series. The major finding herein is that both D-glucal and D-lactal derivatives, where only the primary alcohol functions are protected, undergo regiospecific fucosylation at the allylic alcohol. Furthermore, in the D-lactal series, sialylation occurs specifically at the C3′ hydroxyl in the galactosyl domain. The sum of these findings illustrates the enormous potential to be gained from the use of glycals as glycosyl acceptors.[7]

We first found that 6-*O*-(TBDPS)-D-glucal (**2**)[8] was regio- and stereoselectively glycosylated with fluoride **3a**[9,10] to provide **6a**. Under similar reaction conditions the corresponding tribenzyl donor **3b**[11] gave a 5:3 mixture of α and β anomers favoring **6b**. The stereochemistry observed[12] in **6a,b** was independent of the anomeric stereochemistry of fluorides **3a,b**. The ratio of O3- to O4-fucosylated products was typically 8:1 independent of the fucosyl donor (Scheme I).[12]

Galactosyl trichloroacetimidate **4**[13,14] provided a single β-linked trisaccharide glycal **7a**, which upon debenzoylation gave the required triol **8a**. Coupling with sialyl donor **5**[15] and acetylation of the crude product mixture provided a single stereoisomer of the tetrasaccharide glycal **9a**.[13,16] The above protocol was also successfully demonstrated for the synthesis of **9b** starting from **3b**. By this concise route we synthesized multigram quantities of **9b**. Global deprotection of both **9a** and **9b** provided ready access to sialyl-Lewis X glycal (**10**).

With a view to instituting additional synthetic economies, we explored regioselective glycosylations of D-lactal derivatives. Reaction of 6,6′-bis(*O*-TBS)lactal (**11**)[17] with fucosyl donor **3a** occurred at the allylic alcohol to afford trisaccharide glycal **12**, with no other regio- or stereoisomers detected. In contrast, sialylation of **11** with sialyl donor **5** stereoselectively provided the O3′-sialylated lactal **13**,[18] which was completely deprotected to give sialyllactal **14**.

Both sialyllactal (**14**) and sialyl-Lewis X glycal (**10**) were tested for fucosyltransferase inhibition. **14** was not an inhibitor, but **10** was a moderate inhibitor of α-1,3-fucosyltransferase (IC_{50} = 41 mM). In conclusion, our synthetic approach to **10** provides ready access to a host of small-molecule analogs of sialyl-Lewis X antigen. Specifically, the glycal at the reducing terminus of **9a,b** has been successfully utilized as a handle for introducing the SLe^x unit to other haptens as well as for completing the total synthesis of sialyl-Lewis X antigen (**1**).[19]

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Registry No. **1**, 98603-84-0; **2**, 87316-22-1; **3a**, 142800-26-8; **3b**, 127061-08-9; **4**, 142800-27-9; **5**, 113757-77-0; **6a**, 142800-28-0; α-**6b**, 142800-29-1; β-**6b**, 142865-32-5; **7a**, 142800-30-4; **7b**, 142800-31-5; **8a**, 142800-32-6; **8b**, 142800-33-7; **9a**, 142800-34-8; **9b**, 142800-35-9; **10**, 142800-36-0; **11**, 142800-37-1; **12**, 142800-38-2; **13**, 142800-39-3; **14**, 142810-05-7.

Supplementary Material Available: Listings of complete experimental details and analytical and spectral data for all new compounds (**3–10**, **13**, **14**) (14 pages). Ordering information is given on any current masthead page.

(7) (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (b) Halcomb, R. L.; Danishefsky, S. J. *J. Chem. Soc.* **1989**, *111*, 6661. (c) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811. (d) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863.

(8) Guthrie first demonstrated the reactivity order O6 > O3 > O4 for silylation of D-glucal hydroxyl groups: (a) Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381. (b) Shakhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.

(9) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431.

(10) **3a** was synthesized in five steps from methyl L-fucopyranoside (34% overall yield): (1) $(Bu_3Sn)_2O$, toluene, 110 °C; (2) 4 equiv of benzyl bromide, 2 equiv of Bu_4NBr, toluene, 110 °C; (3) benzoyl chloride cat. DMAP, pyridine; (4) 1 N HCl, acetic acid, 100 °C; (5) DAST, THF, −30 °C.

(11) Dejter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1973**, *28*, 61.

(12) The presence of the glycal as an inert reaction partner required avoiding strongly acidic or electrophilic conditions; fucosylation and sialylation were successful only when conducted in the presence of 2,6-di-*tert*-butylpyridine.

(13) **4** was synthesized in four steps from 6-benzyl-1,2:3,4-diisopropylidene-D-galactopyranose (23% overall yield): (1) 1 N HCl, dioxane, 100 °C; (2) benzoyl chloride, pyridine, $CHCl_3$, −10 °C; (3) saturated ammonia in THF/MeOH (7:3); (4) potassium carbonate, trichloroacetonitrile, CH_2Cl_2.

(14) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257.

(15) Ratcliffe, M. R.; Venot, A. P.; Abbas, Z. S. Eur. Pat. Appl. EP 319,253 (*Chem. Abstr.* **1990**, *112*, 175281a).

(16) The stereochemistry of the NeuAcα(2→3)Gal linkage was assigned based on the chemical shift of the NeuAc H4.

(17) **11** was prepared from D-lactal in one step: 2 equiv of TBDMSCl, cat. DMAP, pyridine (67% yield).

(18) We have also observed that allylation and silylation of **11** occur selectively at O3′. The factors responsible for this inversion of regioselectivity are under investigation. See also: (a) Murase, T.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1988**, *184*, C1. (b) Lönn, H.; Stenvall, K. *Tetrahedron Lett.* **1992**, *33*, 115.

(19) These studies are the subject of a manuscript in preparation.

Azaglycosylation of Complex Stannyl Alkoxides with Glycal-Derived Iodo Sulfonamides: A Straightforward Synthesis of Sialyl-Lewis X Antigen and Other Oligosaccharide Domains

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Our previous communication documented the synthesis of sialyl-Lewis X glycal (**2**).[2] In our initial attempts to synthesize sialyl-Lewis X antigen (**1**) from the fully protected tetrasaccharide glycal **2**, we encountered difficulty in extending our sulfonamidoglycosylation methodology[3] to the synthesis of SLe^x-containing glycoconjugates. More specifically, the glycosylation conditions (lithium or potassium alkoxides of a glycosyl acceptor) were not compatible with acetyl or benzoyl esters. In this communication we disclose the successful application of stannyl alkoxide addition to glycal-derived iodo sulfonamides, resulting in the total synthesis of sialyl-Lewis X antigen (**1**) and a synthesis of hexasaccharide **7** (Scheme I).

Reaction of **2** with iodonium di-*sym*-collidine perchlorate and either benzenesulfonamide[2] or 2-(trimethylsilyl)ethanesulfonamide[4] provided iodo sulfonamides **3a** and **3b** in 91% and 82% yields, respectively. The formation of a simple β-benzyl glycoside **4** containing all of the necessary heteroatoms found in sialyl-Lewis X antigen was achieved under very mild conditions, by reaction of **3b** with tributylstannyl *O*-benzyl alkoxide[5] in the presence of silver triflate. Fluoride-mediated desilylation removed both the silyl ether and the 2-silylethanesulfonamido group; acetylation

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(2) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Oriyama, T.; Griffith, D. A.; Wong, C.-H.; Dumas, D. P. *J. Am. Chem. Soc.*, preceding paper in this issue.

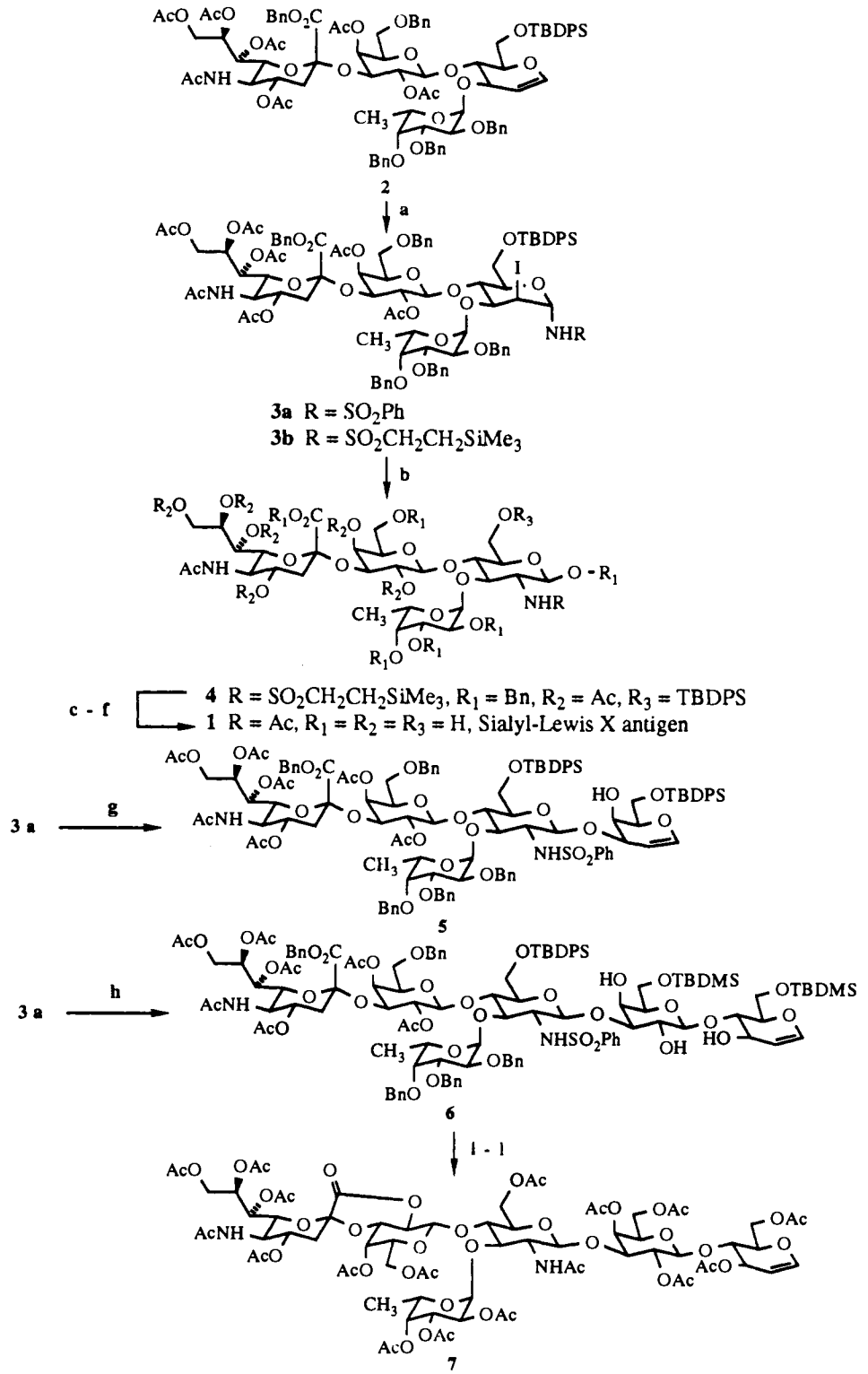
(3) (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863.

(4) (a) 2-(Trimethylsilyl)ethanesulfonamide was synthesized in two steps from sodium 2-(trimethylsilyl)ethanesulfonate (ref 4b) (62% overall): (1) PCl_5, CCl_4; (2) NH_3, CH_2Cl_2, 0 °C. (b) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.

(5) Davies, A. G.; Kleinschmidt, D. C.; Palan, P. R.; Vasishtha, S. C. *J. Chem. Soc. C* **1971**, 3972.

0002-7863/92/1514-8331$03.00/0

Scheme I[a]



[a] (a) 4 equiv of I(*sym*-coll)$_2$ClO$_4$, 4 equiv of H$_2$NR, CH$_2$Cl$_2$: **3a** (91%); **3b** (82%). (b) 10 equiv of Bu$_3$SnOBn, 10 equiv of AgOTf, THF (64%). (c) CsF, DMF, 95 °C. (d) Ac$_2$O, pyridine. (e) LiOH, MeOH, aqueous dioxane. (f) H$_2$, Pd(OH)$_2$, MeOH: c–f combined (22%). (g) 10 equiv of 3-*O*-(tributylstannyl)-6-*O*-(TBDPS)-D-galactal, 5 equiv of AgBF$_4$, THF, 4-Å molecular sieves, −78 °C to room temperature (52%). (h) 17 equiv of 3′-*O*-(tributylstannyl)-6,6′-bis-*O*-(TBDMS)-D-lactal, 7 equiv of AgBF$_4$, THF, 4-Å molecular sieves, −78 °C to room temperature (42%). (i) Bu$_4$NF, THF. (j) Cat. NaOMe, MeOH; then H$_2$O. (k) Na/NH$_3$, THF, −78 °C. (l) Ac$_2$O, pyridine: i–l combined (73%).

of the free amine, followed by deacylation/saponification and hydrogenolysis of benzylic protective groups, provided sialyl-Lewis X antigen (**1**).[6]

Encouraged by our initial success with tributylstannyl *O*-benzyl alkoxide, we explored glycosylation with the stannyl alkoxides of carbohydrate acceptors[7] derived from D-galactal and D-lactal. Namely, the 3-*O*-tributylstannyl ether of 6-*O*-(TBDPS)-D-galactal[8] was successfully coupled with **3a** to provide pentasaccharide glycal **5**. Similarly, hexasaccharide glycal **6** was obtained from the 3′-*O*-tributylstannyl ether of 6,6′-bis-*O*-(TBDMS)-D-lactal[9] and **3a**. Deprotection of **6** and subsequent peracetylation provided the lactone **7**. Detailed NMR experiments [see supplementary material] enabled us to firmly assign the stereochemistry for each glycosidic linkage as shown.

In summary, we have developed new and mild reaction conditions for glycosylation of iodo sulfonamides, which has enabled us to successfully synthesize sialyl-Lewis X antigen. Current studies include the elaboration of glycals **5–7** to the synthesis of gangliosides[10] and glycopeptides.[11]

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Supplementary Material Available: Complete experimental details and analytical and spectral data for all new compounds, **1** and **3–7** (11 pages). Ordering information is given on any current masthead page.

(6) (a) Palcic, M. M.; Venot, A. P.; Ratcliffe, R. M.; Hindsgaul, O. *Carbohydr. Res.* **1989**, *190*, 1. (b) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1991**, *209*, C1. (c) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1991**, *10*, 549. (d) Nicolaou, K. C.; Hummel, C. W.; Bockovich, N. J.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1991**, *10*, 870. (e) Dumas, D. P.; Ichikawa, Y.; Wong, C.-H. *Biomed. Chem. Lett.* **1991**, *1*, 425. (f) Nicolaou, K. C.; Hummel, C. W.; Iwabuchi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3126.

(7) (a) Crowe, A. J.; Smith, P. J. *J. Organomet. Chem.* **1976**, *110*, C57. (b) Alais, J.; Maranduba, A.; Veyrieres, A. *Tetrahedron Lett.* **1983**, *24*, 2383. (c) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.

(8) Prepared in two steps from D-galactal: (1) 1 equiv of TBDPSCl, cat. imidazole, triethylamine, DMF (90% yield); (2) $(Bu_3Sn)_2O$, benzene, reflux, percolation of refluxing solvents through 4-Å molecular sieves.

(9) Prepared in two steps from D-lactal: (1) 2 equiv of TBDMSCl, cat. DMAP, pyridine (67% yield); (2) $(Bu_3Sn)_2O$, benzene, reflux, percolation of refluxing solvents through 4-Å molecular sieves.

(10) (a) Hakomori, S. In *Handbook of Lipid Research, Vol. 3, Sphingolipid Biochemistry*; Plenum Press: New York, 1983; 99. (b) *Glycolipids*; Wiegandt, H., Ed.; Elsevier: New York, 1985.

(11) (a) Lechner, J.; Wieland, F. *Annu. Rev. Biochem.* **1989**, *58*, 173. (b) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 823.

A Remarkable Cyclopropanation: The Total Synthesis of Myrocin C

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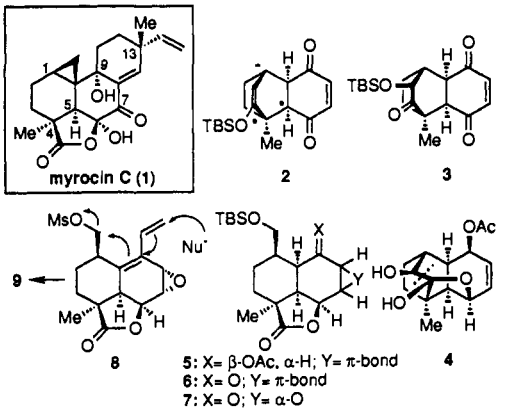
Myrocin C (**1**) is a structurally novel pentacyclic diterpene isolated in 1988 from the soil fungus *Myrothecium verrucaria* strain no. 55.[1] This antitumor antibiotic exhibits half the activity of mitomycin C in an in vivo tumor inhibitory screen.[2] Our interest in the synthesis of myrocin C stemmed from two considerations. The confluence of its structural features posed considerable synthetic challenges which invited several potentially interesting solutions. Furthermore, a proposed mechanism for the biotriggering of **1** could be inferred,[3] the testing of which required access to 6-desoxymyrocin C (**18**). In this paper we report the total synthesis of racemic **1** by way of **18**.

A critical reaction of the synthesis occurs in the first step wherein compound **2** was obtained from Diels–Alder cycloaddition (THF, room temperature, 5 days, 94%) of *p*-benzoquinone with 2-[(*tert*-butyldimethylsilyl)oxy]-1-methylcyclohexa-1,3-diene[4]

Scheme I



(note the stereochemical homology between C-1, C-4, and C-5 of **1** and the corresponding centers of **2**). Oxidation[5] (2,2-dimethyldioxirane,[6] acetone/CH_2Cl_2) of **2** afforded **3**, which upon reduction[7] ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH), acetylation (Ac_2O, Et_3N, DMAP, CH_2Cl_2), and desilylation (TBAF, AcOH, THF) gave **4** (59% overall from **2**). Cleavage of the vicinal "diol" linkage ($NaIO_4$, THF/H_2O) followed by reduction ($NaBH_4$, MeOH) of the lactone aldehyde and protection (TBSOTf, Et_3N, CH_2Cl_2) of the primary alcohol afforded **5** in 99% overall yield from **4**. Deacetylation (NaOMe, MeOH) and subsequent oxidation (PDC,[8] CH_2Cl_2) afforded enone **6**, which was stereospecifically epoxidized[9] (H_2O_2, NaOH, MeOH) to afford epoxy ketone **7** (66% overall yield from **5**). The resulting oxiranyl linkage exhibited surprising stability to the following sequence: (i) enol triflation[10] (NaHMDS, Tf_2NPh, THF), (ii) cross-coupling[11] ($Bu_3SnCH{=}CH_2$, $PdCl_2(PPh_3)_2$, LiCl, THF), (iii) desilylation (TBAF, AcOH, THF), and (iv) mesylation (MsCl, Et_3N, DMAP, CH_2Cl_2). Compound **8** was thus obtained in 40% overall yield from **7** (Scheme I).

The elements were then in place for the defining reaction of the synthesis. Upon treatment of compound **8** with (trimethylstannyl)lithium[12] in THF, cyclopropyl dienol **10** was produced in 66% yield, presumably through the intermediacy of allylstannane **9**.[13] It will be recognized that this transformation accomplishes installation of the cyclopropane while liberating the C-7 alcohol. The latter, of course, is destined to become the C-7 ketone in **1**. However, before that oxidation, this alcohol serves another important strategic end. Thus, condensation (DCC, DMAP, CH_2Cl_2) of **10** with (*E*)-3-methyl-4-oxo-2-butenoic acid[14] afforded **11**, which upon thermolysis (PhH, reflux, 13 h) gave, by *endo* addition of the aldehyde function, the adduct **12**. Wittig olefination ($Ph_3P{=}CH_2$, THF) provided **13** (79% overall yield from **10**) in which C-14 had undergone complete epimerization to the β-configuration. *This intramolecular Diels–Alder reaction,[15] achieved through the C-7 ester tether, has not only provided a usefully functionalized C-ring but has also enabled rigorous control of the remote C-13 chiral center.*

The now extraneous carbon (C-21) was excised as follows. Reduction (DIBAL-H, CH_2Cl_2) of **13** gave a bislactol which upon selective oxidation (PDC, CH_2Cl_2) afforded compound **14** (74%).

(1) Hsu, Y.-H.; Hirota, A.; Shima, S.; Nakagawa, M.; Adachi, T.; Nozaki, H.; Nakayama, M. *J. Antibiot.* **1989**, *42*, 223.

(2) Nakagawa, M.; Hsu, Y.-H.; Hirota, A.; Shima, S.; Nakayama, M. *J. Antibiot.* **1989**, *42*, 218.

(3) Cf. (+)-CC-1065: (a) Reynolds, V. L.; McGovern, J. P.; Hurley, L. H. *J. Antibiot.* **1986**, *39*, 319. (b) Hurley, L. H.; Needham-VanDervanter, D. R. *Acc. Chem. Res.* **1986**, *19*, 230.

(4) Ihara, M.; Ishida, Y.; Fukumoto, K.; Kametani, T. *Chem. Pharm. Bull.* **1985**, *33*, 4102.

(5) Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249.

(6) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.

(7) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(8) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

(9) Wasson, R. L.; House, H. O. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 552.

(10) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

(11) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(12) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.

(13) Cf. Ishii, T.; Kawamura, N.; Matsubara, S.; Utimoto, K.; Kozima, S.; Hitomi, T. *J. Org. Chem.* **1987**, *52*, 4416.

(14) (a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115. (b) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. *Tetrahedron Lett.* **1985**, *26*, 3307.

(15) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.

0002-7863/92/1514-8333$03.00/0