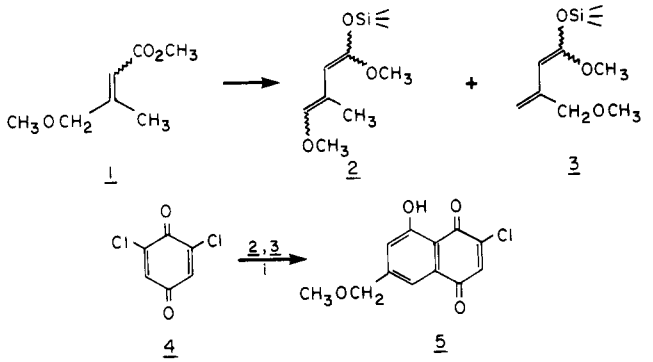
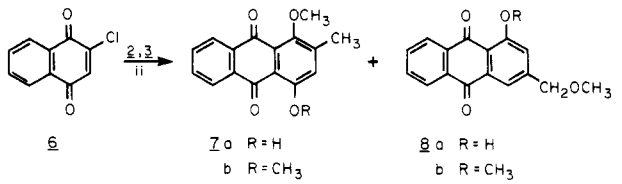
Scheme I[a]



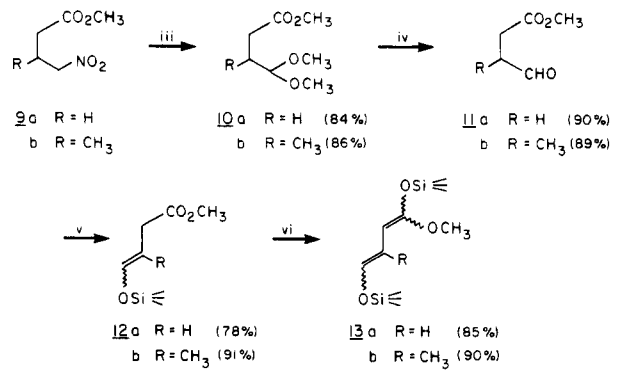
[a] (i) THF, room temperature; silica gel, C_6H_6.

Scheme II[a]



[a] (ii) C_6H_6, room temperature; silica gel, C_6H_6.

Scheme III[a]

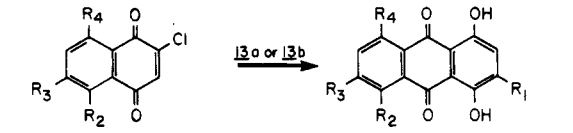


[a] (iii) CH_3ONa; H_2SO_4, CH_3OH, −10 °C; (iv) H_2O, Δ; (v) Et_3N, $ZnCl_2$, $ClSi(CH_3)_3$; (vi) LDA, $ClSi(CH_3)_3$, −78 °C.

A convenient solution to the problem was eventually found in the preparation of 1-methoxy-1,4-bis(trimethylsiloxy)butadiene **13a** and its 3-methyl derivative from the corresponding succinaldehydic esters by double enol silylation. 4-Nitrobutanoates,[8] readily available through Michael addition of nitromethane to α,β-unsaturated esters, undergo a modified Nef reaction,[9] giving acetals which are easily hydrolyzed to the required γ-formyl esters[10] (Scheme III).

Dienes **13a** and **13b** react with dichlorobenzoquinones in benzene at room temperature and give adducts which do not aromatize. These products have been shown in analogous cases to result from addition to one of the quinonic carbonyls, but in these instances decompose rapidly during hydrolysis or chromatography. A variety of naphthoquinones on the other hand combine smoothly with diene **13b** affording the expected anthraquinones regiospecifically and with very satisfactory yields (62–87%). Diene **13a**, however, exhibited poor affinity for quinone **17** and after 7 days without solvent at room temperature yielded only 27% of helminthosporin (**22**).

Scheme IV



	R_2	R_3	R_4
6	H	H	H
14	H	H	OH
15	OAc	H	H
16	H	OCH_3	OH
17	H	CH_3	OH

	R_1	R_2	R_3	R_4
18	CH_3	H	H	H
19	CH_3	H	H	OH
20	CH_3	OH	H	H
21	CH_3	H	OCH_3	OH
22	H	H	CH_3	OH

In a typical example, 2.00 mmol of the diene in 2 mL of dry benzene was added (3–5 min) to 1 mmol of the quinone (**6**, **14–16**) in 3 mL of the same solvent. The mixture was kept at room temperature for 1 h and then refluxed until the cycloaddition was complete (supplemental portions of diene being added as required for prolonged reactions). The crude adduct was stirred for 1 h in a mixture of THF (10 mL), concentrated HCl (2 mL), and then refluxed for 1 h. Extraction of the aromatized product with 2% NaOH, acidification, and purification by dry column chromatography on silica gel (C_6H_6–CCl_4, 1:1) gave the expected product.

The following natural products were obtained in this way: 2-methylquinizarin (**18**) (from **13b** and **6**) (138 h; mp 178 °C; 79%), islandicin (**19**) (from **13b** and **14**) (3 h; mp 218.5–219.0 °C; 77%), digitopurpone (**20**) (from **13b** and **15**) (32 h; mp 211–212 °C; 87%), erythroglaucin (**21**) (from **13b** and **16**) (45 h; mp 206.5–207.5 °C; 62%), and helminthosporin (**22**) (**13a** and **17**) (7 days; mp 227.5–228.5 °C; 27%) (Scheme IV).

Registry No. **1**, 98962-57-3; **2**, 99097-56-0; **3**, 93564-92-2; **4**, 697-91-6; **5**, 99097-57-1; **6**, 1010-60-2; **7a**, 78176-81-5; **7b**, 52541-72-7; **8a**, 93564-93-3; **8b**, 99097-58-2; **9a**, 13013-02-0; **9b**, 16507-06-5; **10a**, 4220-66-0; **10b**, 99097-59-3; **11a**, 13865-19-5; **11b**, 65038-34-8; **12a**, 99097-60-6; **12b**, 99097-61-7; **13a**, 99097-62-8; **13b**, 99097-63-9; **14**, 18855-92-0; **15**, 60549-39-5; **16**, 65120-69-6; **17**, 62993-89-9; **18**, 2589-39-1; **19**, 476-56-2; **20**, 34425-57-5; **21**, 476-57-3; **22**, 518-80-9.

Bruno Simoneau, Jacques Savard, Paul Brassard*

Département de chimie
Université Laval, Québec
Québec, Canada G1K 7P4

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(9) Jacobson, R. M. *Tetrahedron Lett.* **1974**, 3215.
(10) Sumitomo, H.; Kobayashi, K.; Saji, T. *J. Polym. Sci., Polym. Chem. Ed.* **1972**, *10*, 3421.

Chelation- and Non-Chelation-Controlled Additions to 2-*O*-Benzyl-3-*O*-(*tert*-butyldimethylsilyl)-glyceraldehyde

Summary: 2-*O*-Benzyl-3-*O*-(*tert*-butyldimethylsilyl)-glyceraldehyde, prepared from 1,3:4,5-di-*O*-benzylidenemannitol, undergoes chelation- or non-chelation-controlled Grignard-type and aldol additions, depending upon the nature of the organometallic reagent used ($TiCl_4/Me_2Zn$, $TiCl_4$/allylsilane, $SnCl_4$/enol silane, $RTi(OCHMe_2)_3$, and BF_3/allylsilane).

Sir: We have previously shown that Lewis acidic titanium reagents are ideal partners in chelation-controlled Grignard- and aldol-type additions to chiral α- and β-alkoxy carbonyl compounds. Furthermore, analogous titanium

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Table I. Reactions of 2 with Carbon Nucleophiles

entry	reagent	solv	temp, °C	conversion, %	product ratio (syn:anti)
1	$CH_3Ti(OCHMe_2)_3$	Et_2O	−30	>98	11:89
2	$CH_3Ti(OCHMe_2)_3$	THF	−30	80	7:93
3	$TiCl_4/Me_2Zn$	CH_2Cl_2	−78	51	96:4
4	$TiCl_4/CH_2{=}CHCH_2SiMe_3$	CH_2Cl_2	−78 → −10	>98	>98:<2
5	$SnCl_4/CH_2{=}CHCH_2SiMe_3$	CH_2Cl_2	−78	94	>98:<2
6	$BF_3OEt_2/CH_2{=}CHCH_2SiMe_3$	CH_2Cl_2	−78	90	19:81
7	$SnCl_4/CH_2{=}C(CH_3)CH_2SiMe_3$	CH_2Cl_2	−78	>98	>97:<3
8	$BF_3{\cdot}OEt_2/CH_2{=}C(CH_3)CH_2SiMe_3$	CH_2Cl_2	−78	94	23:77

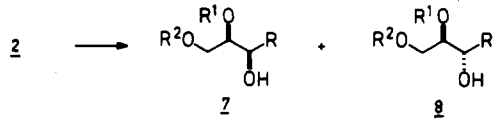
reagents of low Lewis acidity allow entry into the non-chelation-controlled manifold.[1,2] These two methodologies have been successfully used in natural products chemistry.[3] A recent paper by Macdonald concerning application to 2,3-di-*O*-dibenzylglyceraldehyde (1) and similar α,β-dialkoxy carbonyl compounds[4] prompts us to disclose our preliminary results using the related compound **2**.[5]

1 2

R^1 = benzyl; R^2 = *tert*-butyldimethylsilyl

In contrast to **1**,[4,5] **2** has two different protective groups, which means that chemoselective manipulation following nucleophilic additions is possible if so desired. **2** is accessible from commercially available 1,3:4,5-di-*O*-benzylidenemannitol (**3**) in four steps[5] (Scheme I).

A variety of reagents and conditions were used to perform stereoselective additions, providing syn and anti adducts **7** and **8**, respectively (Table I).

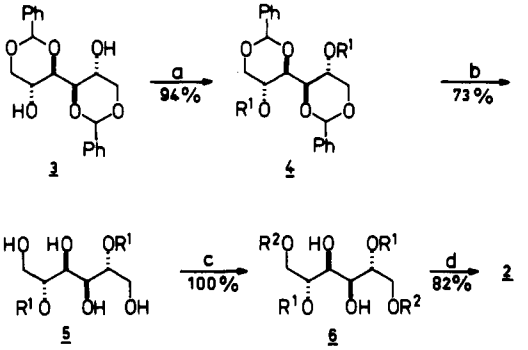


2 → **7** + **8**

a, R = CH_3
b, R = $CH_2{=}CHCH_2$
c, R = $CH_2{=}C(CH_3)CH_2$

Entries 1 and 2 reveal that $CH_3Ti(OCHMe_2)_3$ favors the non-chelation-controlled product **8** (R = CH_3), in line with our previous findings regarding additions to simple α-alkoxy aldehydes[1,2] and to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose.[1b,6a] The Cornforth[7] model explains the results best;[8] i.e., the reacting species has the α-alkoxy group anti periplanar to the carbonyl function.

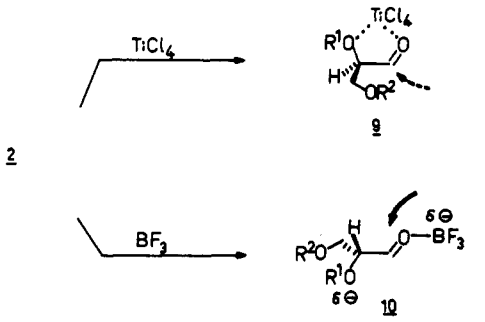
Scheme I[a]



3 → **4** → **5** → **6**

[a] (a) NaH/THF, $PhCH_2Br/N(n\text{-}Bu)_4I$; (b) HCl/EtOH; (c) *t*-$BuMe_2SiCl$/imidazole/DMF; (d) $NaIO_4$/THF.

Opposite diastereofacial selectivity in nucleophilic additions to **2** is observed upon using Lewis acidic reagents capable of bisligation. "Tying up" the molecule with $TiCl_4$ according to **9** followed by addition of soft carbon nucleophiles such as Me_2Zn or $CH_2{=}CHCH_2SiMe_3$ affords almost exclusively the syn adducts **7** (entries 3–5). In case of BF_3-mediated allylsilane addition (entry 6, Table I), non-chelation-control can be rationalized by a Cornforth-type dipolar transition state **10**.[9] Adduct **7b** (entry 5, Table I) was esterified with Mosher's reagent, providing a derivative whose ^{13}C NMR spectrum showed the presence of a single diastereomer. This means that the chiral center in **2** is not racemized to any appreciable extent during preparation or reaction.[5]



2 → **9**; **2** → **10**

Turning to chelation-controlled aldol additions,[1b-d] the $SnCl_4$ analogue of **9** reacts with the *O*-silyl enol ether of methyl acetate to form **11** (90% conversion). Similarly, the *Z* silyl enol ether derived from propiophenone results in mainly one (**13**) of four possible diastereomers in >90% yield. The other two diastereomers related to **13**/**14** are

(1) (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R.; *Angew. Chem.* **1982**, *94*, 133; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135; *Angew. Chem. Suppl.* **1982**, 257–268. (b) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R.; *Angew. Chem.* **1983**, *95*, 1007; Angew. *Chem., Int. Ed. Engl.* **1983**, *22*, 989; *Angew. Chem., Suppl.* **1983**, 1511. (c) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (d) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327.

(2) (a) Review of chelation- and non-chelation-controlled additions to chiral alkoxy carbonyl compounds: Reetz, M. T.; *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Earlier definitive work on chelation-controlled additions to α-alkoxy aldehydes and ketones: Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031. (c) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(3) (a) Danishefsky, S.; DeNinno, M.; *Tetrahedron Lett.* **1985**, *26*, 823. (b) Heathcock, C. H.; Montgomery, S. H. *Tetrahedron Lett.* **1985**, *26*, 1001. (c) Schöllkopf, U. *Pure Appl. Chem.*, in press; (d) Hoppe, D. *Angew. Chem.* **1984**, *96*, 930; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (e) See also: Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.

(4) Mead, K.; MacDonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.

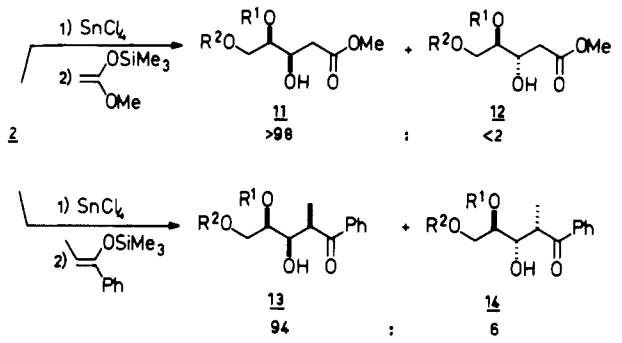
(5) Kesseler, K. Dissertation, Universität Marburg, 1985.

(6) (a) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. (b) Reetz, M. T. "Organotitanium Reagents in Organic Synthesis"; Springer-Verlag: West Berlin, in press.

(7) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. This model refers to chiral α-chloro carbonyl compounds. In our work we extend it to α-alkoxy analogues.

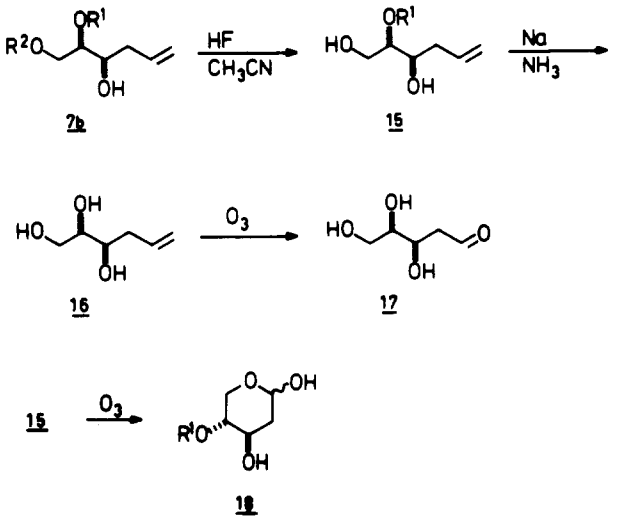
(8) The Felkin–Anh model has been applied in similar cases and does in fact lead to the correct prediction. However, we have previously cast doubt on the validity of this model because it cannot be used in certain cases.[2a]

(9) Reetz, M. T.; Kesseler, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1079.



not formed. On the basis of previous work,[1] we tentatively assign the simple diastereoselectivity to be syn. In these aldol additions, $TiCl_4$ is less efficient.[5] Reversal of diastereofacial selectivity results upon using the nonchelating *Z* triisopropoxytitanium enolate of propiophenone[1b-d] in THF (−78 °C/16 h; >98% conversion), the ratio of **13**/**14** being 10:90.

The configurational assignments are based primarily on chemical correlation.[5] For example, the chelation-controlled adduct **7b** (entry 4 of Table I) was first selectively deprotected to form **15**. Debenzylation afforded the known triol **16** (identical ^{13}C NMR data),[10a] which is a precursor of 2-deoxy-D-*threo*-pentose (**17**).[10] The regiospecifically



monobenzylated derivative **18** is accessible by ozonolysis of **15**; this is an illustration of the use of **2** having two different protective groups.

In summary, **2** is a key compound for synthetically useful transformations. The main advantage relative to the classical acetonide of glyceraldehyde[2] has to do with the fact that both syn and anti adducts are accessible, depending upon the nature of the reagent. The acetonide reacts either nonselectively, or leads preferentially to the anti adducts.[2,11] Concerning the choice of organometallic reagent, weakly Lewis acidic compounds $RTi(OCHMe_2)_3$ and the related triisopropoxytitanium enolates constitute a viable method for non-chelation-controlled Grignard-type and aldol additions to α-alkoxy aldehydes,[1,6] regardless of whether additional alkoxy groups are present or not. Chelation-controlled additions to α,β-dialkoxy aldehydes such as **1** or **2** can be performed with Lewis acidic titanium reagents or sometimes $RMgX/ZnX_2$.[5] In case of methyl addition, $[CH_3Cu]MgBr_2$ works just as well or better.[4] Chelation-controlled aldol additions to **2** are best performed using $SnCl_4$/enol silanes.

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Registry No. **2**, 98944-53-7; **3**, 28224-73-9; **4**, 99096-86-3; **5**, 17618-04-1; **6**, 99112-28-4; **7a**, 99096-87-4; **7b**, 99096-89-6; **7c**, 99096-93-2; **8a**, 99096-88-5; **8b**, 99096-90-9; **8c**, 99096-94-3; **11**, 99096-95-4; **12**, 99096-96-5; **13**, 99096-97-6; **14**, 99096-98-7; **15**, 99096-91-0; **16**, 99096-92-1; $PhCH_2Br$, 100-39-0; *t*-$BuMe_2SiCl$, 18162-48-6; $CH_3Ti(OCHMe_2)_3$, 18006-13-8; $CH_2{=}CHCH_2SiMe_3$, 762-72-1; Me_2Zn, 544-97-8; $CH_2{=}C(CH_3)CH_2SiMe_3$, 18292-38-1; $CH_2{=}C(OMe)OSiMe_3$, 36850-80-3; (*Z*)-$CH_3CH{=}C(Ph)OSiMe_3$, 66323-99-7; propiophenone (*Z*)-triisopropyltitanium enolate, 81643-94-9.

Supplementary Material Available: Details of preparation of **2** and representative reactions and NMR data of **7a–b**/**8a–b** (5 pages). Ordering information is given on any current masthead page.

Manfred T. Reetz,* Kurt Kesseler
Fachbereich Chemie der Universität
Universität Marburg
3550 Marburg, Federal Republic of Germany
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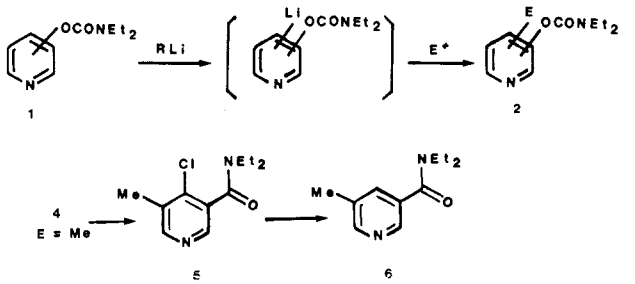
Directed Ortho Metalation of *O*-Pyridyl Carbamates. Regiospecific Entries into Polysubstituted Pyridines

Summary: Ortho-lithiated species of *O*-pyridyl carbamates **1a–c** constitute new synthetic intermediates which provide a variety of polysubstituted pyridines (Table I) by reaction with electrophiles (**2a–c**) and anionic Fries rearrangement (**3**, **4**). Further metalation (**7**), ipso carbodestannylation (**10**, E = I, COMe), and reductive elimination of the carbamate directing group (**5** → **6**) are also described.

Sir: Although a variety of polysubstituted 2- and 4-pyridones and 3-pyridinols are available by classical routes involving de novo pyridine ring-forming reactions,[1] rational methods for the synthesis of functionalized derivatives of these systems are based on the parent systems and are invariably dependent on nonregioselective electrophilic substitution reactions.[2] We report a new, general, and regiospecific method for the preparation of substituted *O*-pyridyl carbamates **2a–c** from the parent isomeric systems **1a–c** involving the powerful ortho metalation directing and 1,3 O → C migratory abilities of the carbamate functionality.[3] This constitutes a new methodology for



(10) (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (b) Concerning stereoselective allyl addition leading to the diastereomeric form, see: Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, *123*, 320. (c) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 1109.

(11) $PhTi(OCHMe_2)_3$ is a rare exception: Mulzer, J.; Angermann, A.; *Tetrahedron Lett.* **1983**, *24*, 2842.

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(1) Tieckelmann, H. In "Pyridine and Its Derivatives", Suppl. Pt. 3; Abramovitch, R. A., Ed.; Wiley: New York, **1984**, p 597.

(2) For example, see ref 1, p 800 ff.

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