pyrophenophorbide *a* with a 2-Et group will be the same as 2-vinyl methyl pyropheophorbide *a* (**3**)]. In the case of meso-nitro compound **15**, 7b′ is shifted upfield relative to **3**, while in δ-cyano derivative **14** the shift of 7b′ is hardly affected. The net result of these changes is that the 7a,7a′ and 7b,7b′ anisochronies are increased in both meso-substituted compounds relative to **3**. Thus, in **15**, 7a and 7b, and 7a′ and 7b′ have switched places relative to their ordering in **3**. The anisochrony of 7a,7b′ (0.45 ppm) is significantly larger in δ-nitro compound **15** than in δ-cyano derivative **14** (0.32 ppm).

A comparison of δ-methyl-substituted compounds **17** and **13** with the corresponding δ-unsubstituted compounds **7** and **9** shows upfield shifts for 7a (0.23, 0.17 ppm) and 7a′ (0.18, 0.11 ppm) in the former. The changes in 7b and 7b′ are much smaller. The changes in the anisochrony of 7a,7a′ and 7b,7b′ within each series do not seem to follow a predictable pattern. Unfortunately, the four protons of metal-free methyl bacteriopheophorbide *c* [Et,Et] (**18**) appeared as a pair of multiplets too closely coupled to simulate, thus a comparison with the corresponding δ-unsubstituted methyl pyropheophorbide a was not possible. The 7-H in all the δ-substituted compounds experienced an upfield shift of 0.07–0.20 ppm relative to their meso-unsubstituted analogues.

## Conclusions

Both the chemcial shifts and coupling constants observed for the propionate ester side-chain protons are consistent with the premise that introduction of a nickel atom into the chlorin ring causes a pronounced conformational change in the side chain, and by inference, in ring D. The introduction of δ substituents, in contrast, appears to have only a local minor perturbation of the ring D substituents, but removal of the exocyclic ring also appears to perturb the side chains appreciably.

**Acknowledgment.** This work was supported by grants from the National Science Foundation (CHE-81-20891) and the Scientific Affairs Division of N.A.T.O. (RG 256.80).

# Asymmetric Synthesis via Acetal Templates. 13.[1] Preparation of Aldol Compounds from Butane-1,3-diol Acetals

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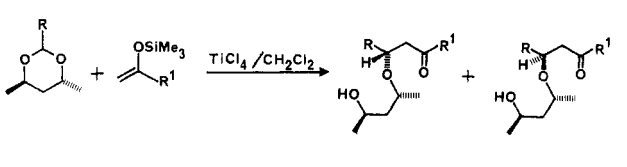
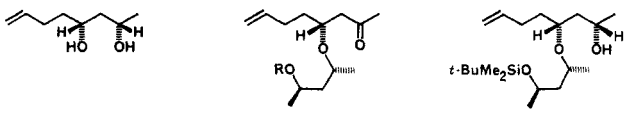
The acetals **8**, derived from (3*S*)-butane-1,3-diol, undergo $TiCl_4$-catalyzed coupling with acetone trimethylsilyl enol ether (**11**) to give the aldol ethers **12**/**13** in high yield and diastereoselectivity in favor of **12** (Table I). The chiral auxiliary is readily removed from **12** by oxidation to the aldehyde **14** followed by selective β-elimination under conditions (dibenzylammonium trifluoroacetate) to which the aldol product **16** is stable (Table II). This methodology has been applied to an efficient asymmetric synthesis of (2*R*,4*S*)-oct-7-ene-2,4-diol (*enantio*-**5**), a key intermediate in the synthesis of nonactic acid.

Recently we disclosed methodology for the asymmetric synthesis of aldol ethers **3**/**4** based upon the coupling of chiral acetals **1**, derived from pentane-2,4-diol, with α-silyl ketones or enol silyl ethers (Scheme I),[2] the product being generated in high yield and with excellent diastereoselectivity (>95:5) in favor of **3**. As previously noted, however, this method is not generally applicable to the production of aldol compounds themselves. Thus removal of the chiral auxiliary from aldol ethers **3**/**4** cannot be achieved via the oxidation/β-elimination sequence without concommitant destruction of the aldol, except when $R^1$ is bulky (e.g., *tert*-butyl).[2] This limitation can be circumvented by appropriate elaboration of the carbonyl group of **3**/**4** prior to removal of the chiral auxiliary, an approach that was successfully applied (see below) to the preparation of diol **5**, a key intermediate in the Bartlett synthesis of nonactic acid.[3]

**Scheme I**




1 2 3 4



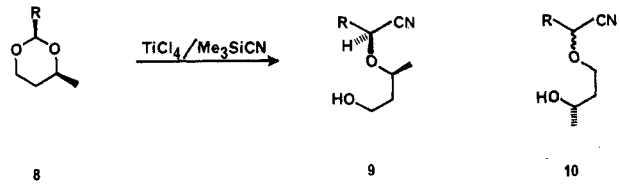
5 6 7

There still remains a need to develop a general route to the free homochiral aldol products. Thus, in our synthesis of **5**, the coupling product **6** (R = H) was conveniently obtained according to the method of Scheme I (89% yield, 94% de). However, stereoselective reduction of the carbonyl group proved to be difficult, and the most favorable result, involving L-Selectride (Aldrich) reduction of **6** (R = $SiMe_2$-*t*-Bu), gave only a 4:1 preference for the desired syn alcohol **7**.[2] On the other hand, reduction of aldol compounds of type **16** with *n*-$Bu_3B$/$NaBH_4$ has been reported[4] to yield the corresponding syn diols highly stereoselectively. The present paper discloses the use of some acetals of butane-1,3-diol in a scheme (Tables I and II) which affords direct access to the free aldol compounds. Also disclosed is the application of this modified methodology to an improved synthesis of the enantiomeric form of diol **5**[5] via the aldol **16a**.

(1) Paper 12: Elliott, J. D.; Steele, J.; Johnson, W. S. *Tetrahedron Lett.* **1985**, *26*, 2535–2538.
(2) Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588–7591.
(3) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304–5311.
(4) Narasaka, K.; Pai, H. C. *Tetrahedron* **1984**, *40*, 2233–2238.

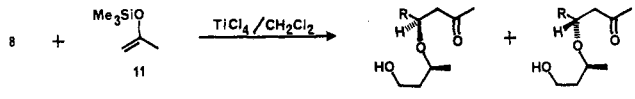
0022-3263/87/1952-0180$01.50/0 

**Scheme II**




8 9 10

**Table I. Aldol Coupling of Chiral Acetals**

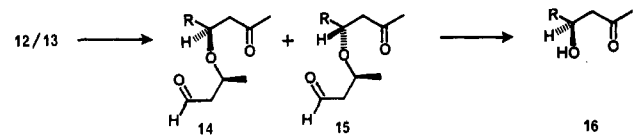



a, R = $CH_2$=$CHCH_2CH_2$
b, R = Cyclohexyl
c, R = n-$C_8H_{17}$

12 13

| entry | acetal | % yield | product[8] | ratio[9] |
|---|---|---|---|---|
| 1 | **8a** | 93 | **12a/13a** | 96:4 |
| 2 | **8b** | 90 | **12b/13b** | 97:3 |
| 3 | 8c | 84 | 12c/13c | >99:1 |

**Table II. Removal of the Chiral Auxiliary**




14 15 16

a, R = $CH_2$=$CHCH_2CH_2$
b, R = Cyclohexyl
c, R = n-$C_8H_{17}$

| entry | coupling product | aldol[15] | % yield | $[\alpha]^{25}_D$ ($CCl_4$) |
|---|---|---|---|---|
| 1 | **12a/13a** | **16a** | 82 | +41° (c 1.8) |
| 2 | **12b/13b** | **16b** | 93 | +52° (c 1.1) |
| 3 | 12c/13c | 16c | 81 | +35° (c 1.8) |

In previous work directed toward the asymmetric synthesis of cyanohydrins, the Lewis acid mediated coupling of acetals derived from (3*S*)-butane-1,3-diol[6] with cyanotrimethylsilane was examined.[7] Under appropriate conditions certain acetals of this type (e.g., **8**, R = *m*-$C_6H_5OC_6H_4$) underwent ring opening to give a primary alcohol product **9** to the almost complete exclusion of the secondary alcohol **10**, arising from the regioisomeric mode of acetal ring opening. The predominant product **9** was also shown to be of very high diastereoisomeric purity at the newly created asymmetric center (Scheme II).[8] These observations suggested a possible solution to the aforementioned problem of generating free aldol products. If the coupling of an acetal of type **8** with an enol silyl ether were to proceed (as in the example **8** → **9**) to give a primary alcohol product **12/13**,[9] it was anticipated that the aldehydes **14/15** obtained by oxidation of **12/13** might selectively undergo β-elimination under conditions that would not lead to destruction of the aldol **16**.

Experimental conditions were developed for the titanium tetrachloride mediated coupling of acetals **8a–c** with acetone trimethylsilyl enol ether **11**, which led to diastereoisomeric mixtures of primary alcohols (entries 1–3, Table I).[9,10] In the course of these studies optimal conditions of temperature, concentration, and order of addition of reagents were determined. It is noteworthy that hexamethyldisiloxane, a contaminant of the acetone silyl enol ether used in these investigations, was found to exert a beneficial effect upon the coupling process with respect to yield and diastereoselection.[11] A general coupling procedure was developed in which the optimal quantity of hexamethyldisiloxane was determined.[11] A preliminary experiment in which the readily available isopropenyl acetate was used in place of acetone trimethylsilyl enol ether showed a considerable preference for the undesired mode of ring opening to the secondary alcohol.

Removal of the chiral auxiliary from the coupling product **12/13** was achieved in each case by oxidation (PCC)[12] to the keto aldehyde **14/15** followed by β-elimination (dibenzylammonium trifluoroacetate,[13] benzene, 50 °C, 15 min) to afford the free aldol product **16**. The novel selectivity observed in the β-elimination process presumably reflects the respective ease of enamine formation, since these are known intermediates in such processes.[14] The results of removal of the chiral auxiliary are shown in Table II.

By analogy to the stereochemical course of the cyanation reaction of butane-1,3-diol acetals,[7] it was presumed that the major diastereoisomer of the coupling reaction with silyl enol ethers is as depicted in Table I. The absolute configuration of aldol **16a** was confirmed as that shown

(5) Both enantiomeric forms of nonactic acid are components of nonactin.

(6) The *S*-diol is available in high optical purity by LAH reduction of the corresponding enantiomer of ethyl 3-hydroxybutyrate produced via microbial reduction of ethyl acetoacetate. See inter alia: Wipf, B.; Kupfer, E.; Bertazzi, R.; Leuenberger, H. G. W. *Helv. Chim. Acta.* **1983**, *66*, 485–488. The optical purity of the (3*S*)-butane-1,3-diol used in the present study was established as 96% by capillary GC (15-m SE-54 column) of the bis-(*R*)-(+)-MTPA esters: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549. Optically pure (3*R*)-1,3-butanediol is readily available by LAH reduction of the inexpensive biopolymer PHB: Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495–503. For the commercial availability of PHB, see: Seebach, D.; Imwinkelried, R.; Stucky, G. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 178–180, footnote 10.

(7) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591–594.

(8) The product was purified by low-pressure column chromatography using "Merck silica gel 60H for thin-layer chromatography".

(9) The diastereoisomeric ratio was determined by GC on a 15-m SE-54 fused silica capillary column which showed a base-line separation of the two peaks except for **12c/13c**, in which case conversion to the TBDMS ethers gave a separable mixture.

(10) The diastereoisomers **12a/13a** were separated by chromatography (see ref 8, gradient elution, 20–50% ether/hexane). Both diastereoisomers upon oxidation (PCC, see ref 12) gave aldehyde products confirming that the two capillary GC peaks in the original mixture correspond to primary alcohol diastereoisomers. Confirmation of the capillary GC peak assignments to diastereoisomers **12b/13b** was also achieved by this method, but in this case HPLC (DuPont Zorbax SIL, eluant 55% ethyl acetate/hexane) was necessary to separate the mixture. Under optimized conditions the crude coupling product contained less than 2% of the secondary alcohol (capillary GC).

(11) Acetone trimethylsilyl enol ether was prepared according to the method of Walshe et al. (Walshe, N. D. A.; Goodwin, G. B. T.; Smith, G. C.; Woodward, F. E. *Org. Syn.*, in press), except that, in the workup, the organic layer was washed with cold, saturated sodium bisulfite which removed the triethylamine. In our hands this procedure gave material containing 4–9% hexamethyldisiloxane ($^1H$ NMR) as the sole contaminant. Before use in the coupling process further hexamethyldisiloxane was added to give a mixture comprising acetone silyl enol ether and hexamethyldisiloxane in a 3:2 molar ratio. The improved selectivity observed with added hexamethyldisiloxane was most noticeable in the conversion **8a** → **12a/13a** (96:4 vs. 91:9 with no added siloxane). This effect may be due to catalyst modification where a chlorine is replaced by a (trimethylsilyl)oxy ligand providing a milder Lewis acid. Since the best selectivities are obtained when the Lewis acid is added last and slowly, we explored the possibility of adding a premixed solution of $TiCl_4$ and $(Me_3Si)_2O$. This approach proved less attractive due to the rapid loss of catalytic activity during the addition (20–30 min)—perhaps the result of catalyst polymerization. Hexamethyldisiloxane has also been observed to improve the $TiCl_4$-catalyzed allylation reaction (ref 17) providing selectivities comparable to those using the $TiCl_4/Ti(OiPr)_4$ catalyst (P. H. Crackett, unpublished results). It is noteworthy that with the latter catalytic mixture, no aldol coupling is obtained. The effect of hexamethyldisiloxane on the aldol coupling of the pentane-2,4-diol acetals (ref 2) has not yet been determined.

(12) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.

(13) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031–8034.

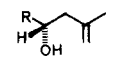
(14) See, inter alia: Roberts, R. D.; Ferran, H. E., Jr.; Gula, M. J.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054–7058.

(15) Aldols **16b** and **16c** are known in racemic form: Kugatova-Shemyakina, G. P. *Vestn. Akak. Nauk SSSR* **1965**, *35*(8), 40–4. Breusch, F. L.; Baykut, F. *Istanbul Univ. Fen Fak. Mecm. Seri A* **1951**, *16A*, 88–94.

in Table II by reduction using $n$-$Bu_3B/NaBH_4$[4] to give a mixture of diols enantio **5** and its C-2 epimer (97:3) (78% yield). This product $[\alpha]^{25}_D$ −16.9° ($c$ 1.1, $CCl_4$), was identical ($^1H$ NMR, IR, GC co-injection) with an authentic sample of the 2*R*,4*S* diol, enantio **5**,[16] $[\alpha]^{25}_D$ −18.3° ($c$ 0.75, $CCl_4$). The present synthesis of diol enantio-**5** in 92% optical purity (59% yield overall in 4 steps from **8a**) constitutes a considerable improvement over our previous route to its antipode.[2] The acetal derived from the readily available (3*R*)-butane-1,3-diol[6] could be used similarly to gain access to diol **5**.[5]

The absolute configurations of the aldols **16b** and **16c** were confirmed by their independent preparation in enantiomeric form, through ozonolysis of the respective homoallylic alcohols **17a** and **17b**, previously synthesized

a, R = Cyclohexyl
b, R = n-$C_8H_{17}$



17

by chiral acetal methodology.[17] This alternative approach to certain aldols is also noteworthy.

## Experimental Section

Acetals **8a–c** were prepared in excellent yield from the corresponding aldehyde and (3*S*)-butane-1,3-diol[6] in the presence of a catalytic quantity of pyridinium $p$-toluenesulfonate.

**(2*R*,4*S*)-2-(But-3′-en-1′-yl)-4-methyl-1,3-dioxane (8a):** $[\alpha]^{25}_D$ + 5° ($c$ 1, MeOH); $^1H$ NMR ($CDCl_3$) 1.23 (d, $J$ = 6.2 Hz, 3, $CH_3$), 1.38–1.45 (m, 1, CH*H*CHCH$_3$), 1.57–1.75 (m, 3, $H_2C$=CHCH$_2$C-$H_2$CH and CH*H*CHCH$_3$), 2.12–2.23 (m, 2, $CH_2$CH=$CH_2$), 3.67–3.78 (m, 2, CH*H*O and $CH_3CHO$), 4.09 (ddd, $J$ = 1.2, 5, and 11.4 Hz, 1, OC*H*H), 4.53 (t, $J$ = 5.2 Hz, 1, OC*H*O), 4.93–5.08 (m, 2, CH=$CH_2$), 5.77–5.91 (m, 1, C*H*=$CH_2$).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.03; H, 10.42.

**(2*R*,4*S*)-2-Cyclohexyl-4-methyl-1,3-dioxane (8b):** $[\alpha]_D^{25}$ + 14° ($c$ 2.1, $CCl_4$); $^1H$ NMR ($CDCl_3$) 0.95–1.88 (m, 16, d at 1.21, $J$ = 6.2 Hz, $CH_3$ superimposed upon m, cyclohexyl and $CH_2CH_2O$), 3.64–3.76 (m, 2, OCH*H* and $CH_3CHO$), 4.09 (ddd, $J$ = 1.2, 5, and 11.4 Hz, 1, OC*H*H), 4.22 (d, $J$ = 5.7 Hz, 1, OCHO).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.78; H, 10.76.

**(2*R*,4*S*)-4-Methyl-2-octyl-1,3-dioxane (8c):** $[\alpha]_D^{25}$ +2.4° ($c$ 2.4 MeOH); $^1H$ NMR ($CDCl_3$) 0.82–0.92 (m, 3, $CH_3CH_2$), 1.15–1.73 (m, 19, d at 1.23, $J$ = 6.2 Hz, $CH_3$ superimposed upon m, 8 × $CH_2$), 3.67–3.78 (m, 2, OCH*H* and $CH_3CHO$), 4.08 (dd, $J$ = 5 and 11.4 Hz, 1, OC*H*H), 4.51 (t, $J$ = 5.2 Hz, 1, OCHO).

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 72.85; H, 12.36.

**Coupling of Acetal (8a) with 2-((Trimethylsilyl)oxy)-propene (11).** A solution of titanium tetrachloride (0.20 mL, 1.82 mmol) in dry dichloromethane (1.8 mL) was instilled via motorized syringe over 85 min into a stirred, cooled (−40 °C) solution of acetal **8a** (0.093 g, 0.60 mmol), 2-((trimethylsilyl)oxy)propene **11**[11] (0.494 mL, 2.91 mmol), and hexamethyldisiloxane (0.430 mL, 2.0 mmol) in dry dichloromethane (25 mL) under argon. After an additional 20 min, methanol (2.5 mL) was added rapidly at −40 °C; then the mixture was immediately poured into water (20 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with 20-mL portions of 1 M aqueous hydrochloric acid, water, 5% aqueous sodium hydrogen carbonate solution, and brine. Drying (anhydrous magnesium sulfate), filtration, and evaporation gave a light yellow oil. GC (110 °C) of the crude product showed two peaks corresponding to the diastereoisomers **12a/13a** in the ratio 96:4.[9,10]

Column chromatography[8] (gradient elution, 20–100% ether/hexane) gave **(4*RS*,1′*S*)-4-(3′-hydroxy-1′-methylpropoxy)-oct-7-en-2-one (12a/13a)** as a colorless oil (0.118 g, 93% yield): IR (film) 3100–3700 (OH), 1710 (C=O), 1640 cm$^{-1}$ (C=C); $^1H$ NMR ($CDCl_3$), 1.13 (d, $J$ = 6.1 Hz, 3, $CH_3$), 1.5–1.75 (m, 4, 2 × $CH_2$), 2.01–2.14 (m, 2, C=CHC$H_2$), 2.17 (s, 3, $CH_3C$=O), 2.44–2.70 (ABq at 2.48, $J$ = 5 and 16 Hz, 1, C*H*HC=O, superimposed upon br s, 1, OH), 2.65 (ABq, $J$ = 7.5 and 16 Hz, 1, CH*H*C=O), 3.68–3.95 (m, 4, 2 × CHO and $CH_2$OH), 4.95–5.08 (m, 2, $CH_2$=CH), 5.73–5.87 (m, 1, $CH_2$=C*H*).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 66.87; H, 10.40.

**Coupling of Acetal (8b) with 2-((Trimethylsilyl)oxy)-propene (11).** By the same procedure used to prepare **12a/13a**, the acetal **8b** (0.130 g, 0.71 mmol) gave **12b/13b**. GC (140 °C) of **12b/13b** showed two peaks, ratio 97:3.[9,10] Column chromatography[8] (gradient elution, 10–50% ether/hexane) gave **(4*RS*,1′*S*)-4-cyclohexyl-4-(3′-hydroxy-1′-methylpropoxy)-butan-2-one (12b/13b)** as a colorless oil (0.154 g, 90% yield). IR (film) 3100–3660 (OH), 1700 cm$^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) 0.9–1.8 (m, 17, 6 × $CH_2$, OH and CH superimposed upon d at 1.11, $J$ = 6.1 Hz, C*H*$_3$CH), 2.17 (s, 3, $CH_3C$=O), 2.39 (ABq, $J$ = 4 and 15.5 Hz, 1, C*H*HC=O), 2.60 (ABq, $J$ = 8.2 and 15.5 Hz, 1, CH*H*C=O), 3.68–3.83 (m, 4, 2 × CHO and $CH_2$OH).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.26; H, 10.78.

**Coupling of Acetal (8c) with 2-((Trimethylsilyl)oxy)-propene (11).** By the same procedure used to prepare **12a/13a** the acetal **8c** (0.115 g, 0.54 mmol) gave **12c/13c**. GC (160 °C) of **12c/13c** failed to show diastereoisomer separation. Column chromatography[8] (gradient elution, 10–35% ether/hexane) gave **(4*RS*,1′*S*)-4-(3′-hydroxy-1′-methylpropoxy)dodecan-2-one (12c/13c)** as a colorless oil (0.123 g, 84% yield). IR (film) 3150–3600 (OH), 1710 cm$^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) 0.88 (br t, $J$ = 6.6 Hz, 3, C*H*$_3$CH$_2$), 1.12 (d, $J$ = 6.1 Hz, 3, C*H*$_3$CH), 1.14–1.73 (m, 16, 8 × $CH_2$), 2.17 (s, 3, $CH_3C$=O), 2.46 (ABq, $J$ = 4.5 and 15.5 Hz, 1, C*H*HC=O), 2.61 (m, 2, ABq, $J$ = 8 and 15.5 Hz, CH*H*C=O superimposed upon br s, OH), 3.71–3.92 (m, 4, 2 × CHO and $CH_2$OH).

Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.28; H, 12.16.

The diastereoisomeric ratio of crude **12c/13c** was shown to be >99:1 by conversion to the *tert*-butyldimethylsilyl ethers.[9]

**(4*S*)-4-Hydroxyoct-7-en-2-one (16a).** The diastereoisomeric mixture of alcohols **12a/13a** (97:3) (0.225 g, 1.05 mmol) was dissolved in dichloromethane (5 mL) and pyridinium chlorochromate[12] (0.69 g, 3.2 mmol) added. The mixture was stirred at room temperature under argon for 2 h in a flask protected from light. Ether (10 mL) was then added and the product filtered through Florisil. The brown residue was washed with ether (100 mL) and the triturant was then passed through the column. The solvent was evaporated to give keto aldehydes **14a/15a** as a pale yellow oil (0.198 g, 89%), GC (110 °C) **14a/15a** ratio 97:3.[9] This material was used directly without purification.

The mixutre of keto aldehydes **14a/15a** (0.198 g, 0.93 mmol) was dissolved in benzene (12 mL). To this stirred solution at 50 °C was added dibenzylammonium trifluoroacetate[13] (1.20 g, 3.86 mmol). After 10 min the solution was applied to a silica gel column and eluted successively with hexane (100 mL), 10% ether/hexane (100 mL), 20% ether/hexane (150 mL). The title compound, **16a**, was thus obtained as a yellow oil (0.109 g, 82% yield); GC (110 °C) retention time 1.20 min (95%). A sample for characterization was prepared by HPLC (DuPont Zorbax SIL, eluants 55% ethyl acetate/hexane): $[\alpha]_D^{25}$ + 41° (c 1.8, $CCl_4$); IR (film) 3100–3650 (OH), 1710 (C=O), 1640 cm$^{-1}$ (C=C); $^1H$ NMR ($CDCl_3$) 1.41–1.67 (m, 2, C$H_2$CHOH), 2.07 (m, 5, s at 2.18, $CH_3C$=O superimposed upon m, C=CHC$H_2$), 2.54 (ABq, $J$ = 8.6 and 17.7 Hz, 1, C*H*HC=O), 2.64 (ABq, $J$ = 3.3 and 17.7 Hz, 1, CH*H*C=O), 2.90–3.10 (br, 1, OH), 4.01–4.12 (m, 1, C*H*OH), 4.95–5.08 (m, 2, HC=C$H_2$), 5.76–5.89 (m, 1, *H*C=$CH_2$).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.60; H, 9.94.

**(4*R*)-4-Cyclohexyl-4-hydroxybutan-2-one (16b).** By the same procedure used to prepare **16a**, the diastereoisomeric alcohols **12b/13b** (96:4) (0.16 g, 0.66 mmol) were converted to aldol **16b**. Column chromatography[8] (gradient elution: 0–45% ether/hexane) gave the title compound **16b** as a pale yellow oil (0.104 g, 93% yield): $[\alpha]_D^{25}$ +52° ($c$ 1.1 $CCl_4$); IR (film) 3100–3650 (OH), 1700

(16) Obtained by saponification of the corresponding cyclic carbonate (a gift from Prof. P. A. Bartlett), prepared from (*S*)-(−)-malic acid by a stereorational synthesis (reference 3).

(17) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951–3954.

cm$^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) 0.85-1.9 (m, 11, cyclohexyl), 2.19 (s, 3, $CH_3C$=O), 2.54 (ABq, $J$ = 9.1 and 17.5 Hz, 1, C*H*HC=O), 2.63 (ABq, $J$ = 3 and 17.5 Hz, 1, CH*H*C=O), 2.88 (br s, 1, OH), 3.77-3.85 (m, 1, C*H*OH).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.26; H, 10.78.

A sample of (4*S*)-4-cyclohexyl-4-hydroxybutan-2-one (*enantio*-**16b**) $[\alpha]_D^{25}$ -53° (*c* 1.1, $CCl_4$) was prepared by ozonolysis (pentane/ethanol, 1:1) of the previously reported[17] (4*S*)-4-cyclohexyl-4-hydroxy-2-methylbut-1-ene (**17a**, 98% ee). The identity of this material and **16b** was established by GC co-injection. The $^1$H NMR and IR of this sample were identical with those given for **16b**.

**(4*S*)-4-Hydroxydodecan-2-one (16c).** By the same procedure used to prepare **16a**, the diastereoisomeric alcohols **12c**/**13c** (0.140 g, 0.51 mmol) were converted to aldol **16c**. Column chromatography[8] (gradient elution, 10-30% ether-hexane) gave the title compound **16c** as a white solid (0.083 g, 81% yield), mp 34-35 °C; $[\alpha]_D^{25}$ +35° (*c* 1.8, $CCl_4$); IR (film) 3300-3650 (OH), 1700 cm$^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) 0.87 (t, $J$ = 7 Hz, 3, $CH_3CH_2$), 1.20-1.55 (m, 14, 7 × $CH_2$), 2.18 (s, 3, $CH_3C$=O), 2.52 (ABq, $J$ = 8.9 and 17.1 Hz, 1, C*H*HC=O), 2.63 (ABq, $J$ = 3 and 17.7 Hz, 1, CH*H*C=O), 2.95 (br s, 1, OH), 3.99-4.08 (m, 1, C*H*OH).

A sample of (4*R*)-4-hydroxydodecan-2-one (*enantio*-**16c**) $[\alpha]_D^{25}$ -37° (*c* 1.3, $CCl_4$) was prepared by ozonlysis (pentane/ethanol, 1:1) of the previously reported[17] (4*R*)-4-hydroxy-2-methyldodec-1-ene (**17b**, 92% ee). The identity of this material and **16c** was established by GC co-injection. The $^1$H NMR and IR of this sample were identical with those given above for **16c**.

**(2*R*,4*S*)-Oct-7-ene-2,4-diol (*enantio*-5).** The stereoselective reduction of aldol **16a** was performed according to the procedure of Narasaka and Pai.[4] Thus aldol **16a** (0.10 g, 0.65 mmol) gave the title compound *enantio*-**5** (0.079 g, 78% yield), $[\alpha]_D^{25}$ -16.9° (*c* 1.1, $CCl_4$). IR, $^1$H NMR, and GC co-injection established the identity of *enantio*-**5** with an authentic sample.[16] In order to establish the amount of the 2*S* diastereoisomer present, the diol (*enantio*-**5**) was bis(acetylated) ($Ac_2O$/pyridine/(4-dimethylamino)pyridine/room temperature/3 h). GC[9] of the diacetate showed the ratio of *enantio*-**5** and its C-2 epimer to be 97:3.

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**Registry No.** **5** (isomer 1), 88390-25-4; **5** (isomer 2), 99340-95-1; **8a**, 105230-22-6; **8b**, 105230-23-7; **8c**, 90457-76-4; **11**, 1833-53-0; **12a**, 105230-24-8; **12b**, 105230-26-0; **12c**, 105230-28-2; **13a**, 105230-25-9; **13b**, 105230-27-1; **13c**, 105230-29-3; **14a**, 105230-32-8; **15a**, 105230-33-9; **16a**, 105230-30-6; **16b**, 93643-66-4; **16c**, 105230-31-7; **17a**, 94340-24-6; **17b**, 94340-23-5; $CH_2$=$CHCH_2CH_2CHO$, 2100-17-6; $CH_3(CH_2)_7CHO$, 124-19-6; (*S*)-$HOCH_2CH_2CH(OH)CH_3$, 24621-61-2; $TiCl_4$, 7550-45-0; formylcyclohexane, 2043-61-0.

# Evaluation of Some Preparations of Trialkoxyphthalic Acid Derivatives

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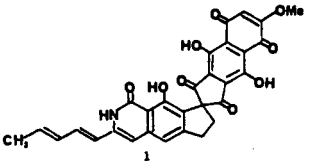
Several approaches to trialkoxyphthalic acid derivatives, potential intermediates in a fredericamycin synthesis, were tested. Sequences based on a Diels-Alder/retro Diels-Alder reaction, a cyanide addition to a quinone, an E1bs oxidation, and an amide-directed ortho-lithiation are discussed in terms of length, yields, convenience, and the versatility of the product of each.

## Introduction

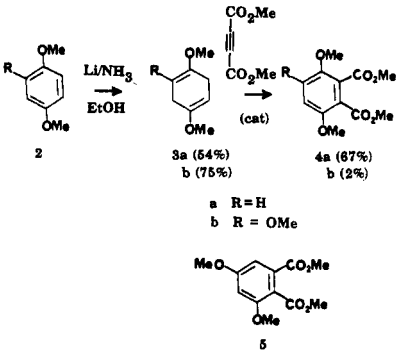
Retrosynthetic dissection of the structure of the antitumor antibiotic fredericamycin A (**1**)[1] is likely to lead to consideration of a trialkoxyphthalic acid derivative as a building block. For pursuit of our own synthesis of fredericamycin[2] and analogues which contain the benzindenedione ring system, we required that this key intermediate be obtained easily and in quantity and we preferred that the preparation be inexpensive.



**1**

Although a search of the literature revealed only two trialkoxyphthalic acid derivatives,[3] we could imagine various, distinct approaches to members of the class. At this stage, we consider carboxylic ester, nitrile, and aldehydo groups to be potentially useful one-carbon appendages, and we have prepared several compounds which could prove useful for the elaboration of structure **1**. In this paper we describe the advantages and disadvantages of these syntheses as entries to the trialkoxy phthalic acid system.

**Scheme I**




## Results

**The Birch Reduction/Diels-Alder Strategy.** Phthalic acid derivatives have been prepared by a two-step

(1) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478.

(2) (a) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181. (b) Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835.

(3) (a) 3,4,6-Trihydroxyphthalonitrile was prepared by Thiele and Gunther (Thiele, J.; Gunther, F. *Justus Liebigs Ann. Chem.* **1906**, *349*, 45). (b) 6-Hydroxy-3,4-dimethoxyphthalic acid was prepared by MacKenzie and Robertson (MacKenzie, J. B. D.; Robertson, A. *J. Chem. Soc.* **1949**, 497).

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