100), 243 (M - CH_3, 9), 228 (M - $2CH_3$, 6). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.04; H, 8.58. Found: C, 79.07; H, 8.66.

3,6-Di-*tert*-butyl-1,7-dimethoxy-8-methylnaphthalene (22). Compound **21** (9.6 g, 37.2 mmol), 10 mL of *tert*-butyl alcohol, 50 mL of trifluoroacetic acid, and 3 drops of concentrated sulfuric acid were stirred for 24 h at room temperature, and ether was added. Evaporation of the washed (2 N NaOH, water) and dried ether phase yielded **22**: 11.7 g (99%); mp 114-115 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 1.38, 1.48 (2 s, 2 × 9 H, *t*-Bu), 2.77 (s, 3 H, CH_3-Ar), 3.78, 3.95 (2 s, 2 × 3 H, OCH_3), 6.85, 7.28 (2 d, J = 1.5 Hz, 2 H, Ar H), 7.53 (s, H-5); MS (70 eV), *m/e* (relative intensity) 314 (M^+, 100), 299 (M - CH_3, 22). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.38; H, 9.60.

3,6-Di-*tert*-butyl-1,7-dihydroxy-8-methylnaphthalene (23). To a solution of 3 g (9.55 mmol) of **22** in 50 mL of dry dichloromethane was added 5 mL of boron tribromide. After it had been stirred for 2 h at room temperature, a further 2 mL of BBr_3 was added, and after 12 h another 2 mL of BBr_3 was added. The mixture was stirred for 12 h and then evaporated to dryness in vacuo. The residue was taken up with ether and water. After the etheral phase was dried, the evaporation residue was sublimed at 160-200 °C in vacuo to give **23**: 2.4 g (88%); mp 167 °C; IR (KBr) 3580 (OH), 3230 (OH), 2960 (CH), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27, 1.48 (2 s, 2 × 9 H, *t*-Bu), 2.80 (s, 3 H, CH_3-Ar), 5.20, 5.50 (2 s, 2 H, OH), 6.62, 7.24 (2 d, J = 2 Hz, 2 H, Ar H), 7.52 (s, H-5); MS (70 eV), *m/e* (relative intensity) 286 (M^+, 100), 271 (M - CH_3, 54), 217 (M - CO - C_3H_5, 15). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.66; H, 9.17. Found: C, 79.73; H, 9.19.

1,7-Diacetoxy-3,6-di-*tert*-butyl-8-methylnaphthalene (25). Compound **23** (1.1 g, 3.85 mmol) was refluxed (0.5 h) in 10 mL of acetic anhydride containing 0.3 g (3.85 mmol) of dry pyridine. After addition of ice and acidification with dilute hydrochloric acid, the solid was purified by preparative TLC (silica gel, Merck 60 PF 254 + 366/dichloromethane) to give **25**: 0.75 g (53%); mp 60-61 °C; ^1H NMR ($CDCl_3$) δ 1.37, 1.40 (2 s, 2 × 9 H, *t*-Bu), 2.33 (s, 6 H, CH_3CO), 2.39 (s, 3 H, CH_3Ar), 7.17, 7.57 (2 d, J = 1.5 Hz, 2 H, Ar H), 7.65 (s, H-5); MS (70 eV), *m/e* 370 (M^+, 17), 328 (M - $COCH_2$, 35), 2.86 (M - $2COCH_2$, 100), 271 (M - CH_3 - $2COCH_2$, 13). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.57; H, 8.07.

3,6-Di-*tert*-butyl-8-methyl-1,7-naphthoquinone (24). After 1.144 g (4 mmol) of **23** and 0.908 g (4 mmol) of DDQ were flushed in an oven-dried closed apparatus with dry, oxygen-free nitrogen for 2 days, 20 mL of ether was added at -40 °C, the mixture was shaken for 10 min, and the ether was evaporated in vacuo below -30 °C. The bright red residue was dried in vacuo (1 Pa) 4 h at -30 °C, 10 mL of absolutely dry deuteriochloroform was added, and the mixture was filtrated. The solution was used directly for measuring the IR, ^1H NMR and UV/vis spectra. For the mass spectra the chloroform was evaporated again. All operations including the measuring of the IR, UV/vis, and ^1H NMR spectra were performed under dry nitrogen and at -30 °C: IR ($CDCl_3$) 2990 (CH), 1615, 1625 (CO), 1690, 1600 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.32 (s, 18 H, *t*-Bu), 2.48 (s, 3 H, CH_3), 6.77, 6.93, 7.04 (3 br s, 3 H, =CH); MS (70 eV), *m/e* (relative intensity) 286/284 (M^+ **23**/**24**, 12/11), 271/269 (**23**/**24** - CH_3, metastable peaks at 256.79 and 254.29), a metastable peak at 159.75 makes the fragmentation **24** - 2CO - CH_3 probable; calcd for $C_{19}H_{24}O_2$ *m/e* 284.178, found *m/e* 284.177.

Reductive Acetylation of 24. To 246 mg (0.87 mmol) of **24**, a spatula tipful of dry zinc, and 20 mg of dry sodium acetate was added 10 mL of freshly distilled acetic anhydride. The mixture was refluxed for 15 min, diluted with ether, and filtered. The filtrate was evaporated to dryness in vacuo and the residue purified by preparative TLC (silica gel Merck 60 PF 254 + 366/methylene chloride) to give 42.6 mg (13%) of a substance which proved to be identical with authentic **25**.

Acknowledgment is made to the Land Niedersachsen and the Fonds der Chemischen Industrie for the support of our work.

Registry No. **1**, 5309-18-2; **2**, 66952-62-3; **3**, 86392-35-0; **5**, 60772-80-7; **6**, 86392-36-1; **7**, 86392-37-2; **9**, 86392-38-3; **10**, 86392-39-4; **12**, 86392-40-7; **13**, 86392-41-8; **14**, 86392-42-9; **15**, 86392-43-0; **16**, 86392-44-1; **17**, 86392-45-2; **18**, 86392-46-3; **19**, 86392-47-4; **20**, 86392-48-5; **21**, 86392-49-6; **22**, 86392-50-9; **23**, 83021-63-0; **24**, 83021-64-1; **25**, 86392-51-0; 1,4-BQ, 106-51-4; 1,2-BQ, 583-63-1; 1,2-NQ, 524-42-5; 1,4-NQ, 130-15-4; 1,5-NQ, 51583-62-1; 1,7-NQ, 46001-16-5; 2,6-NQ, 613-20-7; 2,3-NQ, 4939-92-8; 1,2-AQ, 655-04-9; 1,4-AQ, 635-12-1; 1,10-AQ, 61391-84-2; 2,9-AQ, 61357-65-1; 1,5-AQ, 61357-66-2; 1,7-AQ, 86409-49-6; 2,3-AQ, 86392-52-1; 2,6-AQ, 61357-67-3; 9,10-AQ, 84-65-1; 4,4'-diphenoquinone, 494-72-4; 1,6-[10]annulenoquinone, 58597-76-5.

Asymmetric 9-Hydroxylation of Anthracyclinones. Total Synthesis of (+)-4-Demethoxydaunomycinone

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A method is described for the synthesis of (*R*)-(-)-4-demethoxy-7-deoxydaunomycinone (**3**) from the readily prepared racemic 4-demethoxy-7,9-dideoxydaunomycinone (**6**). Thus, **6** was converted selectively into its 9-bromo derivative (**9**) by (a) cupric bromide in refluxing chloroform-ethyl acetate or (b) bromine in acetic acid in the presence of hydrogen bromide under equilibrating conditions (100 °C for 20 h). Dehydrohalogenation of **9** by lithium carbonate in dimethylformamide gave the enone **11**, which was converted to diacetate **14** by acetic anhydride. Sodium borohydride reduction of **14** in the presence of ceric chloride gave the racemic allylic alcohol **17**. Asymmetric epoxidation of **17** was carried out by using titanium isopropoxide, (+)-diisopropyl L-tartrate, and 0.6 equiv of *tert*-butyl hydroperoxide to give a mixture of epoxide (-)-**18** and (*R*)-(+)-**17**. Chromic acid oxidation of this mixture, followed by silica chromatography, gave enone **14** (minor product) and epoxy ketone (-)-**20** (major product). Sodium dithionite reduction of (-)-**20** gave (-)-**3** in 82% optically pure form, $[\alpha]^{20}_D$ -71°. The latter compound is an intermediate in the synthesis of (+)-4-demethoxydaunomycinone (**8**).

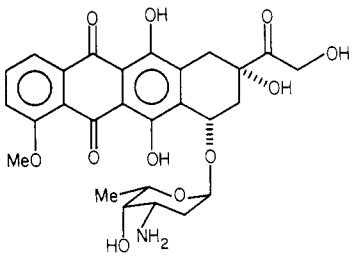
A large number of syntheses of doxorubicin (**1**) related anthracycline aglycones and glycosides have been achieved during the past few years,[1,2] but only recently has much effort been expended on the synthesis of enantiomerically pure aglycones. The availability of such compounds would avoid the complex and wasteful separation of diastereomeric products in the final glycosidation step and, of course, would require the use of less of the valuable sugar moiety.

Reported procedures make use of an optically active tetralin as an AB synthon, i.e., **2** (Chart I), which can be

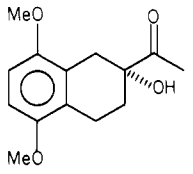
(1) Arcamone, F. "Doxorubicin"; Academic Press: New York, 1981.
(2) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288.

0022-3263/83/1948-2820$01.50/0

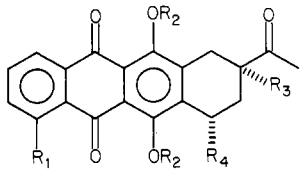
Chart I



1



2

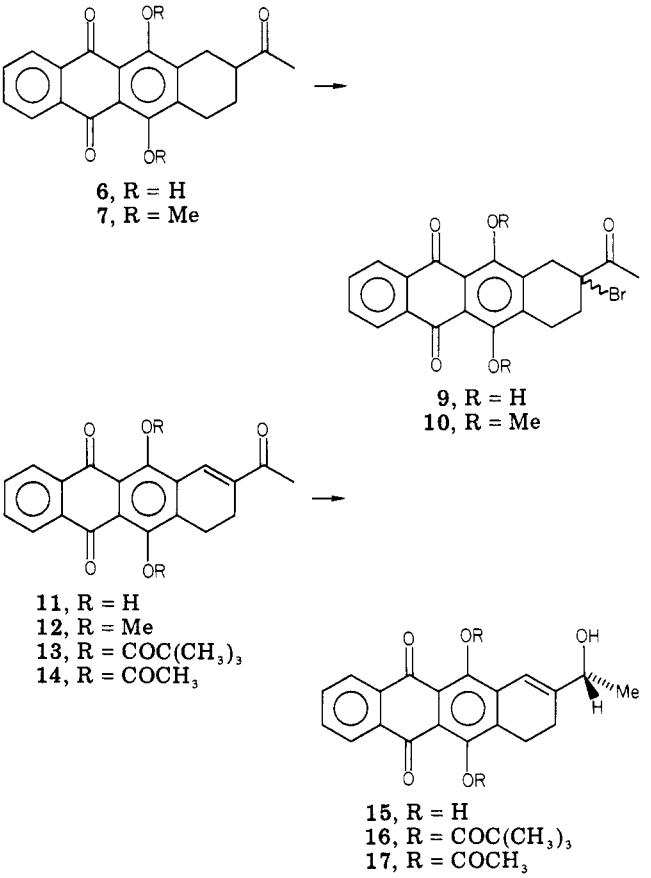


3, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
4, $R_1 = OMe$; $R_2 = R_3 = R_4 = H$
5, $R_1 = OH$; $R_2 = R_3 = R_4 = H$
6, $R_1 = R_2 = R_3 = R_4 = H$
7, $R_1 = R_3 = R_4 = H$; $R_2 = Me$
8, $R_1 = R_2 = H$; $R_3 = R_4 = OH$

obtained either by resolution of racemic material[3] or by asymmetric synthesis.[4] The chiral bicyclic compound is then transformed into a tetracyclic intermediate, i.e., **3**, by using Wong's synthetic sequence,[5a] a reaction that suffers from a lack of regiochemical control, leading to a difficult separation of regioisomers after the formation of ring-D substituted anthracyclinones (i.e., daunomycinone).[5b]

Since several regiocontrolled syntheses of daunomycinone have been achieved through the intermediacy of the tetracyclic ketones **4** or **5**,[6] a method of asymmetric functionalization of the A ring applicable to the preparation of optically active daunomycinone was clearly needed. Using 4-demethoxy-7,9-dideoxydaunomycinone (**6**) as a model,[7] we have recently reported[8] improved procedures for the introduction of the cis diol functionality of 4-demethoxydaunomycinone (**8**), in addition to the resolution of the 9-hydroxy ketone (**3**). Early attempts by Terashima et al.[4a] at the asymmetric introduction of the 9-hydroxy group in a tetracyclic intermediate were fruitless due to functionalization problems. The same group has very recently reported resolutions of **3** by ketalization with an optically active diol[9a] or by asymmetric reduction.[9b] In a different anthracycline series, an asymmetric synthesis of aklavinone has been achieved by Kende.[10]

Scheme I



6, R = H
7, R = Me

9, R = H
10, R = Me

11, R = H
12, R = Me
13, R = $COC(CH_3)_3$
14, R = $COCH_3$

15, R = H
16, R = $COC(CH_3)_3$
17, R = $COCH_3$

Results and Discussion

A general asymmetric synthesis starting from any of the tetracyclic ketones **4–6** would provide an entry for the preparation of a variety of daunorubicin (daunomycin) and doxorubicin analogues (including 11-deoxyanthracyclines[11]) through the intermediacy of the corresponding chiral aglycones.

Since our *o*-quinodimethane approach provides us with a very efficient preparation of the ketones **6** and **7**[12] we chose the above compounds as the starting materials for a chiral synthesis of (+)-4-demethoxydaunomycinone (**8**), the aglycone of the unnatural, but biologically highly active α-7(*S*),9(*S*)-4-demethoxydaunorubicin.[13]

We envisioned that the asymmetric epoxidation of a suitable allylic alcohol would provide us with an optically active epoxy alcohol that could be readily converted to the desired (*R*)-(−)-**3**. To this purpose, allylic alcohols **15–17** were synthesized by the sequence shown in Scheme I.

Selective bromination of ketone **6** was achieved by using a stoichiometric amount of $CuBr_2$ in refluxing $CHCl_3$–EtOAc,[15] compound **9** being obtained in 91% yield with

(3) (a) Arcamone, F.; Bernardi, L.; Patelli, B.; Di Marco, A. *Ger. Pat.* 2601785, 1979. (b) For a fully functionalized optically active tetralin derivative, see: Broadhurst, M. J.; Hassall, G. H.; Thomas, G. J. *J. Chem. Soc., Chem. Commun.* **1982**, 158.

(4) (a) Terashima, S.; Jew, S. S.; Koga, K. *Tetrahedron Lett.* **1978**, 4937. (b) Terashima, S., Tanno, N.; Koga, K. *Ibid.* **1980**, *21*, 2753. (c) Warrener, R. N.; Gee, P. S.; Russell, R. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1100.

(5) (a) Wong, C. M.; Popien, D.; Schwenk, R.; Raa, J. T. *Can. J. Chem.* **1971**, *49*, 2712. (b) Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T. L. *Ibid.* **1973**, *51*, 466.

(6) (a) Swenton, J. S.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6188. (b) Suzuki, F.; Trenbeath, S.; Gleim, R. D.; Sih, C. J. *J. Org. Chem.* **1978**, *43*, 4159. (c) Kine, K. S.; Vannotti, E.; Suarato, A.; Johnson, F. *J. Am. Chem. Soc.* **1979**, *101*, 2483. (d) Parker, K. A.; Kallmerten, J. *Ibid.* **1980**, *102*, 5881. (e) Hauser, F. M.; Prasanna, S. *Ibid.* **1981**, *103*, 6378. (f) Ashcroft, A. E.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1981**, 1075.

(7) Compound **6** is a very common intermediate in a good number of syntheses of 4-demethoxydaunomycinone (**8**): Gleim, R. D.; Trenbeath, S.; Mittall, R. S.; Sih, C. J. *Tetrahedron Lett.* **1976**, 3385. (b) Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822. (c) Suzuki, F.; Gleim, R. D.; Trenbeath, S.; Sih, C. J. *Tetrahedron Lett.* **1977**, 2303. (d) Kerdesky, F. A. J.; Cava, M. P. *J. Am. Chem. Soc.* **1978**, *100*, 3635. (e) Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikantham, M. V.; Cava, M. P. *Ibid.* **1981**, *103*, 1992 and ref 7b and 7f.

(8) Dominguez, D.; Ardecky, R. J.; Cava, M. P. *J. Am. Chem. Soc.* **1983**, *105*, 1608.

(9) (a) Terashima, S.; Tamoto, K.; Sugimori, M. *Tetrahedron Lett.* **1982**, *23*, 4107. (b) Terashima, S.; Tamoto, K. *Ibid.* **1982**, *23*, 3715.

(10) Kende, A. S.; Rissi, P. *J. Am. Chem. Soc.* **1981**, *103*, 4247.

(11) Arcamone, F.; Cassinelli, G.; DiMatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivela, G.; Vigerani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462.

(12) Ardecky, R. J.; Domiguez, D.; Cava, M. P. *J. Org. Chem.* **1982**, *47*, 409.

(13) Arcamone, F.; Bernardi, L.; Giardino, P.; Patelli, B.; DiMarco, A.; Casazza, A. M.; Pratesi, G.; Kiggiani, P. *Cancer Treat. Rep.* **1976**, *60*, 829.

(14) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

no appreciable contamination by isomeric material. However, this procedure was not useful for large-scale preparations of **9**, since the insoluble product precipitates on the bromination reagent unless quite dilute solutions are employed.

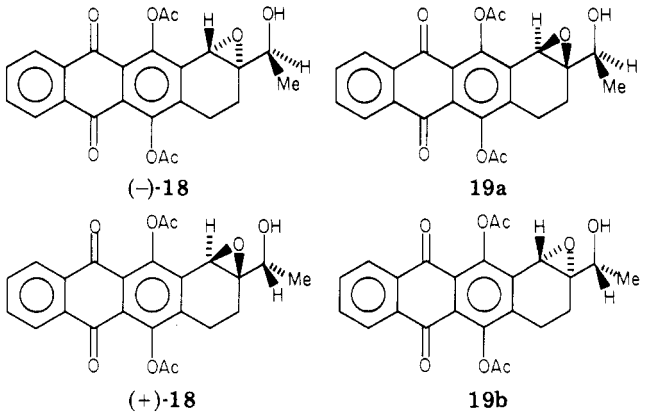
Direct treatment of the red ketone **6** with bromine at room temperature for 5 h in the presence of HBr as catalyst gave a 3:2 mixture of the thermodynamic and kinetic monobromo derivatives [as shown by ^{1}H NMR analysis of an aliquot (=CBrCOCH_3, s at δ 2.57, and =CHCOCH_2Br, s at δ 4.09)] containing less than 10% of starting material and dibrominated product (=CBrCOCH_2Br, s at δ 4.56). However, when the above mixture was heated to 100 °C for 20 h, isomerization took place and the desired bromo derivative **9** separated directly from the solution as orange microcrystals in 88% yield. Lithium carbonate promoted elimination of HBr took place under mild conditions to give the enone **11** in quantitative yield. Sodium borohydride reduction of **11** in $CHCl_3$ in the presence of MeOH or EtOH, followed by air oxidation, was slow and incomplete. Fortunately, the above transformation was cleanly carried out in MeOH in the presence of an equimolar amount of $CeCl_3$,[16] giving the 1,2-reduced product (±)-**15** in 88% yield, after quenching with HOAc.[17]

Our attempts to carry out an asymmetric epoxidation of the allylic alcohol (±)-**15** using the Sharpless conditions[14] were unsuccessful, due to the formation of a highly insoluble chelate formed between the hydroxyanthraquinone system and Ti(O-*i*-Pr)$_4$.[18] In order to avoid this problem, protection of the phenolic groups was necessary, and we investigated the synthesis of the enone methyl ether **12**. The preparation of this compound proved to be difficult, since methylation of **11** (MeOTs, K_2CO_3, DMF, heat) was accompanied by extensive aromatization (50%) and the required product was difficult to separate. The alternative route from the dimethoxy ketone **7**, via bromination–elimination, gave only 37% of enone **12** along with 32% of a mixture of monodemethylated products arising from an HBr-promoted demethylation in the bromination step. As expected, no bromination took place when **7** was treated with $CuBr_2$ in the presence of Li_2CO_3 as an acid scavenger. Due to the above difficulties, the utilization of **12** as the precursor of a protected allylic alcohol was abandoned. We next decided to use an ester as protecting group, the pivalate **13** being chosen in order to prevent a possible hydrolysis during the reduction step. Thus, pivaloyl chloride treatment of **9** in pyridine, followed by $NaBH_4$ reduction in the presence of Ce^{3+}, gave (±)-**16** in good yield.

Attempted epoxidations of (±)-**16** under the Sharpless conditions at −20 °C, or even at room temperature in the presence of an excess of THBP, were completely unsuccessful, the starting material being recovered unchanged. This lack of reactivity, due to steric hindrance of the olefinic bond, led us to next attempt the use of the diacetoxy alcohol (±)-**17** as the substrate in the epoxidation step. Compound (±)-**17** was prepared from **11** in two steps in 67% overall yield.

Fortunately, the allylic alcohol (±)-**17** was in fact kinetically resolved into a mixture of (−)-**18** and (*R*)-(+)-**17**,[19]

Chart II



obtained in 34% and 23% yield, respectively,[20] by using a Sharpless asymmetric epoxidation procedure.[14] At this point we envisioned that besides the kinetic differentiation between both enantiomers of **17**, we could expect the slower reacting one to exhibit a different stereoselectivity, leading to a preferential formation of threo compound **19b**[21] (Chart II). In this ideal situation, starting with (±)-**17** we would end up with a diastereomeric mixture of *erythro*-(−)-**18** and *threo*-**19b**, which on oxidation of the alcohol function would afford the desired optically pure epoxide (−)-**20**. Unfortunately, this proved not to be the case, and reaction of (±)-**17** with an excess of *t*-BuOOH to the point of complete epoxidation showed the same stereoselectivity for both reactive enantiomers, giving *erythro*-(±)-**18** as the sole epoxide present in the reaction mixture, as shown by NMR analysis.[22]

In view of the above result we decided to investigate other epoxidation conditions that might provide us with a *threo*-selective method, to be applied to the remaining (*R*)-(+)-**17** alcohol (obtained after the *erythro*-selective kinetic resolution of (±)-**17** with an L-(+)-tartrate; see (Table I). On the basis of the observed[14] dramatic turnaround in erythro–threo selectivity for Ti(O-*i*-Pr)$_4$ in the presence or absence of tartrate, we tried the above epoxidation of (±)-**17** in the absence of tartrate. Here again we observed a stereoselective reaction, but, to our dismay, the erythro/threo ratio was 18:1, as measured by NMR. A single crystallization gave pure (±)-**18**, mp 198–200 °C. Epoxidation of (±)-**17** with VO(acac)$_2$/*t*-BuOOH was shown to be even more erythro selective, no trace of the desired threo isomer (±)-**19** being found in the crude reaction mixture. Finally, MCPBA epoxidation (±)-**17** showed no stereoselectivity at all, giving a 1:1 mixture of (±)-**18** and (±)-**19**.

As results in Table I show, we were unable to carry out the desired 100% conversion asymmetric epoxidation of (±)-**17** because of our inability to find a threo-selective epoxidation method that could be applied after a 50% oxidative kinetic resolution of (±)-**17**. At this point, we decided to finish our synthesis of (*R*)-(−)-**3** from the ki-

(15) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.
(16) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(17) Surprisingly, we did not find any product derived from the reduction of the anthraquinone moiety. It is known that acid quenching of the sodium borohydride reduction of quinizarin gives 1,4-anthraquinone in almost quantitative yield (Etienne, A.; Lepage, J. *C. R. Hebd. Seances Acad. Sci.* **1955**, *240*, 1233). We have found that this reductive elimination takes place even with the tetracyclic ketone **6**.
(18) Interestingly, Kende's enantioselective aklavinone synthesis uses Sharpless' reaction conditions with a different, unprotected 1,8-dihydroxyanthraquinone system; see ref 10.
(19) Absolute configurations for these compounds have not been rigorously established but have been assigned on the basis of Sharpless' mnemonic. Final chemical correlation with (*R*)-(−)-**3** proved the predictions to be correct concerning the absolute configuration of the epoxide.
(20) Yields were not optimized. Chromatographic separation [PTLC, SiO_2, 95:5 CH_2Cl_2–EtOAc] of **17** and **18** was difficult, because of their close R_f values.
(21) Such a behavior has been recently shown by Sharpless (ref 14).
(22) Both *erythro*-**18** and *threo*-**19** have very differenciated peaks in NMR (see Experimental Section), which allows a quick ratio determination. The reaction proceeded to about 85% completion, as determined by NMR.
(23) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

Table I. Epoxidation of Allylic Alcohol (±)-17

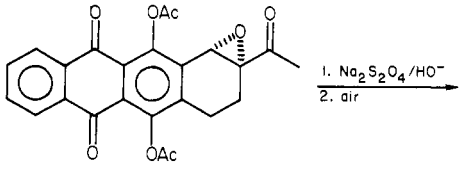
exp	tartrate	temp, °C	time	TBHP, equiv	epoxide[a] (yield, %)	config of recov alcohol[b] (yield, %)
1[c]	(+)-DMT	−20	3 days	0.6	(−)-18 (34)	(R)-(+)-17 (23)
2[c]	(+)-DMT	−20	6 days	1.7	(−)-18 (45)	(R)-(+)-17 (15)
3[c]	(−)-DIPT	−20	20 h	0.6	(+)-18 (44)	(S)-(−)-17 (24)
4[c]	(+)-DIPT	−20	20 h	0.6	(−)-18 (47)[d]	(R)-(+)-17 (32)[d]
5[c]		−20	5 days	1.2	(±)-18 (65)[e]	
6[f]		−20	20 h	2.0	(±)-18 (83)[g]	
7[h]		20	7 h		(±)-18/(±)-19 (82, 1:1 mixture)	

[a] The maximum rotation was obtained in experiment 3: $[\alpha]^{20}_D$ +101° (c 0.94, $CHCl_3$). Unimproved yields are given in parentheses. [b] The resolved allylic alcohol showed very low $[\alpha]_{obsd}$ attributed to low specific rotation; i.e., in experiment 3, $[\alpha]^{20}_D$ −9° (c 1.25, $CHCl_3$). Unimproved yields in parentheses. [c] Carried out as described in ref 14. [d] Calculated yield, separation was not attempted. [e] Less than 10% of threo isomer (±)-19 was present. [f] Performed with $VO(acac)_2$ in the usual manner (ref 23). [g] No threo isomer was detected by NMR. [h] Performed with MCPBA in CH_2Cl_2.

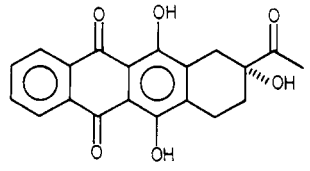
netically resolved mixture of (−)-18 and (R)-(+)-17. Thus, the above mixture was oxidized with chromic acid in a two-phase system, giving a separable mixture of the epoxide (−)-20 and enone 14 in 70% yield.[24]

Attempted hydrogenolysis at the benzylic position of (−)-20 with H_2 (1 atm) and Pd/C in the presence of $N(CH_2CH_2OH)_3$, followed by air oxidation in an alkaline medium,[25] gave complex mixtures of compounds (NMR and TLC analysis).

However, alkaline sodium dithionite cleanly cleaved the epoxide at the desired position, giving (R)-(−)-3 in 47% yield, after silica gel chromatography [$[\alpha]^{20}_D$ −49° (c 0.55, $CHCl_3$), mp 201–2 °C].[26] One single trituration with EtOH–$CHCl_3$ gave (R)-hydroxy ketone 3, 82% optically pure. The only byproduct of the reductive opening of epoxide (−)-20 was enone 11, isolated in 17% yield by column chromatography.



(−)-20



(−)-3

Since stereoselective methods for the introduction of the 7-hydroxy group into racemic 3 are known,[7b,8,9] the described preparation of (R)-(−)-3 constitutes a formal synthesis of (+)-4-demethoxydaunomycinone (8).

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass, infrared (KBr), and ultraviolet spectra were determined by using Perkin-Elmer 270B, 137, and 202 spectrometers, respectively. NMR spectra were recorded on Bruker 200 and 250 FT machines in $CDCl_3$ solutions containing Me_4Si as an internal standard and are reported in δ units. Optical measurements were made on a Perkin-Elmer 241 polarimeter. All organic extracts were washed and dried over anhydrous Na_2SO_4, prior to evaporation.

8-Acetyl-8-bromo-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (9). Method A. To a refluxing solution of ketone 6 (168 mg, 0.5 mmol) in a 1:1 mixture of EtOAc–$CHCl_3$ (12 mL) was added finely powdered $CuBr_2$ (245 mg, 1 × 1 mmol). After 1 h the reaction mixture was cooled, diluted with $CHCl_3$, and washed with H_2O. The organic extract was concentrated, and the residue crystallized from EtOH–$CHCl_3$, giving 9 as orange crystals (188 mg, 91%); mp 219–221 °C; ^1H NMR δ 2.07 (m, 1 H, H-9), 2.53 (m, 1 H, H-9), 2.57 (s, 3 H, $COCH_3$), 3.12 (m, 2 H, H-10), 3.44 and 3.61 (AB q, J_{AB} = 19 Hz, 2 H, H-7), 7.83 (m, 2 H, Ar), 8.34 (m, 2 H, Ar), 13.44 (s, 1 H, OH), 13.49 (s, 1 H, OH); IR 1708 (CO), 1624 (H-bonded quinone), 1587 cm^{-1} (Ar); UV–vis $\lambda_{max}^{CH_3CN}$ 249 (log ε 4.55), 287 (3.96), 320 (3.36), 449 (4.01), 471 (4.04), 500 nm (3.85); MS, m/e (relative intensity) 414 (M^+, 4), 335 (100), 334 (56), 332 (37), 317 (24), 301 (18), 293 (23), 292 (22), 291 (46). Anal. Calcd for $C_{20}H_{15}O_5Br$: 414.0102. Found: 414.0043.

Method B. To a solution of 6 (7.0 g, 20.83 mmol) in a mixture of $CHCl_3$ (150 mL) and HOAc (150 mL) containing 1 mL of HBr (40%) was added 29.4 mL of a 0.71 M solution of bromine in HOAc (20.87 mmol). The resulting solution was stirred at room temperature for 5 h and then heated at 100–110 °C for 20 h. On cooling, bromo ketone 9 was obtained as orange crystals (7.58 g, 88%), being identical with the compound prepared by method A.

8-Acetyl-6,11-dihydroxy-9,10-dihydro-5,12-naphthacenedione (11). To a suspension of bromide 9 (6.90 g) in 150 mL of DMF was added lithium carbonate (7 g). The resulting mixture was stirred at room temperature under nitrogen atmosphere for 24 h. Finally it was warmed to 60–70 °C for 6 h. The purple solution was allowed to cool and slowly poured into an ice–water mixture (500 mL) containing 100 mL of HCl (12%). The brown reddish precipitate was separated by filtration, washed with H_2O, and dried. Crystallization from absolute EtOH–$CHCl_3$ gave 11 (5.52 g, 100%): mp 235–237 °C; ^1H NMR δ 2.53 (s, 3 H, $COCH_3$), 2.66 (t, J = 9 Hz, 2 H, H-9), 3.00 (t, J = 9 Hz, 2 H, H-10), 7.84 (m, 2 H, Ar), 7.87 (s, 1 H, H-7), 8.36 (m, 2 H, Ar), 13.25 (s, 1 H, OH), 13.58 (s, 1 H, OH); IR 1660 (CO), 1621 (H-bonded quinone), 1584 cm^{-1} (Ar); UV–vis $\lambda_{max}^{CH_3CN}$ 282 (log ε 4.57), 298 (4.53), 493 nm (4.05); MS, m/e (relative intensity) 334 (M^+, 100), 332 (43), 319 (24), 317 (25), 316 (18), 301 (50), 291 (82). Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: 71.64; H, 4.31.

8-Acetyl-6,11-dimethoxy-9,10-dihydro-5,12-naphthacenedione (12). Dimethoxy ketone 7 was brominated as in method A, giving a 95% yield of a crude mixture of dimethoxy and monomethoxy 8-bromo derivatives. The above mixture was dissolved in aqueous DMF containing Li_2CO_3 (200 mg) and stirred at room temperature, under nitrogen for 24 h. It was then poured into water and extracted with $CHCl_3$. Chromatography (SiO_2, 95:5 CH_2Cl_2–EtOAc) gave 55 mg (32%) of a 1:1 mixture of regioisomeric monodemethylated enones: ^1H NMR δ 2.53 (s, 3 H, $COCH_3$), 2.64 (m, 2 H, H-9), 3.00 (m, 2 H, H-10), 3.89 and 3.96 (s, 3 H, ArOMe), 7.82 (m, 3 H, Ar and H-7), 8.30 (m, 2 H, Ar), 13.47 and 13.74 (s, 1 H, OH); MS, m/e (relative intensity) 348 (M^+, 100), 346 (25), 332 (36), 317 (45), 305 (62). Continued elution (90:10 CH_2Cl_2–EtOAc) gave dimethoxyenone 12 (67 mg, 37%):

(24) Interestingly, the ratio here was (−)-20/14 4:1, which suggests a selective destruction of (R)-(+)-17 in the reaction conditions. The calculated yield of epoxy ketone, on the basis of the epoxy alcohol present in the starting material was 93%. Compound (−)-20 could be directly crystallized from the above mixture, giving $[\alpha]^{20}_D$ −98° (c 0.57, $CHCl_3$).

(25) For hydrogenolysis of a benzylic hydroxyl in a related system, see: Brockmann, H.; Niemeyer, J.; Brockmann, H., Jr.; Budzikiewiez, H. *Chem. Ber.* **1965**, *98*, 3785.

(26) Recorded values in the literature for (R)-(−)-3 are as follows: mp 228–30 °C: $[\alpha]^{20}_D$ −87° (c 0.1, $CHCl_3$). Arcamone, F.; Bernardi, L.; Patelli, B.; Giardino, P.; DiMarco, A.; Casazza, A. M.; Soranzo, C.; Pratesi, G. *Experientia* **1978**, *34*, 1255.

mp 189–191 °C; ^{1}H NMR δ 2.52 (s, 3 H, $COCH_3$), 2.62 (t, J = 8, 2 H, H-9), 3.01 (t, J = 8, 2 H, H-10), 3.92 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 7.74 (m, 2 H, Ar), 7.81 (s, 1 H, H-7), 8.20 (m, 2 H, Ar); IR 1676 (CO and quinone), 1587 cm^{-1} (Ar); UV–vis $\lambda_{max}^{CH_3CH}$ 252 (log ε 4.03), 291 (4.38), 380 nm (3.80); MS, m/E (relative intensity) 362 (M^+, 100), 348 (19), 347 (20), 345 (16), 333 (16), 331 (20), 319 (56). Anal. Calcd for $C_{22}H_{18}O_5$: 362.1154. Found: 362.1168.

8-Acetyl-6,11-diacetoxy-9,10-dihydro-5,12-naphthacenedione (14). A suspension of 5.4 g of **11** in a mixture of pyridine (100 mL) and Ac_2O (35 mL) was stirred at room temperature for 4 h. The solvent was removed in vacuo and the residue taken up in $CHCl_3$ and washed with H_2O, diluted HCl, and H_2O. Crystallization from absolute EtOH–$CHCl_3$ gave light yellow prisms of **14** (6.59 g, 98%): mp 232–234 °C; ^{1}H NMR δ 2.43, 2.53, and 2.58 (s, 3 each, 2 × OAc and $COCH_3$), 2.6–2.9 (m, 4 H, H-9 and H-10), 7.50 (s, 1 H, H-7), 7.74 (m, 2 H, Ar), 8.13 (m, 2 H, Ar); IR 1760 (br, ArOAc), 1665 ($COCH_3$), 1595 and 1575 cm^{-1} (Ar). UV–vis $\lambda_{max}^{CH_3CN}$ 253 (log ε 4.36), 285 (4.66), 293 (4.60), 365 nm (3.95); MS, m/e (relative intensity) 418 (M^+, 1), 376 (13), 334 (100), 332 (12), 301 (16), 291 (28). Anal. Calcd for $C_{24}H_{18}O_7$: C, 68.90; H, 4.34. Found: C, 68.75; H, 4.51.

8-(1-Hydroxyethyl)-6,11-dihydroxy-9,10-dihydro-5,12-naphthacenedione (15). To a solution of $CeCl_3 \cdot 7H_2O$ (0.23 g, 0.617 mmol) in a mixture of MeOH (4 mL) and $CHCl_3$ (10 mL) were succesively added 0.2 g of **11** (0.599 mmol) and 0.048 g of $NaBH_4$ (1.26 mmol). The resulting mixture was stirred at room temperature for 1 h and then added to dilute HOAc. The red precipitate was extracted with $CHCl_3$. Crystallization from hexane–ether gave the allylic alcohol **15** (167 mg, 88%): mp 147–149 °C; ^{1}H NMR δ 1.43 (d, J = 6.5 Hz, 3 H, CH_3), 2.41 (m, 2 H, H-9), 2.97 (t, J = 9 Hz, 2 H, H-10), 4.53 (m, 1 H, CHOH), 6.96 (s, 1 H, H-7), 7.81 (m, 2 H, Ar), 8.33 (m, 2 H, Ar), 13.43 (s, 1 H, OH), 13.48 (s, 1 H, OH); IR 3500 (OH), 1665 (C=C), 1624 (H-bonded quinone), 1587 cm^{-1} (Ar); UV–vis $\lambda_{max}^{CH_3CN}$ 255 (log ε 4.17), 269 (4.34), 4.91 (3.93), 522 nm (3.87). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.26; H, 4.73.

8-(1-Hydroxyethyl)-6,11-bis(pivaloyloxy)-9,10-dihydro-5,12-naphthacenedione (16). A suspension of **11** (55 mg) in pyridine (3 mL) was treated with an excess of pivaloyl chloride and stirred at room temperature for 4 h. The solvent was removed and the residue taken up in CH_2Cl_2 and washed with H_2O, $NaHCO_3$, and H_2O. Concentration and crystallization from hexane gave **13** (77 mg, 93%): mp 160 °C; ^{1}H NMR δ 1.53 (s, 9 H, $COC(CH_3)_3$), 1.58 (s, 9 H, $COC(CH_3)_3$), 2.44 (s, 3 H, $COCH_3$), 2.5–3.1 (m, 4 H, H-9 and H-10), 7.54 (br s, 1 H, H-7), 7.72 (m, 2 H, Ar), 8.15 (m, 2 H, Ar); MS, m/e (relative intensity) 502 (M^+, 2), 418 (13), 334 (57), 332 (11), 316 (8), 301 (6).

To a solution of enone **13** (53 mg) in $CHCl_3$ (2 mL)–MeOH (2 mL) containing $CeCl_3 \cdot 7H_2O$ (37 mg) was added $NaBH_4$ (8 mg). The resulting solution was stirred at room temperature for 15 min, diluted with $CHCl_3$, washed with H_2O, and concentrated. Crystallization from ether–ligroin gave **16** (44 mg, 83%): mp 135 °C; ^{1}H NMR δ 1.37 (d, J = 6.5 Hz, 3 H, CH_3), 1.52 (s, 9 H, $COC(CH_3)_3$), 1.53 (s, 9 H, $COC(CH_3)_3$), 2.3–3.1 (m, 1 H, H-9 and H-10), 4.42 (m, 1 H, CHOH), 6.68 (br s, 1 H, H-7), 7.62 (m, 2 H, Ar), 8.13 (m, 2 H, Ar); MS, m/e (relative intensity) 504 (M^+, 2), 420 (2), 336 (15), 334 (8), 318 (10), 291 (8).

8-(1-Hydroxyethyl)-6,11-diacetoxy-9,10-dihydro-5,12-naphthacenedione (17). To a stirred solution of enone **14** (1 g, 2.392 mmol) and $CeCl_3 \cdot 7H_2O$ (0.89 g, 2.392 mmol) in a mixture of MeOH (10 mL) and $CHCl_3$ (30 mL) at 0 °C was added $NaBH_4$ (0.091 g, 2.392 mmol) portionwise. After 20 min at 0 °C, it was poured into H_2O and heated in the steam bath for 5 min under an air stream. After cooling, the organic phase was separated and washed with H_2O. Removal of the solvent and trituration of the residue with hexane–ether gave **17** (0.69 g, 68%) as an amorphous yellow powder: mp 183–185 °C; ^{1}H NMR δ 1.37 (d, J = 6.5 Hz, 3 H, CH_3), 2.52 (s, 3 H, OAc), 2.53 (s, 3 H, OAc), 2.3–2.9 (m, 4 H, H-9 and H-10), 4.48 (m, 1 H, CHOH), 6.67 (s, 1 H, H-7), 7.72 (m, 2 H, Ar), 8.14 (m, 2 H, Ar); IR 3500 (OH), 1777 (ArOAc), 1679 and 1665 (quinone and C=C), 1575 cm^{-1} (Ar); UV–vis $\lambda_{max}^{CH_3CN}$ 252 (log ε 4.10), 285 (4.36), 377 nm (3.57); MS, m/e (relative intensity) 420 (M^+, 2), 378 (23), 360 (11), 336 (100), 334 (30), 320 (67), 318 (92). Anal. Calcd for $C_{24}H_{20}O_7$: C, 68.57; H, 4.80. Found: C, 68.28; H, 5.03.

Epoxy Alcohol (±)-18. Method A. A solution of Ti(i-PrO)$_4$ (68 mg, 0.238 mmol) and alcohol (±)-**17** (100 mg, 0.238 mmol) in dry CH_2Cl_2 (10 mL) was stirred under N_2 at −20 °C for 5 min. Then, 90% t-BuOOH (32 mg, 0.265 mmol) was added and the reaction mixture maintained at −20 °C (freezer) for 5 days, with occasional shaking. The cooled reaction mixture was poured into H_2O and the organic phase separated. The NMR showed the crude mixture of (±)-**18** and (±)-**19** in about an 18:1 ratio. Crystallization from hexane–CH_2Cl_2 gave light yellow crystals of (±)-**18** (67 mg, 65%): mp 198–200 °C; ^{1}H NMR δ 1.31 (d, J = 6.5 Hz, 3 H, CH_3), 1.87 and 2.27 (m, 4 H, H-9), 2.20 (br s, 1 H, OH, D_2O interchange), 2.52 (s, 3 H, OAc), 2.57 (s, 3 H, OAc), 2.70 and 2.92 (m, 4 H, H-10), 4.14 (q, J = 7 Hz, 1 H, CHOH), 4.28 (s, 1 H, H-7), 7.75 (m, 2 H, Ar), 8.16 (m, 2 H, Ar); IR 3500 (OH), 1773 (ArOAc), 1675 (quinone), 1585 cm^{-1} (Ar); UV–vis $\lambda_{max}^{CH_3CN}$ 269 (log ε 4.34), 280 (4.09), 330 nm (3.56), MS, m/e (relative intensity) 436 (M^+, 0.5) 394 (7), 352 (61), 334 (10), 324 (38), 318 (18), 308 (100). Anal. Calcd for $C_{24}H_{20}O_8$: C, 66.05; H, 4.62. Found: C, 66.25; H, 4.63.

Method B. To a cooled solution (0 °C) of the alcohol (±)-**17** (50 mg, 0.119 mmol) in a mixture of benzene (2 mL) and CH_2Cl_2 (2 mL) was added a catalytic amount of VO(acac)$_2$ (3.18 mg, 0.012 mmol), followed by t-BuOOH (90%, 0.442 mmol). The resulting mixture was stirred for a few minutes at 0 °C, under a nitrogen atmosphere, and left in the freezer overnight. Dilution with CH_2Cl_2 and washing with water gave a yellow residue after concentration to dryness. Crystallization from hexane–CH_2Cl_2 gave crystals of (±)-**18** (43 mg, 83%), identical (TLC, NMR, IR, mp) with the compound obtained in method A.

Epoxy Alcohol (±)-19. To a CH_2Cl_2 solution (5 mL) of (±)-**17** (130 mg, 0.309 mmol) was added (90 mg of 70%) a 20% excess of MCPBA, and the resulting mixture was stirred at room temperature for 7 h. The reaction mixture was washed with Na_2SO_3, $NaHCO_3$, and H_2O, successively, dried, and concentrated. PTLC separation (95:5 CH_2Cl_2–EtOAc) gave two blue fluorescent bands. The faster one gave a product identical (TLC, NMR) with (±)-**18** (52 mg, 39%). The slower moving one was crystallized from hexane–CH_2Cl_2, giving yellow crystals (58 mg, 43%) of (±)-**19**: mp 122–123 °C dec; ^{1}H NMR δ 1.34 (d, J = 6.5, 3 H, CH_3), 1.81 and 2.21 (m, 2 H, H-9), 2.50 (s, 2 H, ArOAc), 2.55 (s, 3 H, ArOAc), 2.64 and 2.89 (m, 2 H, H-10), 3.88 (q, J = 6.5, 1 H, CHOH), 4.18 (s, 1 H, H-7), 7.73 (m, 2 H, Ar), 8.13 (m, 2 H, Ar); IR 3500 (OH), 1775 (OAc), 1680 (quinone), 1585 cm^{-1} (Ar); UV–vis $\lambda_{max}^{CH_3CN}$ 268 (log ε 4.37), 281 (4.11), 330 nm (3.59); MS, m/e (relative intensity) 436 (M^+, 0.5), 394 (4), 352 (28), 334 (16), 324 (16), 308 (100). Anal. Calcd for $C_{24}H_{20}O_8$: 436.1158. Found: 436.1140.

(−)-8-Acetyl-7,8-epoxy-6,11-diacetoxy-9,10-dihydro-5,12-naphthacenedione (20). To a cooled solution of Ti(i-PrO)$_4$ (338 mg, 1.19 mmol) in CH_2Cl_2 (5 mL) was added (+)-diisopropyl L-tartrate (338 mg, 1.43 mmol). The resulting mixture was stirred under nitrogen at −20 °C for 5 min. Then, a solution of 0.5 g of allylic alcohol (±)-**17** (1.19 mmol) in a CH_2Cl_2 solution (2 mL) of *tert*-butyl hydroperoxide 90% (72 mg, 0.71 mmol) was added. The reaction mixture was stirred at −20 °C for 2 h and then kept in a freezer (−20 °C) for 15 h. The cooled reaction mixture was poured into H_2O and the organic phase separated, dried, and concentrated. Trituration of the residue with ether gave a yellow powder (399 mg), which was shown by NMR to be a mixture of erythro epoxyol (−)-**18** (47%) and recovered allylic alcohol (*R*)-(+)-**17** (32%).

The above mixture was dissolved in CH_2Cl_2 (20 mL) and treated with an excess of chromic acid (≃2.5 equiv, 18 mL of a 0.08 M aqueous solution), and the resulting two-phase system was stirred at room temperature for 6 h. The organic phase was separated, washed with H_2O, and filtered through a silica gel column (90:10 CH_2Cl_2–EtOAc) to give 279 mg of a crude mixture of epoxy ketone **20** and enone **14** in a 4:1 ratio. Crystallization from EtOAc gave light yellow crystals of (−)-**20** (195 mg, ≃85% yield based on epoxy alcohol present in the starting material): mp 235–237 °C; $[\alpha]_D$ −98° (c 0.57, $CHCl_3$); ^{1}H NMR δ 2.25 (s, 3 H, CH_3), 2.52 (s, 3 H, OAc), 2.59 (s, 3 H, OAc), 2.3–3.1 (m, 4 H, H-9 and H-10), 4.33 (s, 1 H, H-7), 7.75 (m, 2 H, Ar), 8.16 (m, 2 H, Ar); IR 1770 (ArOAc), 1704 (CO), 1678 (quinone), 1587 cm^{-1} (Ar); MS, m/e (relative intensity) 434 (M^+, 0.2), 392 (6), 350 (52), 332 (20), 322 (12), 308 (100). Anal. Calcd for $C_{24}H_{18}O_8$: C, 66.36; H, 4.18. Found: C, 66.18; H, 4.01.

(−)-4-Demethoxy-7-deoxydaunomycinone (3). To an air-stirred solution of NaOH (240 mg, 6 mmol) and an excess of sodium dithionite (510 mg, 2.9 mmol) in H_2O (8 mL) was added 60 mg of the epoxy enone (−)-**20** under nitrogen. The dark mixture was stirred for 1 h at room temperature. Then, air was bubbled through for 10 min, the reaction mixture acidified with diluted HCl, and bubbling continued for another 10 min. The resulting red precipitate was separated by filtration and purified by silica gel chromatography. Elution with CH_2Cl_2 gave 8 mg of enone **11**, identified by direct comparation (TLC, NMR) with a sample obtained as described before. Further elution with 5% EtOAc in CH_2Cl_2 yielded (−)-**3** (23 mg, 47%): mp 201–202 °C; $[\alpha]_D$ −49° (*c* 0.55, $CHCl_3$) optical yield: 56%); identical with an authentic sample[12] (TLC, NMR, IR). A single trituration with EtOH–$CHCl_3$ gave an 82% optically pure sample of (−)-**3**: mp 201–203 °C; $[\alpha]_D$ −71° (*c* 0.15, $CHCl_3$) (literature value in ref 26).

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Registry No. (*R*)-(−)-**3**, 63229-48-1; (±)-**6**, 67122-26-3; (±)-**7**, 84498-97-5; (±)-**9**, 86309-10-6; (±)-**10**, 86323-10-6; (±)-**10** 6-demethyl, 86309-11-7; (±)-**10** 11-demethyl, 86309-12-8; **11**, 86309-13-9; **12**, 86309-14-0; **12** 6-demethyl, 86309-15-1; **12** 11-demethyl, 86309-16-2; **13**, 86309-17-3; **14**, 86309-18-4; (±)-**15**, 86309-19-5; (±)-**16**, 86309-20-8; (±)-**17**, 86309-21-9; (*R*)-(+)-**17**, 86362-06-3; (*S*)-(−)-**17**, 86362-07-4; (±)-**18**, 86309-22-0; (−)-**18**, 86362-08-5; (+)-**18**, 86362-09-6; (±)-**19**, 86362-10-9; (−)-**20**, 86309-23-1.

Cyclodehydration and Chlorination of Simple Diols with Triphenylphosphine and *tert*-Butyl Hypochlorite

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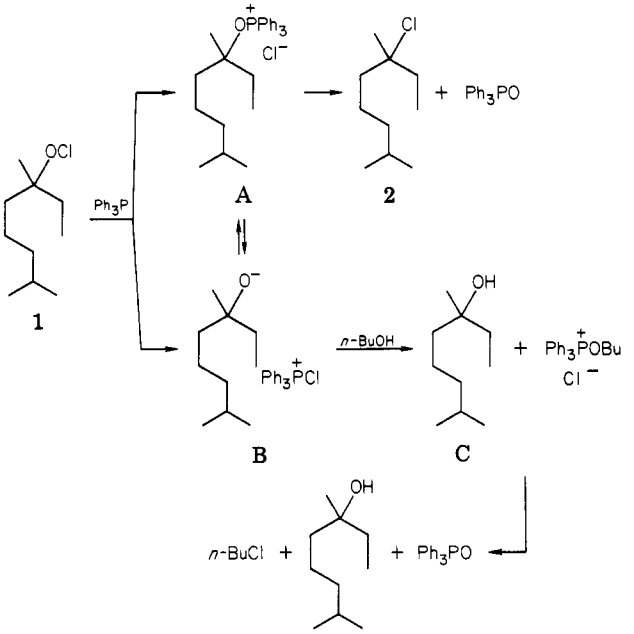
The reagent triphenylphosphine–*tert*-butyl hypochlorite converts 1,4-diols into the corresponding tetrahydrofurans and 1,2-diols into a mixture of the regioisomeric chlorohydrins and the epoxides at −78 °C followed by warming to ambient temperature (ca. 30 °C). Symmetrical diols give largely chlorohydrins and dichlorides.

Introduction

Various halogenating and cyclodehydrating reagents, consisting of phosphines and phosphites with halogens[1,2] and carbon tetrahalides,[3] have found useful preparative utility for primarily alkyl halides and, to a limited extent, cyclic ethers[4] from alcohols and diols, respectively.

It has been previously shown that triphenylphosphine (TPP) reacts with tetrahydrolinalyl hypochlorite (**1**) at −78 °C to afford oxyphosphonium chloride A, presumably through phosphonium ion B, which subsequently decomposes to tetrahydrolinalyl chloride (**2**) and triphenylphosphine oxide (TPPO), albeit in low yield.[5] However, in the presence of 1-butanol, trace amounts of 1-chlorobutane are obtained. A reasonable rationale for formation of 1-chlorobutane requires initial nucleophilic attack on the chlorine atom[6] of **1** to afford chlorophosphonium alkoxide B. Proton transfer between salt B and 1-butanol would ultimately lead to oxyphosphonium chloride C,

Chart I



which could decompose to 1-chlorobutane and TPPO[7] (Chart I).

These results strongly suggest that a potentially useful parallel may exist in the reactivity of triphenylphosphine (TPP)–tetrachloromethane (CCl_4) and triphenylphosphine–*tert*-alkyl hypochlorites in the chlorination of

(1) For a general review and recent references, see Cadogan, J. I. G., Ed. "Organophosphorus Reagents in Organic Synthesis"; Academic Press: New York, 1979.
(2) (a) Schaefer, J. P.; Weinberg, D. S. *J. Org. Chem.* **1965**, *30*, 2635, 2639. (b) See Mackie, R. K. In "Organophosphorus Reagents in Organic Synthesis"; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 433–466.
(3) (a) Harrison, C. R.; Hodge, P. *J. Chem. Soc., Chem. Commun.* **1978**, 813. (b) See Appel, R.; Halstenberg, M. In "Organophosphorus Reagents in Organic Synthesis"; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 378–424.
(4) (a) Barry, C. N.; Evans S. A. Jr. *J. Org. Chem.* **1981**, *46*, 3361–3364. (b) Erickson, G. W.; Fry, J. L. *Ibid.* **1980**, *45*, 970–972.
(5) Denney, D. B.; DiLeone, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 4737–4743.
(6) Denney, D. B.; Hanifin, J. W., Jr. *Tetrahedron Lett.* **1963**, 2177–2180.
(7) Brett, D.; Downie, I. M.; Lee, J. B.; Matough, M. F. S. *Chem. Ind. (London)* **1969**, 1017.

0022-3263/83/1948-2825$01.50/0