Asymmetric Synthesis of the AB Ring Segments of Daunomycin and 4-Demethoxydaunomycin

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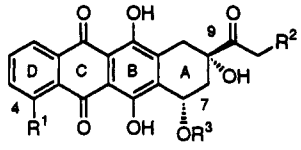
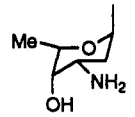
Asymmetric hydroxylation of the potassium enolate of β-keto ester **14**, with (camphorsulfonyl)-oxaziridine (−)-**7c** [tetrahydro-9,9-dimethyl-8,8-dimethoxy-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]-benzisothiazole 3,3-dioxide] affords α-hydroxy β-keto ester (*R*)-(+)-**15** in >95% ee. The high ee's are attributed to the fact that this enolate probably exists in one geometric form as a consequence of intramolecular chelation. Reduction of the ketone in **15** with triethylsilane and conversion of the ester group into the methyl ketone results in a highly efficient synthesis of the AB ring building block (*R*)-(−)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**3b**), a key intermediate in the asymmetric synthesis of the antitumor agent 4-demethoxydaunomycin (**1c**). Selective deprotection of the 8-methoxy group in **3b** with BBr_3 gives **3a**, important in the enantioselective synthesis of the clinically useful antitumor agent adriamycin (**1b**). Attempts to prepare **3a** and **3b** more directly by asymmetric hydroxylation of the enolates of methyl 5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (**9**) or the 8-benzyloxy derivative of **16** resulted in low ee's, attributable to the formation of *E*/*Z* enolate mixtures and increased steric congestion in the transition state for hydroxylation.

There is considerable current interest in the chemistry of the anthracycline antibiotics because of their significant clinical utility in the treatment of various human solid tumors and leukemias.[1] Prominent members of this class of antibiotics are daunomycin (**1a**) and adriamycin (**1b**), which are among the most often used drugs in antitumor combination chemotherapy. Their utility is limited, however, due to a number of toxic side effects, the most serious being dose-related cardiotoxicity.[2] More recently, improved pharmacological profiles have been reported for the totally synthetic demethoxy analogs 4-demethoxydaunomycin (**1c**) and 4-demethoxyadriamycin (**1d**).[3] For example, anthracycline **1c** is five–ten times more effective and less toxic than **1a**.





a: R^1=OMe, R^2=H
b: R^1=OMe, R^2=OH
c: R^1=H, R^2=H
d: R^1=H, R^2=OH

2: R^3=H

The biological activity of the glycosidic anthracyclines **1** is critically dependent upon the configuration of the C-9 α-hydroxy ketone moiety, and they are active only in their natural absolute configuration.[4] Consequently, enantiomerically pure aglycons **2** are needed for the efficient synthesis of **1**.[5] Earlier preparations of these materials relied on the wasteful and complex separation of diastereoisomers in the final glycosidation step.[6] With the availability of the enantiopure aglycons **2**, these problems are avoided, also conserving the valuable sugar moiety.[7] While resolution of **2** and construction of the A ring from chiral pool fragments has been utilized, the most often used approach is the convergent, regioselective coupling of chiral AB ring fragments **3** with phthalide or phthalide anions to produce the tetracyclic skeleton.[7] The latter approach is preferable because the harsh conditions required of the Friedel–Crafts coupling leads to racemization.[8] This 1,4-dipole-metalated strategy, pioneered by Hauser,[9] Swenton,[10] and others,[11] involves the addition of a phthalide anion (1,4-dipole), in this case 3-(phenylsulfonyl)phthalide (**5**), to a quinone or quinone monoacetal **4** (Scheme 1). The monoacetal **4** is necessary to control the regioselective coupling with **5a** to give the 4-methoxy-7-deoxyanthracyclines **6** and has been explored in detail

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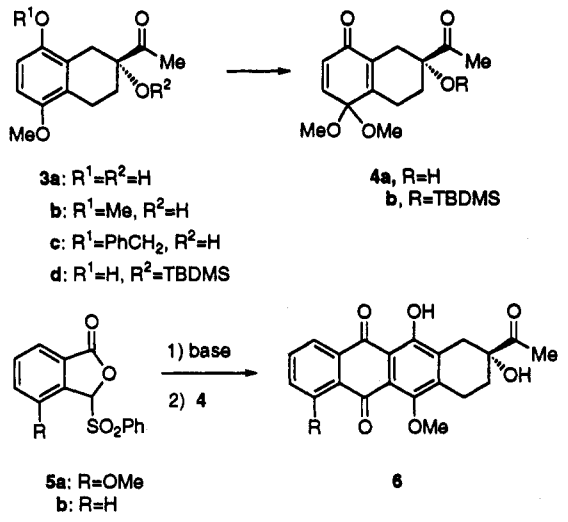
Scheme 1

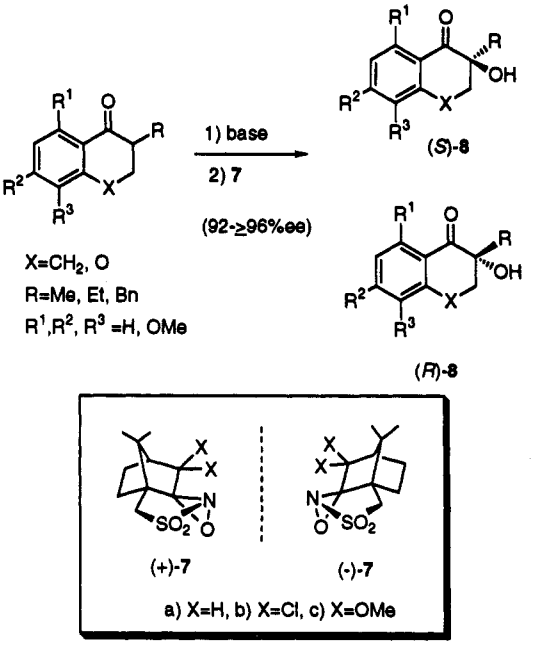


by Russell and co-workers.[12] The methodology outlined in Scheme 1 is quite general, working not only with **4** to give the 7-deoxyanthracyclinones[13] but with C-4 functionalized quinones[10] and various phthalide anions as well, affording access to many derivatives important in the search for more effective drug candidates.[5]

Easy access to the enantiopure AB ring building blocks is required by the phthalide annelation strategy and many syntheses have been devised.[7] This is particularly true of (*R*)-(−)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**3b**), which has played a key role in the asymmetric synthesis of anthracyclinones.[5] Methods for the synthesis of nonracemic (*R*)-(−)-**3b** include resolution,[14] asymmetric bromolactonizations,[15] asymmetric reduction–epoxidation,[12d,16] Sharpless asymmetric epoxidation,[17] asymmetric dihydroxylation,[18] and others.[19] With only one exception,[18] all of these procedures are multistep, affording this important AB ring building block in generally low overall yields. In this context, we report details of a highly efficient enantioselective synthesis of (*R*)-(−)-**3b** using the asymmetric enolate oxidation protocol.[20,21] In addition, this methodology has been extend to the synthesis of AB synthons (*R*)-(−)-**3a** and (*R*)-(−)-**3d** required for the asymmetric synthesis of daunomycin (**1a**).

Results and Discussion

Earlier studies from these laboratories have demonstrated that the enolate oxidation protocol, using (camphorsulfonyl)oxaziridines **7** [tetrahydro-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxides], is particularly effective for the asymmetric synthesis of 2-hydroxy-1-tetralone derivatives **8** with ee's in the range of 92 to >96%.[20] Since the configuration of the three-membered oxaziridine ring controls the absolute stereochemistry of the product, either enantiomer is readily available by choice of the antipodal oxaziridine, e.g., (+)-**7** affords (*R*)-**8** while (−)-**7** gives (*S*)-**8**. These hydroxy tetralones have been utilized in highly efficient enantioselective syntheses of the homoisoflavonoids (−)- and (+)-5,7-*O*-dimethyleucomol,[22] (+)-*O*-trimethylbrazilin,[23] the AB ring segments of a γ-rhodomycinone, α-citromycinone,[24] and aklavinone.[25] Thus the extension of this methodology to the synthesis of AB ring segments **3** appeared straightforward.



Preliminary experiments were, however, not encouraging. Hydroxylation of the lithium enolate of methyl 5,8-dimethoxy-1-1,2,3,4-tetrahydro-2-naphthoate (**9**) with (+)-(camphorsulfonyl)oxaziridine (**7**) afforded the desired 2-hydroxy derivative **10** in 61–63% yield, but the material was racemic (3–4% ee).[15a] Use of (8,8-dimethoxycamphorsulfonyl)oxaziridine **7c** gave similar results, and attempts to form the more reactive sodium enolates with sodium bis(trimethylsilyl)amide (NaHMDS) failed. In retrospect, the low ee's exhibited by **10** are not surprising considering the likelihood that the enolate of **9** exists as

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(20) For a review of the asymmetric hydroxylation of enolates using enantiopure *N*-sulfonyloxaziridines see: Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.

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(22) Davis, F. A.; Chen, B. C. *Tetrahedron Lett.* **1990**, *31*, 6823.

(23) Davis, F. A.; Chen, B. C. *J. Org. Chem.* **1993**, *58*, 1751.

(24) Davis, F. A.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1991**, *56*, 1143.

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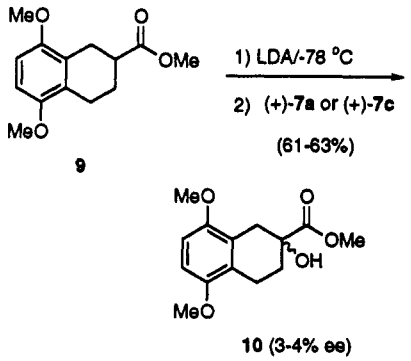
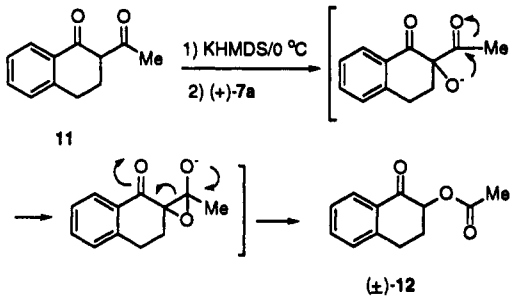
an E/Z mixture. Low ee's are associated with the asymmetric hydroxylation of acyclic enolate E/Z mixtures.[26]



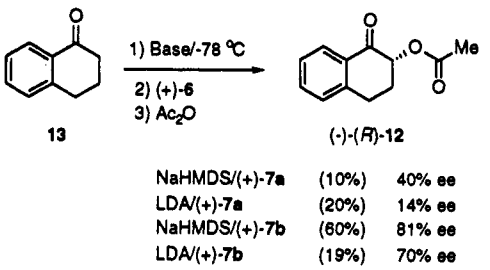
β-Dicarbonyl compounds on the other hand are more likely to form a single enolate geometric isomer because of the possibility of intramolecular chelation with the counterion.[27] In the absence of steric constraints, lithium β-dicarbonyl enolates exist nearly exclusively in the *ZZ* conformation. However, hydroxylation of the lithium enolate of 2-acetyl-1-tetralone (**11**) by (+)-**7a** resulted in no reaction at −78 °C, but on warming to room temperature, this model compound gave a new product isolated in low yield, ca. 20% yield. The yield was improved to 58% using the potassium enolate. However, this material lacked an exchangeable proton in the ^{1}H NMR as well as infrared OH absorption. Surprisingly this material was identified as 2-(acetyloxy)-1-tetralone (**12**), prepared earlier by Koyama and co-workers in 85% yield, by oxidation of 1-tetralone with lead tetraacetate.[28] A plausible mechanism for the formation of **12** involves the initial formation of an α-alkoxy diketone anion which rearranges via the alkoxy epoxide and is consistent with the fact that **12** is racemic. This transformation is an example of a base-catalyzed α-hydroxy β-diketone to α-ketol ester rearrangement[29] and will be described in more detail elsewhere.



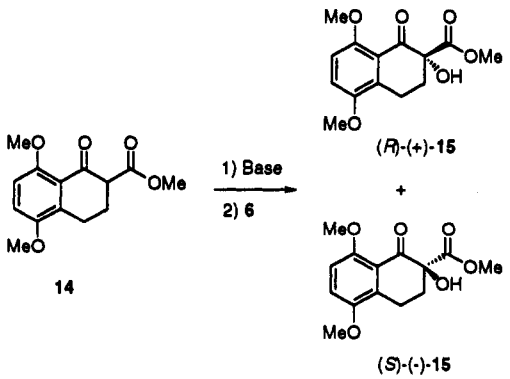
It proved possible to prepare **12** independently by hydroxylation of the enolate of 1-tetralone (**13**) with **7** and trapping the intermediate α-hydroxy ketone with acetic anhydride. This hydroxylation is of particular interest because all previous attempts to hydroxylate the enolate of **13** using 2-(phenylsulfonyl)-3-phenyloxaziridine resulted in complex mixtures from which 2-hydroxy-1-tetralone could not be abstracted.[30] The highest ee's and yields were observed for the sodium enolate of **13** with (+)-**7b**. The enantiopurity of **12** was determined using the chiral shift reagent Eu(hfc)$_3$ and is predicted to have the *R*-configuration on the basis of the chiral recognition mechanism developed for these oxidizing reagents.[26]

Table 1. Asymmetric Hydroxylation of 14 with (Camphorsulfonyl)oxaziridine Derivatives 7

			hydroxy β-keto ester 15	
entry	oxaziridine 7	conditions: base/°C	% ee[a] (config)[b]	% yield[c]
1	(+)-**7a** (X = H)	LDA/20	72 (*S*)	35
2	(+)-**7a** (X = H)	NaHMDS/0	34 (*S*)	68
3	(+)-**7a** (X = H)	KHMDS/−78	41 (*S*)	67
4	(+)-**7b** (X = Cl)	LDA/20	no reaction	
5	(+)-**7b** (X = Cl)	NaHMDS/0	47 (*S*)	63
6	(+)-**7b** (X = Cl)	KHMDS/−78	6 (*S*)	72
7	(+)-**7c** (X = OMe)	LDA/0	no reaction	
8	(+)-**7c** (X = OMe)	NaHMDS/0	56 (*S*)	73
9	(+)-**7c** (X = OMe)	KHMDS/−78	>95 (*S*)	70
10	(−)-**7c** (X = OMe)	KHMDS/−78	>95 (*R*)	68



Fortunately, the asymmetric hydroxylation of β-keto ester **14**[31] occurs without rearrangement to give the corresponding α-hydroxy β-keto ester **15**. Thus treatment of **14** with 1.2 equiv of base at 0 °C followed by addition of 1.2 equiv of **7** at 0 or −78 °C affords the hydroxy β-keto ester **15**, which was isolated by preparative TLC (Table 1). This new compound gave a satisfactory elemental analysis and had an exchangeable (D_2O) proton in the NMR and an OH absorption at 3479 cm^{-1} in the infrared. The ee's were determined with the chiral shift reagent Eu(hfc)$_3$, and the absolute configuration was established by conversion into **3b** (vide infra).



As previously observed for the asymmetric hydroxylation of enolates, the yields and stereoselectivity are highly dependent on the structures of the enolate and oxidant as well as the reaction conditions (Table 1).[20] While the

(26) Davis, F. A.; Weismiller, M. C.; Murphy, C. K; Thimma Reddy, R.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274.
(27) For a review, see: Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.
(28) Koyama, J.; Okatani, T.; Tagahara, K.; Irie, H. *Heterocycles* **1989**, *29*, 1649.
(29) For examples of the rearrangement of α-(acyloxy)acetates to α-hydroxy β-keto esters see: Lee, S. D.; Chan, T. H.; Kow, K. S. *Tetrahedron Lett.* **1984**, *25*, 3399. Rubin, M. B.; Inbar, S. *J. Org. Chem.* **1988**, *53*, 3355. Eichinger, P. C. H.; Hayes, R. N.; Bowie, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 1949.
(30) Vishwakarma, L. C. Unpublished results from these laboratories.
(31) Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 1561.

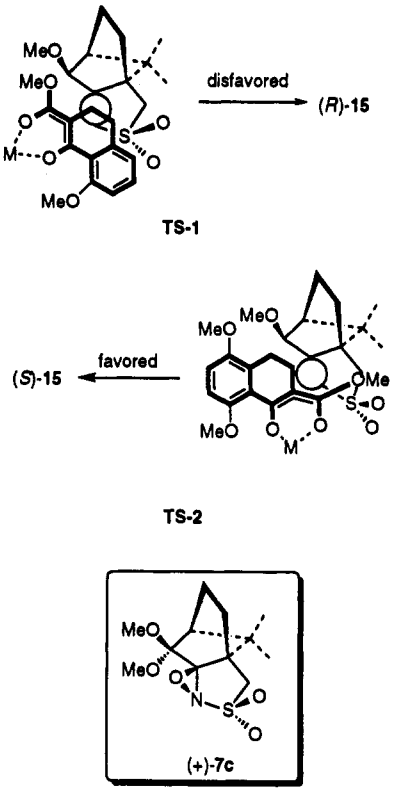


Figure 1. Transitions states for the hydroxylation of the enolate of **14** by (+)-**7c** (selected atoms have been omitted for clarity).

results summarized in Table 1 reflect these earlier observations, several additional trends are worth mentioning. Only the potassium enolate of **14** was reactive enough to be oxidized at −78 °C, likely reflecting the lower reactivity of β-keto ester enolates. At −78 °C hydroxylation of the potassium enolate of **14** with the (8,8-dimethoxycamphorsulfonyl)oxaziridine **7c** gave **15** in better than 95% ee and 68–70% isolated yield (Table 1, entries 9 and 10).

In these oxidations it was found essential, particularly with larger scale reactions (>12 mmol), that the reaction temperature be kept as close as possible to −78 °C, otherwise the ee's of product deteriorate from >96% to 90% ee. This is easily accomplished by cannula addition of a −78 °C solution of the oxaziridine to the metal enolate at −78 °C. It is worth mentioning that recrystallization of (+)-**15** (90% ee) from EtOAc/*n*-pentane readily upgraded it to >96% ee. Finally the results summarized in Table 1 take on added significance considering the fact that there are few reagents available for the hydroxylation of stabilized enolates such as β-keto ester, e.g., Vedejs MoOPH reagent fails with such compounds.[32,33]

The hydroxylation of 2-alkyl-1-tetralone enolates with (+)-**7** gave a predominance of the (*R*)-**8** hydroxy tetralone which could be predicted by a consideration of nonbond steric interactions in the transition state.[20,26] A similar consideration of the relevant steric interactions for the hydroxylation of β-keto ester enolate **13** at first suggested that (+)-**7** should favor (*R*)-**15**. However, just the opposite is observed where (+)-**7c** gave (*S*)-**15** and (−)-**7c** gave (*R*)-**15**. This result suggests, as shown in Figure 1, that **TS-2** is favored over **TS-1** and may be a consequence of unfavorable nonbonded interactions between the 8-methoxy group in the oxaziridine and the β-keto ester functionality in the substrate. Disruption of intramolecular chelation in the enolate may be the result. Although a stabilizing interaction between the metal enolate and one of the sulfone oxygens in **TS-2** is possible, this type of association is believed to be secondary to metal chelation with the oxaziridine oxygen and nitrogen atoms.[26]

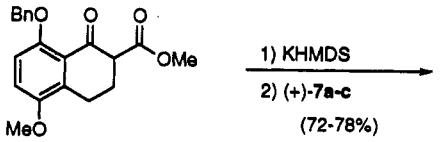
With enantiopure (*R*)-(+)-**15** in hand, the keto group was reduced, without racemization, by treatment with 3.0 equiv of Et_3SiH in 4 equiv of CF_3CO_2H at 0 °C to give α-hydroxy ester (*R*)-(−)-**10** in 75% isolated yield.[15a] The methyl ester was transformed into the methyl ketone by reaction of **10** with dimsylsodium and reduction with Al(Hg) following the procedures of Broadhurst and co-workers[6] to give (*R*)-(−)-**3b** in 66% yield and in better than 95% enantiomeric purity.

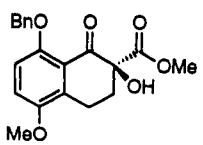
$$(R)\text{-}(+)\text{-}\mathbf{15} \xrightarrow[(75\%)]{Et_3SiH/CF_3CO_2H} (R)\text{-}(-)\text{-}\mathbf{10} \xrightarrow[2.\ Al(Hg)\ (66\%)]{1.\ MeS(O)CH_2Na} (R)\text{-}(-)\text{-}\mathbf{3b}\ (>95\%\ ee)$$

Earlier, Russell and co-workers had reported the preparation of hydroxy phenol (−)-(*R*)-**3a**, required for the synthesis of anthracyclones **2a** and **2b**, by deprotection of the 8-benzyloxy derivative **3c** with H_2/Pd.[12d] This material was prepared using a combination of asymmetric reduction and epoxidation. Our initial approach to **3a** was the asymmetric hydroxylation of β-keto ester **16**, prepared as previously described from 5,8-dimethoxy-1-tetralone.[34,35] Unfortunately, asymmetric hydroxylation of **16** with (+)-**7a** or (+)-**7c**, under a variety of conditions, gave (*S*)-**17** in only 65% ee.[36] A seemingly small structural change in the vicinity of the metal enolate apparently has a major effect on its reactivity/stereoselectivity, e.g. the bulkier 8-benzyloxy group may destabilize **TS-2** (Figure 1).

$$(R)\text{-}(+)\text{-}\mathbf{15} \xrightarrow[(75\%)]{Et_3SiH/CF_3CO_2H} (R)\text{-}(-)\text{-}\mathbf{10}$$

$$\xrightarrow[2)\ Al(Hg)\ \ (66\%)]{1)\ MeS(O)CH_2Na} (R)\text{-}(-)\text{-}\mathbf{3b}\ (>95\%\ ee)$$





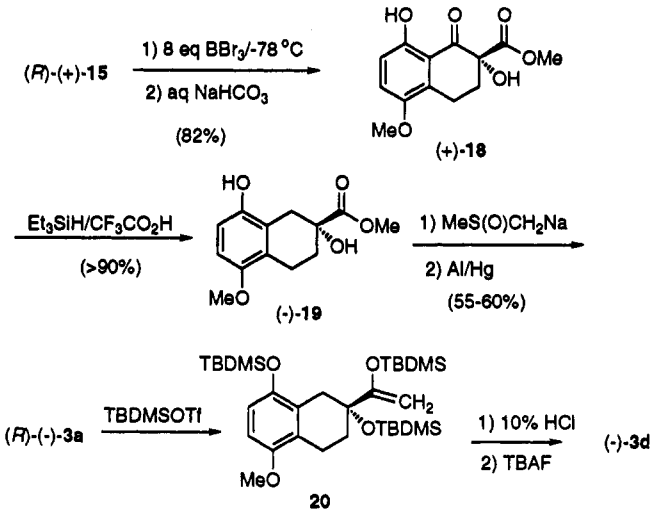
(*S*)-(+)-**17** (65% ee)

(*R*)-(−)-2-Acetyl-5-methoxy-8-hydroxy-1,2,3,4-tetrahydro-2-naphthol (**3a**) was successfully prepared as outlined in Scheme 2. Hydroxy β-keto ester (*R*)-(+)-**15**, prepared earlier, was selectively demethylated using 8 equiv of BBr_3 at −78 °C to give **18** in 82% yield. Higher temperatures

(32) Vedejs, E.; Larsen, S. *Org. Synth.* **1985**, *64*, 127. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. Vedjes, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944.

(33) Details of the hydroxylation of stabilized enolates with *N*-sulfonyloxaziridines will be reported elsewhere.

Scheme 2



result in deacylation, and fewer equivalents of BBr_3 gave much lower yields. Reduction of the carbonyl group was accomplished with 3 equiv of Et_3SiH using CF_3CO_2H as the solvent, affording **19** in near quantitative yield which was converted as before into the methyl ketone (*R*)-(+)-**3a** using, this time, 8 equiv of dimsylsodium followed by reduction with Al/Hg.

Although the annelation reaction (Scheme 1) has been reported using the 2-hydroxy monoketal derivatives of **4a**,[10a,37,38] yields are often better if the 2-hydroxy group is first protected as the *tert*-butyldimethylsilyl (TBDMS) ether **4b**.[10a,12,37] The TBDMS ether (−)-**3d** was prepared by treating **3a** with 4.5 equiv of *tert*-butyldimethylsilyl triflate (TBDMSOTf)/2,6-dimethylpyridine to give an intermediate tris-silylated derivative **20** in the form of the enol silyl ether **20**. The structure of **20** is supported by presence of three *tert*-butyl groups at δ 1.02, 0.93, and 0.81 and vinyl ether protons at δ 4.40 and 4.10. Hydrolysis of the silyl enol and phenolic ethers in crude **20** was readily accomplished by shaking with 10% HCl, followed by reaction with 1 equiv of tetrabutylammonium fluoride to give (−)-**3d**[12b] in better than 85% yield following purification by preparative TLC.

Summary. The enolate hydroxylation protocol, employing (camphorsulfonyl)oxaziridine **7**, has been utilized in the highly enantioselective synthesis of AB ring synthon (*R*)-(−)-**3b**, an important intermediate in the asymmetric synthesis of the antitumor agent 4-demethoxydaunomycin (**1c**). The key step in the synthesis of **3b** was the highly enantioselective hydroxylation (>95% ee) of the potassium enolate of β-ketone ester **14**, which likely exists as a single enolate isomer because of intramolecular chelation. AB ring synthon (*R*)-(−)-**3b** was readily transformated into **3a** and **3d**, intermediates in the asymmetric synthesis of the clinically useful anticancer agent daunomycin (**1a**).

(34) Watanabe, M.; Maenosono, H.; Furukawa, S. *Chem. Pharm. Bull.* **1983**, *31*, 2668.
(35) Russell, R. A.; Gee, P. S.; Irvine, R. W.; Warrener, R. N. *Aust. J. Chem.* **1984**, *37*, 1709.
(36) The absolute configuration of (*S*)-(+)-**17** was established by benzylation of (*R*)-(−)-**18** with benzyl bromide to give (*R*)-(−)-**17** in 76% yield.
(37) Warrener, R. N.; Gee, P. S.; Russell, R. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1100.
(38) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318.

Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points, elemental analyses, and the purification of solvents (freshly distilled) have been previously reported.[26] HRMS were run on a VG ZAB-E instrument. LDA (1 mmol/mL) was prepared by treatment of 1.4 mL of diisopropylamine in 4.6 mL of THF by addition of 4.0 mL of a 2.5 M solution of *n*-butyllithium (Aldrich) at 0 °C. All reactions were performed under an argon/nitrogen atmosphere. *n*-Butyllithium, 2-acetyl-1-tetralone (**11**), and 1-tetralone (**13**) were purchased from Aldrich. (Camphorsulfonyl)oxaziridine derivatives **7a**,[39] **7b**,[26] and **7c**,[24] methyl 5,8-dimethoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoate (**14**),[31] and 5,8-dimethoxy-1-tetralone[40] were prepared as previously described.

Methyl 5,8-Dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (9). In a 50-mL, single-neck, round-bottom flask equipped with a magnetic stir bar, rubber septum, and an argon inlet and outlet was placed 1.5 g (5.7 mmol) of β-keto ester **14**[31] in 20 mL of CF_3CO_2H, and the dark brown solution was cooled to 0 °C. Added dropwise to the reaction mixture was 3 mL (35 mmol, 6 equiv) of Et_3SiH, and the color changed to a pale yellow. Stirring was continued at 0 °C for 2 h, at which time the solvent was concentrated, the residue was treated with a few milliliters of *n*-hexane, and the resulting white crystals were isolated by filtration to give 1.41 g (99%) of **9** having spectral properties identical with literature values. mp 65–66 °C [lit.[34] mp 65–65.5 °C].

(+)-Methyl 2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (10). In a 25-mL, oven-dried, two-necked round-bottomed flask fitted with an argon inlet, a rubber septum, and a magnetic stirring bar was placed 0.050 g (0.2 mmol) of **9** in 2 mL of freshly distilled THF. The reaction flask was cooled to −78 °C (dry ice–acetone bath), 0.3 mL (0.3 mmol, 1.5 equiv) of freshly prepared lithium diisopropylamide (LDA) was added, and the reaction mixture was stirred for 30 min at 0 °C, followed by cooling to −78 °C. A solution of 0.3 mmol of oxaziridine (+)-**7a** or (+)-**7c** in 2 mL of THF was added dropwise, and the mixture was stirred for 30 min at −78 °C and then for 1 h at 0 °C. The reaction mixture was quenched at −78 °C by addition of 2 mL of a 10% aqueous HCl solution and diluted with 10 mL of diethyl ether. The aqueous layer was extracted with diethyl ether (2 × 5 mL), and the combined organic extracts were washed successively with saturated aqueous $Na_2S_2O_3$ (2 × 15 mL) and brine (2 × 10 mL) and dried over anhydrous $MgSO_4$. Concentration in vacuo gave an oil that was purified by preparative TLC (eluting with 95% CH_2Cl_2/Et_2O) to give 0.033 g (61%) of **10** as a clear oil:[15a] $[\alpha]^{20}_D$ −1.25° (*c* 0.8, $CHCl_3$) [lit.[15a] $[\alpha]^{20}_D$ −33.3° (*c* 1.76, $CHCl_3$)].

Hydroxylation of 2-Acetyl-1-tetralone (11) to 2-(Acetyloxy)-1-tetralone (12). In a 25-mL, oven-dried, two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.094 g (0.5 mmol) of **11** in 5 mL of freshly distilled THF. The reaction flask was cooled to −78 °C (dry ice–acetone bath), and 1.2 mL (0.6 mmol, 1.2 equiv) of a 0.5 M solution of KHMDS in toluene was added. After 30 min, a solution of 0.137 g (0.6 mmol, 1.2 equiv) of the (+)-(camphorsulfonyl)oxaziridine **7a** in 3 mL of THF was added dropwise via syringe, and the reaction mixture was warmed to rt. After completion (typically 2 h), the reaction mixture was quenched by addition of 3 mL of a saturated aqueous NH_4Cl solution and diluted with 10 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 × 5 mL), and the combined organic extracts were washed successively with saturated aqueous $Na_2S_2O_3$ (2 × 15 mL) and brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and filtered. Concentration in vacuo and subsequent purification of the residue by preparative TLC using ether/hexane (1:1) as eluant gave 0.059 g (58%) of 2-(acetyloxy)-1-tetralone (**12**) as an oil.

Preparation of (*R*)-(+)-2-(Acetyloxy)-1-tetralone (12) via Oxidation of 1-Tetralone (12) with (Camphorsulfonyl)-

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(40) Moore, J. A.; Rahm, M. *J. Org. Chem.* **1961**, *26*, 1109.

oxaziridine 7. In a 25-mL, oven-dried, two-necked round-bottomed flask fitted with a three-way stopcock having an argon-filled balloon attached, a rubber septum, and a magnetic stirring bar was placed 0.146 g (1 mmol) of 1-tetralone (**13**) in 5 mL of freshly distilled THF. The reaction flask was cooled to −78 °C, and 1.25 mL of a 1.0 M solution of NaHMDS in THF was added. The reaction was stirred for 30 min, and a solution of the appropriate oxaziridine (+)-**7** (1.4 mmol, 1.4 equiv) in 5 mL of THF was added dropwise via syringe. After 5 h at this temperature (TLC indicates the absence of starting material), 1 mL of dry pyridine and 1 mL of dry acetic anhydride were added. The reaction mixture was warmed to rt and stirred for 8 h, and 5.0 mL of a saturated NH_4Cl solution was added. The reaction mixture was extracted with ether (2 × 15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give an oil, which was purified by preparative TLC, eluting with 3:1:1 *n*-pentane/ether/CH_2Cl_2 to give 0.171 g (61%) of 2-(acetyloxy)-1-tetralone (**12**): mp 58–59 °C [lit.[41] mp 72–73 °C]; 81.3% ee, $[\alpha]^{20}_D$ +65.5° (*c* 1.46, $CHCl_3$); IR (KBr) cm^{-1} 1714, 1682; ^1H NMR ($CDCl_3$) δ 8.03 (dd, J_1 = 7.83 Hz, J_2 = 1.24 Hz, 1H), 7.52 (td, J_1 = 7.49 Hz, J_2 = 1.44 Hz, 1H), 7.36–7.25 (m, 2H), 5.55 (dd, J_1 = 13.1 Hz, J_2 = 5.36 Hz, 1H), 3.29–3.03 (m, 2H), 2.46–2.20 (m, 2H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182.3, 169.9, 142.9, 133.7, 131.5, 128.5, 127.7, 126.8, 74.6, 29.7, 28.0, 20.9; MS *m/z* (rel intensity) M^+ 204, 149, 144 (100), 105, 85, 71. Anal. Calcd: C, 70.58; H, 5.92. Found: C, 70.58; H, 5.73.

The ee was determined using the shift reagent $Eu(hfc)_3$ in $CDCl_3$, monitoring the C-8 proton at 9.0 ppm or the acetyloxy methyl group at 4.0 ppm.

(*R*)-(+)-Methyl 2-Hydroxy-5,8-dimethoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoate (15). In a 100-mL, oven-dried, two-necked flask fitted with a three-way stopcock, an argon balloon, a rubber septum, and a magnetic stirring bar were placed 5.0 mL of potassium bis(trimethylsilyl)amide [0.5 M in toluene, 2.51 mmol, 1.2 equiv] and 5.0 mL of THF. The solution was cooled to −78 °C, 0.553 g (2.09 mmol) of β-keto ester **14** in 7.0 mL of THF was added dropwise, and the mixture was stirred for 30 min at this temperature. In a separate 50-mL, oven-dried, single-necked flask, equipped with a three-way stopcock and magnetic stirring bar, was placed 0.94 g (3.14 mmol, 1.5 equiv) of (−)-(8,8-dimethoxycamphorsulfonyl)oxaziridine (**7c**). The flask was thoroughly flushed with argon, the stopcock was replaced with a rubber septum, 20 mL of THF was added, and the solution was cooled to −78 °C. After 5–10 min, the solution of (−)-**7c** was added dropwise via cannula, with stirring, to the β-keto ester enolate of **14** prepared above. The reaction was monitored by TLC for the disappearance of starting material by removal of a 0.1-mL aliquot and immediately adding it to an equal volume of a saturated NH_4Cl solution and eluting with 3:1:1 *n*-pentane/CH_2Cl_2/Et_2O). On completion (typically 5 h), the reaction was quenched at −78 °C by addition of 5 mL of a saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$ and filtered. Evaporation of the solvent in vacuo gave a solid which was purified by flash chromatography, eluting with 3:1:1 *n*-pentane/CH_2Cl_2/Et_2O to afford 0.410 g (70%) of (*R*)-(+)-**15** as a colorless solid: mp 142–143 °C; >95% ee, $[\alpha]^{20}_D$ +55.2° (*c* 0.8, $CHCl_3$); IR (KBr) cm^{-1} 1614, 1684 (C=O), 1723 (CO_2Me), 3479 (OH); ^1H NMR ($CDCl_3$) δ 6.93 (ab q, J_1 = 51.6 Hz, J_2 = 9.0 Hz, 2H), 4.72 (s, 1H, D_2O exchangeable), 3.88 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.15–3.05 (m, 1H), 2.98–2.81 (m, 1H), 2.79–2.71 (m, 1H), 2.14–2.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 193.24, 169.98, 154.09, 149.86, 134.03, 119.79, 116.32, 109.86, 56.20, 55.76, 52.57, 31.42, 20.28; MS *m/z* (rel intensity) M^+ 280 (14.2), 262 (13), 221 (15.6), 178 (100), 163 (48.2), 121 (41), 77 (30). Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.71. Found: C, 60.12; H, 5.72.

The ee was determined using the shift reagent $Eu(hfc)_3$ in $CDCl_3$, monitoring the ester methyl group at 4.9 ppm.

Triethylsilane Reduction of (*R*)-(+)-14 to (*R*)-(−)-Methyl 2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (10). In a 5-mL, one-necked flask equipped with a magnetic stir bar, rubber septum, and an argon inlet and outlet was placed 0.067 g (0.22 mmol) of (*R*)-(+)-**15** and 1.0 mL CF_3CO_2H, and the reaction was cooled to 0 °C. Triethylsilane (0.10 mL, 0.62 mmol, 2.8 equiv) was added dropwise, and the reaction was stirred at 0 °C for 2 h. Then the solvent was removed under reduced pressure. The crude product was purified by preparative TLC, eluting with ether to give 0.057 g (97%) of the ester as a colorless oil:[15a] >95% ee, $[\alpha]_D$ −32.8° (*c* 3.3, $CHCl_3$), [lit.[15a] $[\alpha]^{20}_D$ −34.5°]; IR (KBr) cm^{-1} 3495 (OH), 2943, 2837, 1731 (CO_2Me), 1596, 1472, 1249; ^1H NMR ($CDCl_3$) δ 6.64 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.06–2.70 (m, 4H), 2.03–1.98 (m, 2H), 2.97 (s, 1H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ 177.1, 151.3, 150.9, 125.2, 122.9, 107.0, 106.8, 72.1, 55.5, 55.44, 52.7, 33.4, 30.4, 19.3; MS *m/z* (rel intensity) M^+ 266 (63.8), 248 (43.5), 189 (100), 164 (32), 149 (41), 91 (36), 77 (33); HRMS calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1158.

(*R*)-(−)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (3b). The reaction was carried out on 0.266 g of (*R*)-(−)-**10** following the procedure of Broadhurst and co-workers[6] to give (*R*)-(−)-**3b** in 66% yield, having properties in agreement with literature values; >95% ee, $[\alpha]_D$ −47.6° (*c* 1.63, $CHCl_3$) [lit.[42] $[\alpha]_D$ −48.7° (*c* 0.825, $CHCl_3$)].

(*R*)-(+)-Methyl 2,8-Dihydroxy-5-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoate (18). In a 50-mL, two-necked, oven-dried flask equipped with three-way stopcock, an argon-filled balloon, and a magnetic stir bar was placed 1.06 g (3.78 mmol) of (*R*)-(+)-**15** in 10.0 mL of dry CH_2Cl_2, and the solution was cooled to −78 °C. To the reaction mixture was added dropwise 10.1 mL (8 equiv) of a 1 M solution of BBr_3 in CH_2Cl_2 [Aldrich], and stirring was continued at −78 °C until the reaction was complete. Careful monitoring of the reaction by TLC was essential to minimize side products. The reaction was monitored by removal of a 0.1-mL aliquot, immediately adding it to an equal volume of a saturated aqueous $NaHCO_3$ solution, and eluting with 8:1:1 *n*-pentane/CH_2Cl_2/Et_2O twice (I_2 visualization). On disappearance of the starting material (typically 2–3 h), the reaction was quenched at −78 °C by addition of 15.0 mL of a saturated aqueous $NaHCO_3$ solution. The reaction mixture was warmed to rt and extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, and filtered. Evaporation in vacuo gave a bright yellow oil which was purified by flash chromatography eluting with 8:1:1 *n*-pentane/CH_2Cl_2/Et_2O to give 0.82 g (82%) of (*R*)-(+)-**18** as a bright yellow solid: mp 59–60 °C; >95% ee, $[\alpha]^{20}_D$ +3.54° (*c* 8.50, $CHCl_3$); IR (KBr) cm^{-1} 3463, 2931, 1734, 1645, 1474; ^1H NMR ($CDCl_3$) δ 11.05 (s, 1H, D_2O exchangeable), 6.98 (ab q, J_1 = 73.48 Hz, J_2 = 9.07 Hz, 2H), 4.25 (s, 1H, D_2O exchangeable), 3.81 (s, 3H), 3.78 (s, 3H), 3.16–3.04 (m, 1H), 2.97–2.84 (m, 1H), 2.68–2.58 (m, 1H), 2.26–2.14 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 199, 156, 148, 131, 120, 115, 77.3, 56, 53, 31, 19; MS *m/z* (rel intensity) M^+ 266 (25), 216 (20), 207 (40), 189 (48), 179 (30), 164 (55), 149 (40), 136 (100), 106 (65), 77 (88). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.75; H, 5.68.

(*R*)-(−)-Methyl 2,8-Dihydroxy-5-methoxy-1,2,3,4-tetrahydro-2-naphthoate (19). In an oven-dried, 25-mL, single-necked, round bottomed flask equipped with a rubber septum, magnetic stir bar, and an argon inlet and outlet was placed 0.37 g (1.37 mmol) of (*R*)-(+)-**18** and 5.0 mL of CF_3CO_2H (Aldrich) at 0 °C. Et_3SiH, 0.66 mL (4.12 mmol, 3.0 equiv), was slowly added dropwise via syringe, and the reaction mixture warmed to rt with stirring. After approximately 16 h, the yellow solution becames colorless, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with Et_2O, to give 0.31 g (90%) of **19** as a white solid: mp 152–153 °C; >95% ee, $[\alpha]^{25}_D$ −23.8° (*c* 0.69, acetone); IR (KBr) cm^{-1} 3362, 2939, 1736, 1613; ^1H NMR ($CDCl_3$) δ 6.57 (s, 2H), 4.37 (s, 1H, D_2O exchangeable), 3.83 (s, 3H), 3.77 (s, 3H), 3.11–2.70 (m, 4H), 2.93 (s, 1H, D_2O exchangeable), 2.04–1.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 177, 151, 147, 125, 121, 111, 107, 72, 55, 53, 33, 30, 19; MS *m/z* (rel intensity) M^+ 252 (56), 234 (41), 192 (24), 175 (100), 150 (27), 83 (34), 77 (24). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.99; H, 6.38.

(*R*)-(−)-2-Acetyl-8-hydroxy-5-methoxy-1,2,3,4-tetrahydro-2-naphthalenol (3a). In a 25-mL, oven-dried, two-necked flask equipped with a rubber septum, magnetic stir bar, and three-way stopcock fitted with an argon-filled balloon was placed 0.520 g (10.6 mmol, 8 equiv) of a 50% dispersion of NaH. The NaH

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(42) Sodeoka, M.; Iimori, T.; Shibasaki, M. *Chem. Pharm. Bull.* **1991**, *39*, 323.

was washed with *n*-pentane (3 × 5 mL) and pumped to dryness, 3.0 mL of dry DMSO was added, and the solution was heated to 65 °C until H_2 evolution ceasd (approx 1 h). At this time 20 mL of THF was added, the solution was cooled to 0 °C, and 0.335 g (1.33 mmol) of (−)-**19** in 10 mL of THF was added dropwise. Stirring was continued at 0 °C for an additional 1 h. The reaction was poured into 20 mL of water, the pH was brought to ca. 3 with concd HCl, and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The CH_2Cl_2 solution was dried over anhydrous $MgSO_4$ and filtered and the solvent was removed in vacuo to give a thick yellow oil. The oil was taken in THF (10 mL) and added dropwise to an argon-filled flask containing the aluminum amalgam cooled to 10 °C, prepared from 0.30 g of Al according to the method of Corey,[43] followed by addition of 1 mL of H_2O. The reaction was monitored by TLC using Et_2O as eluant and, on completion (typically 12–16 h), the solution was filtered to remove the inorganic salts, which were washed once with EtOAc (10 mL), and the washings were combined. The combined organic washings were evaporated under reduced pressure, and the residue was taken up in 20 mL of EtOAc, washed with H_2O (10 mL), dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave a solid residue which was purified by preparative TLC, eluting with Et_2O to give 0.188 g (60% yield) of (*R*)-(−)-**3a**: mp 173–174 °C;[35] 95% ee, $[\alpha]^{28}_D$ −22.5° (*c* 1.05, acetone); IR (KBr) cm^{-1} 3448, 2952, 1701, 1607; ^1H NMR ($CDCl_3$) δ 6.57 (s, 2H), 4.58 (s, 1H, D_2O exchangable), 3.77 (s, 3H), 3.69 (s, 1H, D_2O exchangable), 3.03–2.72 (m, 4H), 2.34 (s, 3H), 2.05–1.8 (m, 2H); ^{13}C ($CDCl_3$) δ 186, 182, 147, 125, 121, 112, 108, 77.2, 55, 32, 29, 24, 19; MS *m/z* (rel intensity) M^+ 236 (100), 193 (99), 175 (89). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.82. Found: C, 65.57; H, 6.66.

Hydroxylation of Methyl 8-(Benzyloxy)-5-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoate (16) to (*S*)-(−)-17. The hydroxylation of 16 to (*S*)-(−)-17 was accomplished as described above by treating 0.043 g (0.13 mmol) of 16 with 1.2 equiv of KHMDS at −78 °C and then hydroxylation with 0.051 g of (+)-**7c** to give 0.026 g (58%) of (*S*)-(−)-17 as a solid, mp 127–9 °C; 65% ee, $[\alpha]_D$ −37.9° (*c* 1.60, $CHCl_3$), identical to an authentic sample prepared as described below. Similar results were observed with oxaziridines (+)-**7a** and (+)-**7b**.

Benzylation of (*S*)-(−)-Methyl 2,8-Dihydroxy-5-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoate (18) to (*S*)-(−)-17. Into a 25-mL, one-necked flask equipped with a reflux condenser and argon bubbler were placed 0.218 g (0.818 mmol) of (*S*)-(−)-18 (>95% ee), 0.11 mL of benzyl bromide (0.900 mmol, 1.1 equiv), 0.20 g of anhydrous K_2CO_3, and 10 mL of dry acetone. The mixture was refluxed for 12 h, after which time, 0.11 mL of benzyl bromide was added and refluxing continued for an additional 5 h. The reaction was cooled and the solvent was removed under reduced pressure to give an oily residue, which was purified by flash chromatography, eluting with 10% Et_2O/*n*-pentane to give 0.222 g (76%) of (*S*)-(−)-17: mp 127–129 °C; $[\alpha]_D$ −58.3° (*c* 2.38, $CHCl_3$) (>95% ee); IR (KBr) cm^{-1} 3412, 2927, 1734, 1690, 1591, 1480; ^1H NMR ($CDCl_3$) δ 7.52–7.28 (m, 5H), 6.90 (ab q, J_1 = 31.59 Hz, J_2 = 9.04 Hz, 2H), 5.16 (ab q, J_1 = 16.42 Hz, J_2 = 12.47 Hz), 4.75 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.16–3.05 (m, 1H), 2.98–2.84 (m, 1H), 2.80–2.71 (m, 1H), 2.17–2.04 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 193.1, 182.3, 152.9, 150.4, 136.8, 134.2, 128.4, 127.6, 126.8, 116.1, 112.7, 71.3, 64.4, 55.9, 52.8, 31.8, 29.8, 20.6; MS *m/z* (rel intensity) M^+ 356 (19), 338 (11), 254 (35), 247 (33), 218 (42), 195 (25), 181 (39), 163 (50), 135 (46), 121 (41), 92 (100), 89 (26), 79 (33), 77 (35). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41, H 5.66; Found: C, 67.66, H, 5.69.

(*R*)-(−)-2-Acetyl-5-methoxy-8-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-2-ol (3c). In an oven-dried, 5 mL, single-necked, round-bottomed flask equipped with a magnetic stir bar, a reflux condenser, and an argon bubbler were placed 0.022 g (0.093 mmol) of (*R*)-(−)-**3a**, 5 mL of acetone, 0.03 mL (0.027 mmol, 3 equiv) of benzyl bromide, and 0.07 g of anhydrous K_2CO_3, and the solution was brought to reflux for 16 h. Upon completion as seen by ^1H NMR (disappearance of ArH peak at δ 6.57) the reaction was filtered, and the solvent was removed under reduced pressure. The oily residue was subjected to preparative TLC, eluting twice with *n*-pentane and then once with 50% Et_2O/*n*-pentane to afford 0.0134 g (44%) of **3c** with spectral properties in agreement with literature values:[35] $[\alpha]^{20}_D$ −22.5° (*c* 0.39, $CHCl_3$) (>95% ee) [lit.[35] $[\alpha]_D$ −22.9° (*c* 1.03, $CHCl_3$)].

(−)-(*R*)-2-Acetyl-2-(*tert*-butyldimethylsiloxy)-5-methoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene (3d). In an oven-dried, two-necked, round-bottomed flask equipped with a magnetic stir bar and three-way stopcock fitted with an Ar-filled balloon was placed 0.089 g (0.375 mmol) of (*R*)-(−)-**3a** in 3 mL of dry CH_2Cl_2, and the solution was cooled to 0 °C. 2,6-Lutidine, 0.26 mL (2.25 mmol, 6 equiv), was added followed by 0.39 mL (1.69 mmol, 4.5 equiv) of *tert*-butyldimethylsilyl triflate, and the reaction mixture was stirred for 2 h at 0 °C, at which time TLC (5% EtOAc/*n*-pentane) showed the absence of starting material. Dry MeOH, 1 mL, was added, and the solution was stirred for an additional 10 min at 0 °C, at which time the solution was washed with 5 mL of H_2O and the aqueous solution was extracted with CH_2Cl_2 (2 × 5 mL). The organic portions were combined, washed with 5 mL of 10% HCl and 5 mL of H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a light yellow oil which was placed under vacuum until it was brought to constant mass (8 h).

The flask containing the crude oily bis-silylated product was fitted with a rubber septum and a magnetic stir bar and flushed with Ar. Into the flask was introduced 1.5 mL of dry THF, the solution was cooled to 0 °C with stirring, and 0.38 mL (1.0 equiv) of a 1 M solution of *n*-Bu_4NF in THF (Aldrich) was added dropwise. Stirring was continued for 35 min, at which time the reaction mixture was quenched with 2 mL of a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (2 × 5 mL). After being dried over anhydrous $MgSO_4$, the solvent was removed and the resulting oil was purified by preparative TLC, eluting with 1:1 Et_2O/*n*-pentane to give 0.118 g (90%) of an oil having spectral properties in agreement with literature values:[12b] >95% ee, $[\alpha]_D$ −3.16° (*c* 8.26, $CHCl_3$) [lit.[12b] $[\alpha]_D$ −3.3° (*c* 1.10, $CHCl_3$)].

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