starting from tetraethylene glycol.

**1-Hydroxy-11-(4'-nitrophenoxy)-3,6,9-trioxaundecane (A9).**[20] **A9** was prepared by the parallel method for **A7** using tetraethylene glycol and 4-fluoronitrobenzene in 92% yield: yellow oil; $^1$H NMR $\delta$ 2.91 (br s, 1 H), 3.5–4.0 (m, 14 H), 4.1–4.3 (m, 2 H), 6.94 (d, 2 H, $J$ = 9 Hz), and 8.15 ppm (d, 2 H, $J$ = 9 Hz); IR (neat) $\nu$ 1340, 1510 ($-NO_2$), and 3420 (-OH) cm$^{-1}$.

The reaction of **A8** and 2,4-dinitrofluorobenzene gave **14** in 65% yield. **14**: yellow crystals; mp 60.5–61.5 °C; $^1$H NMR $\delta$ 3.5–4.5 (m, 16 H), 6.97 (d, 2 H, $J$ = 9 Hz), 7.32 (d, 1 H, $J$ = 9 Hz), 8.15 (d, 2 H, $J$ = 9 Hz), 8.40 (dd, 1 H, $J$ = 3 Hz and $J$ = 9 Hz), and 8.76 ppm (d, 1 H, $J$ = 3 Hz); IR (Nujol) 1340 and 1510 ($-NO_2$) cm$^{-1}$; UV (MeCN) $\lambda_{max}$ (log $\epsilon$) 217 (4.21) and 301 nm (4.26). Anal. Calcd for $C_{20}H_{23}N_3O_{11}$: C, 49.9; H, 4.82; N, 8.74. Found: C, 50.1; H, 4.92; N, 8.65.

**1-Methoxy-11-(2'-nitrophenoxy)-3,6,9-trioxaundecane (17)** was prepared through the following two steps starting from tetraethylene glycol.

**1-Hydroxy-11-(2'-nitrophenoxy)-3,6,9-trioxaundecane (A10).**[20] A suspension of 4-nitrofluorobenzene (500 mg, 3.5 mmol), potassium carbonate (735 mg, 5.3 mmol), and tetraethylene glycol (6.9 g, 35 mmol) was heated for 22 h under an atmosphere of nitrogen gas. After the usual workup, the crude product (1.2 g) was isolated and purified by column chromatography on silica gel eluting with 10% ethyl acetate to give pure **A10** (1.0 g, 3.2 mmol): yellow oil; 90% yield; $^1$H NMR $\delta$ 2.63 (br s, 1 H), 3.4–4.0 (m, 14 H), 4.1–4.3 (m, 2 H), 6.8–7.8 ppm (m, 4 H); IR (neat) $\nu$ 1340, 1520 cm$^{-1}$ ($-NO_2$).

**17** was prepared by the methylation of **A10** with diazomethane in ether:[19] $^1$H NMR (500 MHz) $\delta$ 3.37 (s, 3 H), 3.5–3.7 (m, 12 H), 3.90 (t, 2 H, $J$ = 4.8 Hz), 4.26 (t, 2 H, $J$ = 4.8 Hz), 7.03 (pseudo t, 1 H, $J$ = 7.8 Hz), 7.11 (d, 1 H, $J$ = 8.5 Hz), 7.51 (pseudo t, 1 H, $J$ = 7.8 Hz), and 7.82 ppm (d, 1 H, $J$ = 8.1 Hz); IR (neat) $\nu$ 1520, 1340, 1240, and 1035 cm$^{-1}$; UV (MeCN) $\lambda_{max}$ (log $\epsilon$) 260 (3.51) and 326 nm (3.35).

**1-Methoxy-11-(4'-nitrophenoxy)-3,6,9-trioxaundecane (18)** was prepared by the method for **17**: yellow oil; $^1$H NMR (500 Mz) $\delta$ 3.37 (s, 3 H), 3.5–3.7 (m, 12 H), 3.89 (t, 2 H, $J$ = 4.8 Hz), 4.22 (t, 2 H, $J$ = 4.8 Hz), 6.98 (d, 2 H, $J$ = 9.3 Hz), and 8.19 ppm (d, 2 H, $J$ = 9.3 Hz); IR (neat) 1505, 1330, 1250, and 1040 cm$^{-1}$; UV (MeCN) $\lambda_{max}$ (log $\epsilon$) 227 (3.98) and 308 nm (4.18). Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.7; H, 7.04; N, 4.21. Found: C, 54.8; H, 7.10; N, 4.33.

**Trimethylsilyl Nitrate (TMSN).** (a) Silver nitrate (1 g, 5.9 mmol) and trimethylsilyl chloride (540 $\mu$L, 5.6 mmol) were mixed at -5 °C (ice-salt bath) and stirred for 30 min under an atmosphere of nitrogen at 0 °C (ice bath) in a dark room. Decantation of the reaction mixture gave pure trimethylsilyl nitrate in quantitative yield (0.68 g, 5.6 mmol, 93%): IR and NMR spectra were shown in ref 11c. Anal. Calcd for $C_3H_9NO_3Si$: C, 26.7; H, 6.71; N, 10.36. Found: C, 26.2; H, 7.10; N, 10.12. (b) A practical procedure for the preparation of a $CH_3CN$ solution of TMSN (0.42 mM): A solution of silver nitrate (73.2 mg, 0.42 mmol) and trimethylsilyl chloride (69 $\mu$L, 0.54 mmol) in $CH_3CN$ (2 mL) was stirred for 2 h at 0 °C in a dark room. Silver chloride formed was removed by decantation. The $CH_3CN$ layer is a pure trimethylsilyl nitrate solution, the concentration of which was measured to be 0.4 ± 0.02 mM by comparison of the corresponding methyl peak integration area with that of a standard solution of TMSN prepared by the above (a) method in $CH_3CN$.

**General Method for Nitration of Podands with TMSN.** To a solution of podands in $CCl_4$ or $CH_3CN$ (20 mL) in the presence of Lewis acids was added a freshly prepared $CH_3CN$ solution (2 mL) of TMSN over 1 min via glass pipet. After stirring for 3 h at 0 °C under $N_2$ in a dark room, the reaction mixture was diluted with 20 mL of $CHCl_3$ and washed with 50 mL of water three times. The $CHCl_3$ layer was separated and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed by HPLC (COSMOSIL, methanol) to give nitrated podands.[9]

**Acknowledgment.** M.K. thanks the NMR Center (Okayama University) for 500-MHz NMR spectra of the compounds.

# Regioselective Ring Opening of Polycyclic Aromatic Hydrocarbon Epoxides by Polymer-Supported $N_3^-$ Anion

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The benzylic ring opening of some polycyclic aromatic hydrocarbon (PAH) tetrahydro epoxides and one diol epoxide has been achieved by Amberlite supported $N_3^-$ ion, in a regio- and stereoselective manner. The resulting azidohydrins have been converted to the corresponding $\beta$-acyloxy amines and/or amino alcohols. The $\beta$-acyloxy amino compounds are suitable for incorporation into synthetic oligonucleotides, whereas the amino alcohols were synthesized in order to establish the regiochemistry of the ring-opening step. The tetrahydro models studied were the naphthalene (Np), benz[c]acridine (BcAr), benzo[a]pyrene (BaP), and benzo[e]pyrene (BeP) epoxides. In the Np and BcAr cases, the amino group is equatorial whereas in the BaP and BeP cases, it is axial. In the final stage of these ring-opening reactions, the racemic diol epoxide of benzo[a]pyrene (BaPDE) **24** was converted to the corresponding amines. In each of the cases studied, the attack by $N_3^-$ ion occurred at the benzylic site. The relative stereochemistry of the azido and hydroxyl groups in every case was trans. No other regio- or stereoisomer was observed in any of these compounds in the ring-opening step.

Metabolic activation of PAH occurs through conversions of the parent hydrocarbon to "bay region" diol epoxides.[1,2] The resulting activated PAH, that is the electrophilic diol epoxides, bind to nucleophilic sites in DNA, resulting in the formation of PAH–DNA adducts. The major adducts result from a trans ring opening of the oxirane ring with

(1) This work was supported in part, by Grant CA 22985 from the National Cancer Institute to R.E.L. Thakker, D. M.; Levin, W.; Yagi, H.; Conney, A. H.; Jerina, D. M. In *Advances in Experimental Medicine and Biology: Biological Reactive Intermediates IIA*; Snyder, R., Parke, D. V., Kocsis, J. J., Jollow, D. J., Gibson, C. G., Witmer, C. M., Eds.; Plenum Publishing Co.: New York, 1982; pp 525–540.

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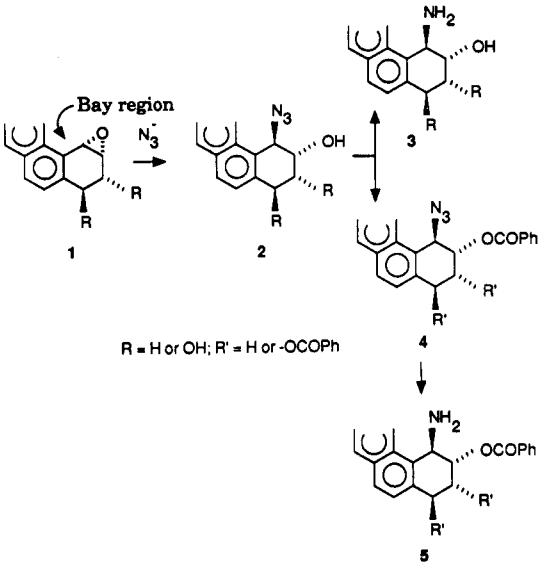
**Scheme I**

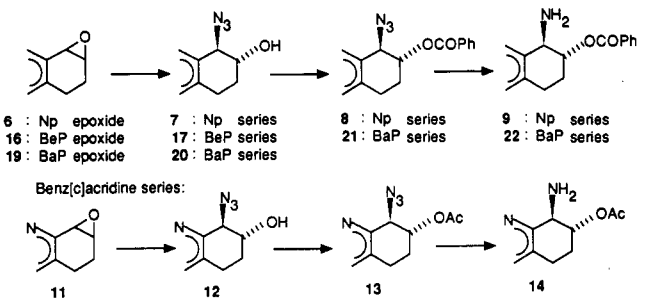



the exocyclic amino groups on the purine bases being attached to the benzylic carbon of the PAH.[3-5] In spite of the vast array of information available on preference for binding (deoxyadenosine versus deoxyguanosine) of these PAH diol epoxides,[4] and the interactions of these diol epoxides with DNA,[5,6] the exact mechanism of cancer induction is as yet unknown. It is quite likely that intercalation of the PAH diol epoxides into DNA precedes covalent binding, and mutations occur as a direct consequence of adduct formation.[5,7]

In an attempt at elucidating the steps involved in the process of cancer induction, we have embarked on the synthesis of PAH-substituted mononucleosides. These mononucleosides could be incorporated into oligonucleotides for site-directed mutagenesis studies and to study conformational changes in DNA which result from the binding of the PAH. Toward these goals, we have been investigating the synthesis of suitably protected amino derivatives of these PAH, which can be coupled to appropriately modified purine derivatives. Our overall strategy for the synthesis of PAH amines is shown in Scheme I.

The desired stereochemistry between the bay region benzylic amino group and the adjacent substituent should

**Scheme II**




be trans, since this is the stereochemistry in the major DNA adducts of these PAH. A number of methods are known for the introduction of an azido group by displacement of the epoxide oxygen.[8] However, we were particularly interested in developing a new method using Amberlite supported $N_3^-$ ion, which has recently been used for the replacement of halogens from alkyl and benzyl halides.[9] In this strategy, the azide functionality could be used as the amine precursor, since this group can be reduced under relatively mild, neutral conditions. Further, the hydroxyl group can be selectively protected at the azidohydrin stage, to prevent possible phosphorylation of the PAH hydroxyl group during oligonucleotide synthesis.

## Results and Discussion

Scheme II shows the conversions of various tetrahydroepoxides to the corresponding amines.

**Synthesis of Azidohydrins.** As described in the literature,[9] the $Cl^-$ form of Amberlite IRA 400 resin was washed with a 30% aqueous solution of $NaN_3$ (see the Experimental Section for preparation of resin). Through this entire process, a flow rate of 1 mL/min was maintained. After complete passage of the azide solution through the resin, the resin was washed with water, methanol, chloroform and dry THF (or dry acetonitrile) sequentially. The epoxide and the resin were then shaken in a dry solvent (THF or acetonitrile) at 37 °C until no starting epoxide was visualized by TLC. Two noteworthy features of this process are: (1) THF seems to be a slightly better solvent as compared to acetonitrile, since it dissolves the starting material well and causes less leaching of the resin as compared to acetonitrile and (2) the reaction mixture is mechanically shaken instead of stirred, since the resin tends to fracture on stirring. After completion of the reaction, the resin was washed with dry THF and the azidohydrin was recovered by washing the resin with a large excess of methanol. Small amounts of azidohydrin could also be recovered from the THF washing. In the Np and the BcAr cases, the azidohydrins were also separately synthesized through a phase-transfer catalytic method. However, this method was not applied to the BaP diol epoxide due to its limited solubility in toluene.

**Synthesis of the Acylated Azidohydrin Derivatives.** As mentioned earlier, protection of the hydroxyl group was deemed necessary. Acetate protection was initially used and was found to be unsuitable due to reactions with the primary amino group produced by azide reduction. The only isolable amino acetate was that of BcAr **14**. All others seemed to decompose during workup. The azido acetate **13** was synthesized by stirring the corresponding azidohydrin **12** in dry pyridine with acetic anhydride. Benzoate protection was found to produce suitable stable derivatives.

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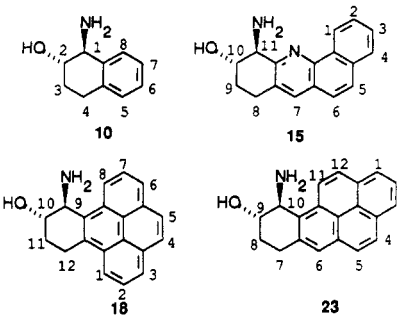

**Figure 1.** Structures of the amino alcohols and the numbering schemes for the four PAH skeletons.

**Table I. Chemical Shifts of Benzylic "B" (Bearing the $N_3$ or $NH_2$ Group) and Nonbenzylic "NB" (Bearing the Hydroxyl Group)**

| azide | H (B) | H (NB) | J (Hz) | amine | H (B) | H (NB) | J (Hz) |
|---|---|---|---|---|---|---|---|
| 7 | 4.41 | 4.04 | 1,2:7.2 | 10 | 3.69 | 3.61 | 8.7 |
| 12 | 4.81 | 4.00 | 10,11:8.1 | 15 | 4.00 | 3.88 | 9.6 |
| 17 | 5.15 | 4.56 | 9,10:3.4 | 18 | 4.80 | 4.40 | –[a] |
| 20 | 5.30 | 4.54 | 9,10:3.4 | 23 | 4.9 | 4.35 | 3.4 |

[a] Could not be measured since H-9 appears as a singlet.

The azido benzoates **8** and **21** were prepared by stirring the corresponding azidohydrins **7** and **20** with 5 equiv of sodium hydride (NaH) in dry pyridine for a few minutes, followed by addition of excess benzoyl chloride (PhCOCl). This procedure was used in order to assure complete acylation of the axial hydroxyl groups in the bay region compounds. The crude benzoates were purified by chromatography on silica gel. Initially, THF was tried as solvent for the acylation. However, products resulting from reaction of THF with PhCOCl were observed. Monomeric 4-chlorobutan-1-ol benzoate from the reaction of 1 mol each of THF and PhCOCl was obtained. Similar dimeric and trimeric derivatives were also observed from reactions of 1 mol of PhCOCl with 2 and 3 mol of THF, respectively.

**Synthesis of Amino Acetate and Benzoates.** For unstable β-acetoxy amines, side products resulting from acylation of the amino group were found to appear upon concentration and storage. The BcAr case was the only instance where a stable β-acetoxy amine could be isolated. The stability of **14** may result from lower basicity of the amino group due to the presence of the β-nitrogen. In all cases the amino esters (**9**, **14**, and **22**) were obtained by catalytic reduction of the azido group, using Lindlar catalyst.[10] Generally, these reactions were carried out in ethanol or a 1:1 mixture of ethanol/THF. The latter proved to be superior, since the substrates were completely soluble in the solvent mixture.

**Synthesis of the Amino Alcohols.** These compounds were initially synthesized during our search for suitable reducing agents for the azide moiety; therefore, a variety of different methods were attempted. The Np amino alcohol **10** (Figure 1) was synthesized by reduction of the $N_3^-$ group with 1,3-propanedithiol (1,3-PDT) in triethylamine ($Et_3N$)/methanol (MeOH).[11] In order to compare the product with an authentic sample of the amine, *trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydronaphthalene was reacted with ammonia as is reported in the literature.[12] Amino alcohol **10** was produced in 37% yield. The BcAr amino alcohol **15** was also prepared by reduction of the azido group using 1,3-PDT in $Et_3N$/MeOH, whereas the BeP amino alcohol was obtained by catalytic reduction. The BaP amino alcohol **23** was obtained by use of the Staudinger reaction,[13] but could not be rigorously purified.

**Scheme III**

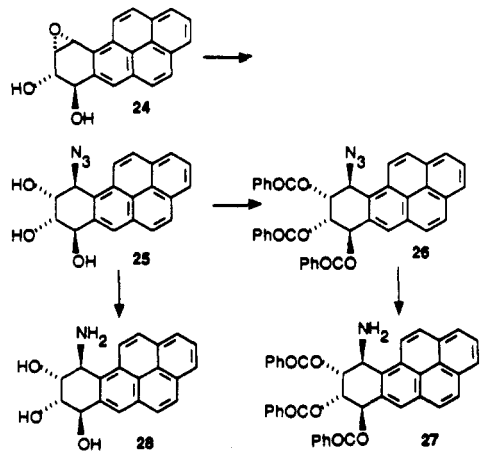

Table I shows the chemical shifts for the benzylic and nonbenzylic protons which bear substituents. The chemical shifts for the carbinol protons (nonbenzylic) are quite similar in the azidohydrins and the corresponding amino alcohols. Reduction of the azide functionality results in a characteristic upfield shift of a doublet, indicating the presence of a benzylic azide moiety (if the $N_3$ group had been nonbenzylic, such an effect would not be observed). In the cases of **7** and **12**, the relatively large coupling constant is consistent with a trans-diequatorial conformation.[14,15] In the cases of BaP and BeP, the coupling constants are of the same order as in other trans-diaxial derivatives of the same series.[14,16] Thus, in each of these cases, a trans ring opening of the epoxide had occurred at the benzylic carbon of the PAH.

**Azide Ring Opening of a Diol Epoxide.** Once the synthetic strategy had been established for the tetrahydro derivatives, the next step was to attempt the synthesis of the amino derivatives of a diol epoxide. As mentioned earlier, the diol epoxide of choice was BaPDE **24** (Scheme III). The ring opening proceeded as in the tetrahydro derivatives, with a benzylic attack of the $N_3^-$ ion. The resulting azido triol was reduced catalytically after protection of the hydroxyl groups as benzoate esters. Direct catalytic reduction of the azido triol gave the amino triol **28**. In this case also, an upfield shift of the benzylic doublet (from δ 5.56 ppm in the azide to δ 4.74 ppm in the amine) indicated the presence of a benzylic azide functionality. The only other doublets in **25** and **28** are the $H_7$ protons, and in each of these cases, the hydroxyl groups are trans-diequatorial. This results in 8.6- and 8.4-Hz coupling constants for the benzylic $H_7$ proton in **25** and **28**, respectively. The chemical shifts and the coupling constants of protons of the tetrahydrobenzo ring of BaP, resulting from both cis and trans opening of the oxirane ring of BaPDE, are shown in Table II. Comparison of the coupling constants of protons 7, 8, 9, and 10 in both **25** and **28** with those of literature[17] compounds **29** and **30** shows

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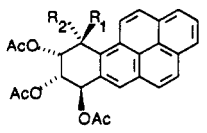
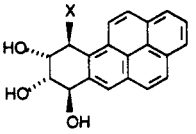
**Table II. Coupling Constants for Protons of the Tetrahydro Ring of BaP in the Products Arising from Cis and Trans Ring Opening of the Oxirane Ring in BaPDE**





**29**: $R_1$ = OMe $R_2$ = H
**30**: $R_1$ = OAc $R_2$ = H
**31**: $R_1$ = H $R_2$ = OAc

**25**: X = $N_3$
**28**: X = $NH_2$

| compd | J (7,8), Hz | J (8,9), Hz | J (9,10), Hz |
|---|---|---|---|
| **25** | 8.6 | 2.1 | 3.6 |
| **28** | 8.4 | 2.1 | 3.0 |
| **29**[a] | 9.0 | 2.5 | 3.6 |
| **30**[a] | 8.8 | 2.5 | 3.6 |
| **31**[a] | 3.5 | 2.5 | 4.6 |

[a] Described in ref 17.

a marked similarity. The cis ring-opened product **31**,[17] on the other hand, has distinctly different $J_{7,8}$ and $J_{8,9}$. Finally, the chemical shift of $H_{10}$ in **27** is similar to that of (±)-7β,8α,9α-triacetoxy-10β-anilino-7,8,9,10-tetrahydrobenzo[*a*]pyrene **32** (δ 5.46 ppm in **27** and 5.59 ppm in **32**).[17]

Thus, the Amberlite supported $N_3^-$ ring opening of PAH epoxides is stereo- and regioselective. A potential advantage of the method relative to phase-transfer catalysis[18] is the higher solubility of polar substrates such as diol epoxides in THF and $CH_3CN$ relative to toluene and the ability to exclude moisture prior to workup.

## Experimental Section

Proton NMR spectra were recorded on a Varian XL-300 spectrometer using $CDCl_3$ unless noted otherwise. Chemical shifts are reported in δ units and coupling constants are reported in hertz. Nominal mass spectra were recorded on a Hewlett-Packard 5985 quadrupole spectrometer (EI) or on a Kratos MS25 RF spectrometer (ammonia CI). Solvents were dried according to standard procedures. During workup procedures, organic layers were dried over anhydrous $Na_2SO_4$ unless noted otherwise.

**General Method for the Preparation of $N_3^-$ Form of Amberlite Resin.** In a typical experiment, 20 g of Amberlite IRA 400 $Cl^-$ form was loaded into a column, and a wad of cotton was added. The resin was washed with about 200 mL of distilled water. A 30% aqueous solution of sodium azide (60 g $NaN_3$ in 200 mL of distilled water) was passed through the resin at a rate of 1 mL/min. The resin was then washed with about 200 mL each of distilled water, methanol, and chloroform. Finally, the resin was washed with about 300 mL of dry THF (or dry $CH_3CN$).

**(±)-*trans*-1-Azido-2-hydroxy-1,2,3,4-tetrahydronaphthalene (7).** Approximately 20 g of the $N_3^-$ form of Amberlite resin and the Np epoxide **6** (46 mg, 0.315 mmol) were placed in an Erlenmeyer flask with a 24/40 joint, and dry THF was added to barely cover the resin. The flask was stoppered and shaken mechanically for 3 days at 37 °C. The resin was reloaded into the column using dry THF and washed with THF and about 600 mL of MeOH sequentially, under air pressure. Since no starting epoxide was observed by TLC, the THF and MeOH washings were combined and evaporated under reduced pressure. Chromatography of the crude product on silica gel using $CHCl_3$ and EtOAc sequentially gave 40.3 mg (68%) of pure Np azidohydrin **7**.

The same reaction was performed on 70 mg of the Np epoxide **6** with about 20 g of resin at room temperature. In this case, the reaction was complete in 1 week, and 70.8 mg (78%) of the azidohydrin was obtained after workup as mentioned above.

In a phase-transfer catalytic reaction, the epoxide **6** (20 mg, 0.137 mmol) in PhMe (2 mL) was stirred in a screw-cap vial, with 25% aqueous $NaN_3$ solution (2 mL) and a few drops of Aliquat 336, for 72 h. The reaction mixture was diluted with PhMe (10 mL) and washed with water (4 × 10 mL). Evaporation of the organic layer under reduced pressure gave 20 mg (81%) of the azidohydrin **7**. NMR spectrum: 1.95 and 2.2 (m, 1 $H_3$ each), 2.25 (br s, O*H*), 2.92 (m, 2 $H_4$), 4.04 (m, 1 $H_2$), 4.41 (d, 1 $H_1$, $J$ = 7.2), 7.14–7.41 (4 H, aromatic). Mass spectrum (12 eV): *m/z* (relative intensity) 189 ($M^+$, 9.5), 161 (60), 132 (100).

**(±)-*trans*-1-Azido-2-(benzoyloxy)-1,2,3,4-tetrahydronaphthalene (8).** The Np azidohydrin **7** (70.8 mg, 0.375 mmol) and NaH (45 mg, 5 equiv) were placed in a screw-cap vial. Dry pyridine (2 mL) was added, and the mixture was stirred for about 10 min at room temperature. PhCOCl (0.1 mL) was added, and the mixture was stirred at room temperature overnight. The mixture was transferred to a 50-mL round-bottomed flask using PhH, and the solvent was removed under reduced pressure. Water (about 25 mL) and 30% aqueous $NH_4OH$ (0.4 mL) were added, and the mixture was sonicated for 20 min. The mixture was extracted with EtOAc, and the organic layer was washed with water, 10% aqueous HCl (3 × 33 mL), and brine sequentially. The crude mixture obtained after evaporation of EtOAc was chromatographed on silica gel using $CH_2Cl_2$. This gave 82 mg (75%) of pure azido benzoate **8**. NMR spectrum: 2.1 (dt, 1 $H_3$, $J$ = 7.2), 2.35 (m, 1 $H_3$), 3.0 (t, 2 $H_4$, $J_{app}$ = 6.4), 4.76 (d, 1 $H_1$, $J$ = 6.2), 5.4 (m, 1 $H_2$), 7.2–8.0 (9 H, aromatic). Mass spectrum (12 eV): *m/z* (relative intensity) 171 (42), 143 (100), 105 (261).

**(±)-*trans*-1-Amino-2-(benzoyloxy)-1,2,3,4-tetrahydronaphthalene (9).** In a 25-mL two-necked round-bottomed flask were placed the Np azido benzoate **8** (82.3 mg, 0.281 mmol) and Lindlar catalyst (5% Pd on $CaCO_3$ poisoned with Pb, 90 mg), in absolute EtOH (8 mL). The mixture was stirred for 17 h, under 1 atm of hydrogen at room temperature. The reaction mixture was filtered through anhydrous $MgSO_4$, and the residue was washed with EtOH. The combined filtrate was evaporated under reduced pressure. Chromatography of the crude product on silica gel using 10% MeOH in $CHCl_3$ afforded 57.1 mg (76%) of the Np amino benzoate **9**. NMR spectrum: 2.05 (dt, 1 $H_3$, $J$ = 8.0), 2.35 (m, 1 $H_3$), 3.0 (t, 2 $H_4$, $J_{app}$ = 6.5), 4.15 (d, 1 $H_1$, $J$ = 6.7), 5.17 (m, 1 $H_2$), 7.2–8.2 (9 H, aromatic). Mass spectrum (12 eV): *m/z* (relative intensity) 145 (100).

**(±)-*trans*-1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene (10).** Though **10** is a known compound, the exact experimental details were not available in the literature.[12] Therefore, we have described our procedure for the synthesis. In a dry screw-cap vial were placed (±)-*trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydronaphthalene (30 mg, 0.133 mmol) and aqueous ammonia (prepared by bubbling ammonia gas into aqueous ammonium hydroxide, 7 mL). The vial was capped and stirred at 0–5 °C for 72 h. (Initially the bromohydrin was insoluble in the solution; however, after 24 h the reaction mixture was homogeneous and had attained a yellow color.) The reaction mixture on concentration under reduced pressure yielded 8 mg (37%) of pure amino alcohol **10**.

In a separate procedure, the Np azidohydrin **7** (20 mg, 0.106 mmol) was dissolved in dry MeOH (2 mL). This was stirred with $Et_3N$ (43 mg, 0.425 mmol) and 1,3-propanedithiol (46 mg, 0.425 mmol), for 70 h, under nitrogen. During the course of the reaction, a white precipitate (a sulfur polymer) separated, hence the reaction mixture was filtered and the filtrate was evaporated. Traces of $Et_3N$ and MeOH were removed under oil pump vacuum. Chromatography of the resulting mixture on silica gel using $CHCl_3$ removed 1,3-propanedithiol. Subsequent elution with a 1:1 mixture of $CHCl_3$/MeOH afforded 8.5 mg (49%) of pure Np amino alcohol **10**. NMR spectrum: 1.82 (m, 1 $H_3$), 2.24 (m, 1 $H_3$), 2.9 (m, 2 $H_4$), 3.61 (m, 1 $H_2$), 3.69 (d, 1 $H_1$, $J$ = 8.7), 7.0–7.5 (4 H, aromatic). Mass spectrum (12 eV): *m/z* (relative intensity) 146 (33), 119 (100), 106 (14), 92 (28).

**(±)-*trans*-11-Azido-10-hydroxy-8,9,10,11-tetrahydrobenz[*c*]acridine (12).** As described for the synthesis of **7**, except that $CH_3CN$ was used as solvent, BcAr epoxide **11** (100 mg, 0.405 mmol) and the $N_3^-$ form of Amberlite (ca. 50 g) were shaken mechanically for 72 h to give 91 mg (77%) of pure BcAr azidohydrin **12** after chromatography of the crude product on silica gel using $CHCl_3$ as solvent.

In a separate procedure the epoxide **11** (15 mg, 0.061 mmol) was also converted to **12** (11 mg, 64%) using phase-transfer

(18) Reeves, P. W.; Bahr, M. L. *Synthesis* **1976**, 823.

conditions as described for the preparation of 7, except that more forcing conditions were required (3 days at room temperature, then 2 days at 50 °C and finally 2 days at 70 °C). NMR spectrum: 2.0 (m, 1 $H_9$), 2.28 (m, 1 $H_9$), 3.13 (m, 2 $H_8$), 4.0 (m, 1 $H_{10}$), 4.81 (d, 1 $H_{11}$, $J$ = 8.1), 7.6–8.0 (6 H, aromatic), 9.28 (d, 1 $H_1$, $J$ = 7.8). Mass spectrum (12 eV): $m/z$ (relative intensity) 290 ($M^+$, 100), 248 (40), 233 (32).

**(±)-*trans*-11-Azido-10-acetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (13).** The BcAr azidohydrin **12** (18.8 mg, 0.065 mmol), acetic anhydride (0.4 mL), and dry pyridine (0.11 mL) were stirred at room temperature for 24 h under nitrogen. The reaction mixture was poured slowly into cold saturated aqueous $Na_2CO_3$ solution (8 mL) with stirring. The mixture was then extracted with diethyl ether (10 mL), and the ether layer was washed with water. After drying and evaporation of solvent under reduced pressure, 17.5 mg (81%) of pure BcAr azido acetate **13** was obtained. NMR spectrum: 2.0 (m, 1 $H_9$), 2.1 (s, 3 H), 2.27 (m, 1 $H_9$), 3.08 (m, 2 $H_8$), 4.98 (d, 1 $H_{11}$, $J$ = 5.9), 5.2 (m, 1 $H_{10}$), 7.6–8.0 (6 H, aromatic), 9.26 (d, 1 $H_1$, $J$ = 7.8). Mass spectrum (ammonia CI): $m/z$ (relative intensity) 333 ($M^+$, 100), 305 (31), 244 (54).

**(±)-*trans*-11-Amino-10-acetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (14).** As described for the synthesis of **9**, BcAr azido acetate **13** (10 mg, 0.03 mmol) and Lindlar catalyst (20 mg) were reacted in a 1:1 mixture of EtOH/EtOAc (3 mL) for 20 h. Chromatography of the crude product on silica gel using 20% PhH in EtOAc yielded 4 mg (44%) of amine **14**. Based on NMR analysis the net conversion of the azide to the amine was estimated at 55–60%. NMR spectrum: 2.0 (m, 1 $H_9$), 2.1 (s, 3 H), 2.37 (m, 1 $H_9$), 3.1 (m, 2 $H_8$), 4.38 (d, 1 $H_{11}$, $J$ = 7.8), 5.15 (m, 1 $H_{10}$), 7.6–8.0 (6 H, aromatic), 9.28 (d, 1 $H_1$, $J$ = 7.6). Mass spectrum (70 eV): $m/z$ (relative intensity) 306 ($M^+$, 9), 288 (15), 246 (100), 218 (60).

**(±)-*trans*-11-Amino-10-hydroxy-8,9,10,11-tetrahydrobenz[*c*]acridine (15).** As described for the synthesis of **10**, BcAr azidohydrin **12** (11 mg, 0.038 mmol) was reduced using an equimolar mixture of 1,3-propanedithiol/$Et_3N$ (16.4 mg, 15.3 mg, respectively, 0.15 mmol each) in 2.3 mL of MeOH. Chromatography in a manner identical with the one described for **10** afforded 5.5 mg (55%) of pure amino alcohol **15**. NMR spectrum: 1.99 (m, 1 $H_9$), 2.4 (m, 1 $H_9$), 3.1 (m, 2 $H_8$), 3.88 (m, 1 $H_{10}$), 4.0 (d, 1 $H_{11}$, $J$ = 9.6), 7.8–8.0 (6 H, aromatic), 9.29 (d, 1 $H_1$, $J$ = 7.5). Mass spectrum (ammonia CI): $m/z$ (relative intensity) 265 ($M^+$, 100), 247 (19), 220 (23), 193 (15).

**(±)-*trans*-9-Azido-10-hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (17).** As described for the ring opening reaction of **7**, 20 g of $N_3^-$ form of Amberlite resin was shaken at 37 °C with the BeP epoxide **16** (20 mg, 0.074 mmol) for 36 h in dry $CH_3CN$. Workup as in the case of **7** followed by chromatography of the crude product on silica gel gave 25 mg (86%) of the azidohydrin **17**.

In a separate procedure, the epoxide **16** (15 mg, 0.056 mmol) was subjected to ring opening under phase-transfer conditions as described for the preparation of **7**. The reaction was complete in 60 h at room temperature. Workup as described for **7** followed by chromatography on silica gel using $CHCl_3$ yielded 16 mg (92%) of the azidohydrin. NMR spectrum: 2.35 (m, 2 $H_{11}$), 3.52 (m, 2 $H_{12}$), 4.56 (br s, 1 $H_{10}$), 5.15 (d, 1 $H_9$, $J$ = 3.4), 8.0–8.5 (8 H, aromatic). Mass spectrum (12 eV): $m/z$ (relative intensity) 313 ($M^+$, 100), 271 (66).

**(±)-*trans*-9-Amino-10-hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (18).** The BeP azidohydrin **17** (9 mg, 0.032 mmol), Lindlar catalyst (20 mg), and 20% THF in absolute EtOH (4.5 mL) were placed in a two-necked round-bottomed flask. The mixture was stirred under 1 atm of hydrogen at room temperature for 10–12 h. The reaction mixture was filtered, and the filtrate was dried over anhydrous $MgSO_4$. Chromatography on silica gel using THF gave 2.6 mg (32%) of pure BeP amino alcohol **18**. NMR spectrum: 2.2 (m, 1 $H_{11}$), 2.6 (m, 1 $H_{11}$), 3.5 (m, 2 $H_{12}$), 4.4 (br s, 1 $H_{10}$), 4.8 (br s, 1 $H_9$), 8.0–8.6 (8 H, aromatic). Mass spectrum (12 eV): $m/z$ (relative intensity) 287 ($M^+$, 21), 270 (100), 241 (43), 228 (68).

**(±)-*trans*-10-Azido-9-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (20).** The $N_3^-$ form of Amberlite resin (30 g of the $Cl^-$ form washed with 75 g of $NaN_3$ dissolved in 250 mL of distilled water) and the BaP epoxide **19** (70 mg, 0.259 mmol) were reacted as described for the synthesis of **7** at 37 °C for 2 days in dry THF. Chromatography of the crude azidohydrin on silica gel using EtOAc gave 40 mg (50%) of pure azidohydrin **20**. NMR spectrum: 1.9 (br d, O*H*), 2.2 (m, 1 $H_8$), 2.3 (m, 1 $H_8$), 3.3 (dt, 1 $H_7$, $J$ = 17.3, 4.0), 3.46 (dt, 1 $H_7$, $J$ = 17.3, 6.2), 4.54 (br s, 1 $H_9$), 5.3 (d, 1 $H_{10}$, $J$ = 3.4), 7.9–8.2 (7 H, aromatic), 8.35 (d, 1 $H_{11}$, $J$ = 9.3). Mass spectrum (12 eV): $m/z$ (relative intensity) 313 ($M^+$, 52), 285 (27), 271 (100).

**(±)-*trans*-10-Azido-9-(benzoyloxy)-7,8,9,10-tetrahydrobenzo[*a*]pyrene (21).** As described for the synthesis of **8**, the BaP azidohydrin **20** (39.1 mg, 0.125 mmol) was acylated using NaH (0.015 mg, 5 equiv) and PhCOCl (0.1 mL), in dry pyridine (2 mL). Workup and chromatography as in the case of **8** gave 38.2 mg (73%) of pure azido benzoate **21**. NMR spectrum: 2.5 (m, 2 $H_8$), 3.4 (dt, 1 $H_7$, $J$ = 16.4, 3.0), 3.55 (dt, 1 $H_7$, $J$ = 16.4, 3.9), 5.55 (d, 1 $H_{10}$, $J$ = 2.6), 5.83 (br s, 1 $H_9$), 7.2–8.4 (12 H, aromatic), 8.34 (d, 1 $H_{11}$, $J$ = 9.2). Mass spectrum (12 eV): $m/z$ (relative intensity) 417 ($M^+$, 20), 389 (20), 295 (54), 267 (100), 105 (96).

**(±)-*trans*-10-Amino-9-(benzoyloxy)-7,8,9,10-tetrahydrobenzo[*a*]pyrene (22).** The BaP azido benzoate **21** (38.2 mg, 0.1 mmol) and Lindlar catalyst (50 mg) were stirred in a 1:1 mixture of absolute EtOH/THF (6 mL), under 1 atm of hydrogen pressure, at room temperature for 11 h. The mixture was filtered through anhydrous $MgSO_4$, and the residue was washed with EtOH. The combined filtrate was evaporated under reduced pressure. Chromatography on a 500 μm silica gel preparative TLC plate using 5% MeOH in $CHCl_3$ gave 32.6 mg (91%) of amino benzoate **22**. NMR spectrum: 2.0 (br, N*H*), 2.4 (m, 1 $H_8$), 2.6 (dt, 1 $H_8$, $J$ = 6.8, 6.4), 3.33 (dd, 1 $H_7$, $J$ = 17.4, 4.9), 3.53 (dt, 1 $H_7$, $J$ = 17.4, 6.4), 5.12 (d, 1 $H_{10}$, $J$ = 2.0), 5.64 (br s, 1 $H_9$), 7.2–8.2 (12 H, aromatic), 8.35 (d, 1 $H_{11}$, $J$ = 9.3). Mass spectrum (12 eV): $m/z$ (relative intensity) 391 ($M^+$, 5), 269 (100).

**(±)-*trans*-10-Amino-9-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (23).** The BaP azidohydrin **20** (10 mg, 0.035 mmol) was dissolved in dry, freshly distilled THF (2.5 mL). Triphenylphosphine (16.7 mg, 0.064 mmol) was added, and the mixture was stirred at room temperature for 48 h. Water (1 mL) was added, and the stirring was continued for another 48 h. The mixture was then extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography on silica gel using $CHCl_3$ and 10% MeOH in $CHCl_3$ sequentially yielded 1.2 mg of the amino alcohol **23** along with some impurity. No further purification was attempted on this product. NMR spectrum (partial): 2.16 and 2.4 (1 $H_7$ each), 4.35 (br s, 1 $H_9$), 4.9 (d, 1 $H_{10}$, $J$ = 3.4).

**(±)-7β,8α,9α-Trihydroxy-10β-azido-7,8,9,10-tetrahydrobenzo[*a*]pyrene (25).** The $N_3$ form of Amberlite resin (20 g) and BaPDE **24** (66.3 mg, 0.22 mmol) were mechanically shaken at 37 °C for 24 h in dry THF. The resin was washed with dry THF (~200 mL) and then with MeOH (~300 mL) under air pressure. Since no starting epoxide was present, the THF and MeOH washings were combined and evaporated under reduced pressure. Chromatography of the crude product on a 500 μm silica gel preparative TLC plate using EtOAc gave 37.8 mg (55%) of fairly pure azido triol **25**. NMR spectrum ($CD_3OD$): 4.16 (dd, 1 $H_8$, $J$ = 8.6, 2.1), 4.47 (dd, 1 $H_9$, $J$ = 3.6, 2.1), 5.17 (d, 1 $H_7$, $J$ = 8.6), 5.56 (d, 1 $H_{10}$, $J$ = 3.6), 8.0–8.3 (5 H, aromatic), 8.03 (t, 1 $H_2$, $J$ = 7.8), 8.42 (d, 1 $H_{11}$, $J$ = 9.2), 8.51 (s, 1 $H_6$). Mass spectrum (12 eV): $m/z$ (relative intensity) 345 ($M^+$, 70), 317 (29), 285 (40), 284 (49), 257 (100).

**(±)-7β,8α,9α-Tris(benzoyloxy)-10β-azido-7,8,9,10-tetrahydrobenzo[*a*]pyrene (26).** In a dry screw-cap vial were placed the BaP azido triol **25** (42.1 mg, 0.122 mmol) and NaH (0.015 g, 5 equiv) in dry pyridine (2 mL). The mixture was stirred for 10 min at room temperature followed by the addition of PhCOCl (0.1 mL). The mixture was capped and stirred at room temperature for 11 h. The mixture was transferred to a 50-mL round-bottomed flask using PhH, and the solvent was removed under reduced pressure. Water (about 30 mL) and 30% aqueous $NH_4OH$ (0.4 mL) were added, and the mixture was sonicated for 30 min. The mixture was extracted with EtOAc, and the organic layer was extracted with water, 10% aqueous HCl (3 × 33 mL), and brine sequentially. Evaporation of the solvent under reduced pressure after drying followed by chromatography on silica gel using $CH_2Cl_2$ gave 31.8 mg (44%) of pure azido tribenzoate **26**. NMR spectrum: 6.0 (d, 1 $H_{10}$, $J$ = 3.3), 6.3–6.4 (overlapping signals

for 1 $H_8$ and 1 $H_9$), 7.3-8.5 ($H_7$ and 22 aromatic protons). Mass spectrum (12 eV): $m/z$ (relative intensity): 629 (24), 507 (7), 105 (100).

**(±)-7β,8α,9α-Tris(benzoyloxy)-10β-amino-7,8,9,10-tetrahydrobenzo[a]pyrene (27).** In a 25-mL two-necked round-bottomed flask were placed the BaP azido tribenzoate **26** (31.8 mg, 0.048 mmol) and Lindlar catalyst (35 mg), in absolute EtOH (3 mL). The mixture was stirred under 1 atm of hydrogen for 24 h. Due to limited solubility of **26** in EtOH, the reaction progressed very slowly. Therefore, dry THF (3 mL) was added, and the stirring was continued as before for 48 h. At this point, TLC still showed presence of starting material. Therefore, an additional 15 mg of catalyst was added, and the reaction was continued for 24 h at the end of which no starting azide was visualized by TLC. The reaction mixture was filtered through anhydrous $MgSO_4$, and the residue was washed with EtOH. The combined filtrate was evaporated under reduced pressure. Chromatography on silica gel using 5% MeOH in $CHCl_3$ afforded 22 mg (77%) of pure amino tribenzoate **27**. NMR spectrum: 5.46 (d, 1 $H_{10}$, $J$ = 3.0), 6.1 (br s, 1 $H_9$), 6.57 (d, 1 $H_8$, $J$ = 10.7), 7.3-8.5 ($H_7$ and 22 aromatic protons), 8.45 (d, 1 $H_{11}$, $J$ = 9.3). Mass spectrum (12 eV): $m/z$ (relative intensity) 387 (29), 105 (100).

**(±)-7β,8α,9α-Trihydroxy-10β-amino-7,8,9,10-tetrahydrobenzo[a]pyrene (28).** The BaP azido triol **25** (7.7 mg, 0.022 mmol), Lindlar catalyst (50 mg), and 1:1 EtOH/THF (4 mL) were placed in a two-necked 25-mL round-bottomed flask. The mixture was stirred under 1 atm of hydrogen pressure for 24 h. The mixture was filtered through anhydrous $Na_2SO_4$, and the filtrate was evaporated under reduced pressure. Chromatography on a 200 μm C-18 reverse-phase preparative TLC plate using 15% water in MeOH gave 4 mg (57%) of fairly pure amine **28**. NMR spectrum (acetone-$d_6$): 4.38 (dd, 1 $H_8$, $J$ = 8.4, 2.1), 4.5 (m, 1 $H_9$), 4.74 (d, 1 $H_{10}$, $J$ = 3.0), 5.14 (d, 1 $H_7$, $J$ = 8.4), 8.0-8.4 (7 H, aromatic), 8.55 (s, 1 $H_6$). In $CD_3OD$ the aliphatic protons have identical chemical shifts as in acetone-$d_6$: the aromatic $H_6$ is a singlet at 8.5 ppm and the remaining aromatic protons appear at 8.0-8.3 ppm. Mass spectrum (12 eV): $m/z$ (relative intensity) 319 ($M^+$, 0.4), 303 (4.1), 302 (13.7), 286 (8.1), 284 (100), 268 (3.5).

# Enzymes in Organic Synthesis: Synthesis of Highly Enantiomerically Pure 1,2-Epoxy Aldehydes, Epoxy Alcohols, Thiirane, Aziridine, and Glyceraldehyde 3-Phosphate

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This paper describes a chemoenzymatic procedure for the synthesis of (*R*)- and (*S*)-glycidaldehyde diethyl acetal [2-(diethoxymethyl)oxirane] (**4** and **5**). 2-Acetoxy-3-chloropropanal diethyl acetal (**1c**) was enantioselectively hydrolyzed by LP-80 lipase to give (*S*)-3-chloro-2-hydroxypropanal diethyl acetal (**2c**) and the unreacted acetate (**3c**), both in >95% calculated yield and >98% ee. Both products were subsequently converted to epoxides **4** and **5**, respectively. Resolutions of 2-acetoxy-1-(benzyloxy)-3-chloropropane (**11a**) and 3-(allyloxy)-2-acetoxypropyl *p*-toluenesulfonate (**14b**) were similarly carried out to give the corresponding optically active 2-hydroxy and 2-acetoxy derivatives in 90% and >95% ee. These products were subsequently converted to the corresponding 1,2-epoxides. Nucleophilic opening of epoxide **4** was exemplified by the syntheses of (*R*)-3-azido-2-hydroxypropanal and D-glyceraldehyde 3-phosphate. Conversion of the chiral epoxides to thiirane and aziridine was also described.

Optically active 1,2-epoxides are useful building blocks in organic synthesis. Asymmetric epoxidation of various allylic alcohols based on the Sharpless procedure[1] has been widely used for synthesis of this type of compounds. Resolution of epoxy alcohols[2] and epoxy acids[3] catalyzed by esterases, and asymmetric epoxidation of olefins catalyzed by monooxygenases,[4] are useful alternatives complementary to the chemical approach. In this paper, we describe a simple and practical chemoenzymatic route to highly enantiomerically pure epoxy aldehydes and epoxy alcohols and the use of these epoxides for the synthesis of other enantiomerically pure, yet not readily available, compounds including (diethoxymethyl)thiirane, (diethoxymethyl)aziridine and D-glyceraldehyde 3-phosphate.

Our previous success in the LP-80 lipase catalyzed resolution of 2-acetoxy-3-azidopropanal diethyl acetal (**1a**) for use in enzymatic aldol condensations[5] led us to exploit the possible synthesis of various 3-substituted 2-hydroxy

**Table I. LP-80 Lipase Catalyzed Hydrolysis of 1 and 14 at pH 7.0**

| substrate | % convn | product, ee[a] | *E* value[b] |
|---|---|---|---|
| **1a** | 50 | **2a**, >98% **3a**, >98% | >100 |
| **1b** | 50 | **2b**, >98% **3b**, >98% | >100 |
| **1c** | 50 | **2c**, >98% **3c**, >98% | >100 |
| **1d** | 50 | **2d**, 50% **3d**, 50% | 4 |
| **14a** | 45 | **15a**, 70% **16a**, 57% | 10 |
| **14b** | 51 | **15b**, 90% **16b**, 94% | 60 |

[a] Determined with $^1H$ NMR (300 MHz) by measuring the shift of acetoxy group in the presence of Eu(hfc)$_3$. [b] Enantioselectivity value. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *Am. Chem. Soc.* **1982**, *104*, 7294.

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