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Stereospecific Synthesis of Highly Functionalized Tricyclic β-Lactams by Radical Cyclizations Using Titanocene Monochloride

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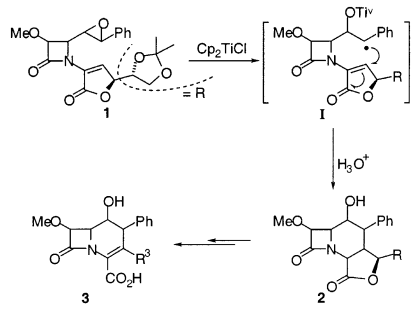
Abstract: The reductive opening of epoxyimonobactams **1** with titanoncene (III) chloride gives rise to radicals that can be trapped by intramolecular π systems (i.e., conjugated alkenes and lactone and amide carbonyls) in a stereospecific way to give new carbocyclic compounds such as tribactam **2**.

The reductive opening of an epoxide via single-electron transfer (SET) to a radical intermediate promoted by titanocene monochloride (Cp_2TiCl) and the subsequent radical trapping reaction represent a valuable synthetic tool that has been used in deoxygenations, reductions, and intra- and intermolecular carbon−carbon bond-forming reactions.[1] In our ongoing project directed toward developing short and efficient routes to prepare bicyclic β-lactam systems, we have introduced the use of D-glucosamine[2] as a chiral auxiliary in the Staudinger reaction[3] to synthesize monocyclic azetidin-2-ones as precursors of important bicyclic β-lactams.[4] The possibility of applying the reductive opening of an epoxide such as **1** by SET with Cp_2TiCl as a novel and rapid access to highly functionalized chiral tricyclic β-lactams **2** (Scheme 1) seemed to be attractive, and herein we disclose our first results in this area. These tribactams could be interesting intermediates for preparing chiral 3-substituted[5] carbacephem antibiotics **3**.[6]

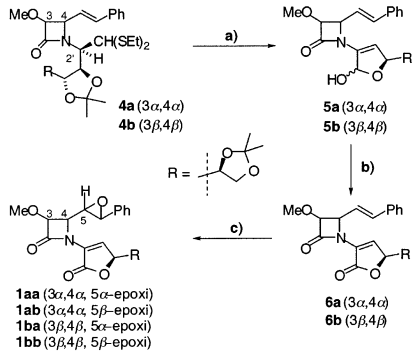
The starting substrates for this study, the enantiomerically pure epoxides **1aa**, **1ab**, **1ba**, and **1bb**, were

SCHEME 1. Anticipated Mechanism for the Preparation of Tribactams 2



obtained as shown in Scheme 2. The readily available *cis*-2-azetidinones **4a** and **4b**[7] were reacted with $PhI(CF_3CO_2)_2$ and $NaHCO_3$[4d] and the crude reaction products purified by column chromatography on silica gel with 3% TEA in 7:3 hexane/ethyl acetate as the eluent to give a diastereomeric mixture of hemiketals **5a** and **5b** in 54 and 75% yields, respectively. The quantitative conversion of these hemiketals into the isomeric epoxides **1** was carried out by oxidation with PDC and selective epoxidation of the purified lactones **6a** and **6b** with *m*-CPBA. Chromatography of the reaction products obtained as 1:1 diasteromeric mixtures afforded the pure epoxides **1aa** ($[\alpha]_D = -37$) and **1ab** ($[\alpha]_D = -29$) from **6a** and **1ba** ($[\alpha]_D = -45$) and **1bb** ($[\alpha]_D = -63$) from **6b**.

SCHEME 2[a]



[a] Reagents and conditions: (a) $PhI(CF_3CO_2)_2/NaHCO_3/CH_3CN/H_2O$ 85:15, rt, 30 min. (b) PDC, CH_2Cl_2, rt, 24 h. (c) *m*-CPBA, CH_2Cl_2, rt, 17 h.

The C-5 and C-6 configuration for the isomeric epoxides **1** was tentatively assigned on the basis of the ^1H NMR data and the geometrical parameters obtained from the C-4−C-5 rotational isomers of lower energy[8] (Table 1). From these data, it emerges that isomers **1** can be paired off as isometric epoxides. Thus, for the isomers with ^3J(H-4, H-5) = 8.0 Hz and the strongest NOE between H-4

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(7) *cis*-Monobactams **4a** and **4b** were obtained as a 1:2.1 mixture by Staudinger reaction of methoxyacetyl chloride with the imine produced from D-glucosamine and *trans*-cinnamaldehyde, in the presence of Et_3N. The absolute configuration of these compounds was deduced from their $[\alpha]_D$ data by comparison with reference 2-azetidinones of known absolute configuration by X-ray crystal analysis.[2]

(8) Preferred conformations for epoxides **1** were derived from the CS Chem3D Pro 5.0 (1999) software (CambridgeSoft Corporation, Cambridge, MA) using MM2 calculations.

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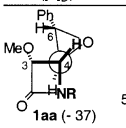
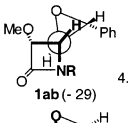
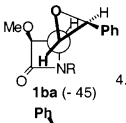
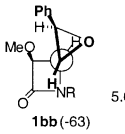
TABLE 1. Spectral Data and Geometrical Parameters of Epoxides 1

Epoxide ([α]D)	H-4	^{1}H NMR[a] H-5	H-6	NOE H-4/ H-6	d / θ [b]
 **1aa** (- 37)	4.69 *dd* 5.2, 5.2	3.27 *dd* 5.2, 2.0	3.80 *d* 2.0	+	2.57 / 162
 **1ab** (- 29)	4.37 *dd* 4.8, 8.0	3.16 *dd* 8.0, 2.0	4.16 *d* 2.0	++	2.48 / 175
 **1ba** (- 45)	4.36 *dd* 4.8, 8.0	3.16 *dd* 8.0, 2.0	4.17 *d* 2.0	++	2.48 / 175
 **1bb** (-63)	4.68 *dd* 5.6, 5.2	3.26 *dd* 5.2, 2.0	3.81 *d* 2.0	+	2.57 / 162

[a] δ (ppm)/multiplicity/*J* (Hz). [b] d = distance H-4−H-6 Å; θ = dihedral angle H-4−H-5 (°).

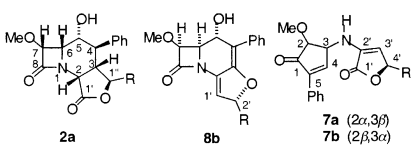
and H-6, the configurations 3*R*,4*S*,5*R*,6*S* for **1ab** and 3*S*,4*R*,5*S*,6*R* for **1ba** were proposed. Accordingly, the configurations 3*R*,4*S*,5*S*,6*R* and 3*S*,4*R*,5*R*,6*S* were assigned to **1aa** and **1bb**, respectively.

The diastereomeric epoxides were reacted separately with Cp_2TiCl, generated "in situ" from Cp_2TiCl_2 and zinc at room temperature in THF[1a] (see Experimental Section).

The addition of a THF solution of the epoxy β-lactam **1aa** to the titanium(III) solution at room temperature, followed by acidic workup, afforded a mixture of three compounds in 71% yield. The most abundant product was identified as the tricyclic β-lactam **2a** (43%), and the minor constituents were the deoxygenated monobactam **6a** and the amine **7a** (entry 1, Table 2). Similar results were obtained using the isomer **1ba** as starting material (entry 3, Table 2), which gave in 77% yield the unsaturated 2-azetidinone **6b**, the amine **7b**, and the new tricyclic β-lactam **8b** as the major reaction product (57%). In contrast, when the same reactions were carried out on the β-epoxides **1ab** and **1bb**, only mixtures of compounds **6** and **7** (entries 2 and 4, Table 2) were obtained in 80 and 75% yields, respectively.

TABLE 2. Reaction of Epoxides 1 with Cp_2TiCl[a]

Epoxide	Tribactam	Alkene6	Amine7
1aa	**2a** (43%)	**6a** (14%)	**7a** (14%)
1ab	------	**6a** (66%)	**7a** (14%)
1ba	**8b** (57%)	**6b** (6%)	**7b** (14%)
1bb	------	**6b** (64%)	**7b** (11%)



2a **8b** **7a** (2α,3β) **7b** (2β,3α)

[a] All reactions were carried out on ca. 0.32 mmol scale as a 0.2 M solution in THF for 4 h. In parentheses: isolated yield after column chromatography.

The structures of compounds **2a**, **7a**, **7b**, and **8b** were rigorously established by IR, ^{1}H and ^{13}C NMR (including NOE and two-dimensional experiments), and MS analyses.

2a **2a**

FIGURE 1. Stereomodel of tribactam **2a**.

The stereochemistry of the new chiral centers in **2a** was deduced from the coupling constants between the hydrogen atoms of the six-membered ring.[9] The observed proton coupling constants ^3J(H-2, H-3) and ^3J(H-3, H-1′) ≥ 7.5 Hz, suggest dihedral angles between H-2−H-3 and H-3−H-1′ lower than 20° or higher than 140°, while the coupling constants ^3J(H-3, H-4), ^3J(H-4, H-5), and ^3J(H-5, H-6) < 3.0 Hz can be explained if the dihedral angles between these and their vicinal protons are in the 60−110° range. These data agree with a *skew-boat* conformation $^6S_2$ for the six-membered ring, with the phenyl group nearly *isoclinal*. This conformation was supported by the NOEs observed: H-1′/H-4, H-2/H-3, and H-6/H-7. Consequently, as the absolute configuration for C-6 and C-7 was known (from **4a**), the absolute configuration 2*R*,3*S*,4*S*,5*R*,6*S*,7*R* was proposed for the new tricyclic β-lactam **2a** (Figure 1).

Compound **8b** shows a strong hydroxyl IR absorption band (3439 cm^{-1}), a doublet (^3J = 7.6 Hz) of a new proton geminal to hydoxyl group, and two vinylic proton signals, while the oxiranyl protons signals were absent from the NMR spectrum. The new signals observed in the ^{1}H and ^{13}C NMR spectra, as well as the information provided by two-dimensional homo- and heteronuclear correlation experiments, prompted us to propose for **8b** the tricyclic structure depicted in Table 2.

The spectroscopic data for compounds **7a** and **7b** were quite different from those expected for a β-lactam derivative. The IR spectra absorption bands of compounds **7** exhibited characteristic amine bands (3356 and 1507 cm^{-1} for **7a** and 3352 and 1497 cm^{-1} for **7b**), and the carbonyl signals in their ^{13}C NMR spectra are strongly deshielded (δ = 201 ppm) as compared to those of the 2-azetidinones (δ = 165−170 ppm). In addition, new vinylic hydrogen signals were observed, and the geminal protons to the OMe groups absorb as doublets with coupling constants (^3J = 3.2 Hz) quite different from those of the precursors *cis*-azetidin-2-ones (^3J(H-3, H-4) = 4.0−4.5 Hz). These data prompted us to assign the structures depicted for **7a** and **7b**, which were confirmed by HMQC, HMBC, and COSY experiments.

The evolution of the epoxy β-lactams **1** upon reaction with Cp_2TiCl could be explained as shown in Scheme 3. The benzyl radicals **I** generated by the homolytic cleavage of the epoxides **1** can evolve through different pathways. The reduction of the epoxides to the benzylic anions followed by β-elimination of the titanium-oxo moieties (pathway a) gave olefin **6a** or **6b**.[1] The evolution of

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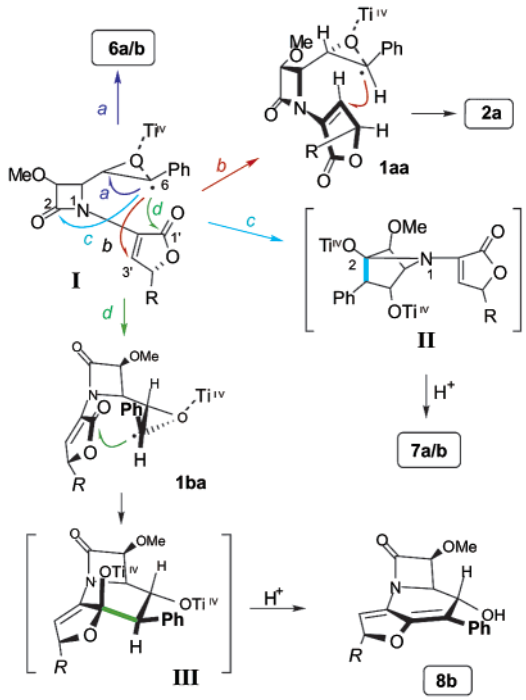
SCHEME 3. Possible Reaction Mechanism for the Formation of Compounds 2a, 6a/b, 7a/b, and 8b



radicals **I** through the pathway b involves the radical trapping by the conjugated electrophilic double bond to give the desired tribactam **2a.**[1a,b] The carbonyl groups of the β-lactam and γ-lactone rings can also trap the benzyl radicals **I** (pathways c and d) to generate intermediates **II** and **III**, respectively. These organotitanium intermediates should progress after acidic workup to the formation of amines **7a** and **7b** or to the tribactam **8b**.

According to our previous studies, an ionic pathway cannot easily explain the formation of the products **7a**, **7b**, and **8b**. We have observed that anions generated on the C-6 position of several monobactams failed to give cyclization products.[4d,e] Also, the absence of hydroxycarbonyl derivatives produced by nucleophilic lactone ring opening seems to support the absence of carbanionic intermediates. Moreover, although further evidence to confirm the proposed radical mechanism would be desirable, the recently reported results by Fernández-Mateos et al. concerning the intramolecular addition of these kinds of radicals to aldehyde and ketone carbonyls[1c] support the formation of the proposed intermediates **II** and **III**.

The product distribution in these reactions seems to be directed by stereoelectronic effects. The specific formation of the compounds **2a** and **8b** suggests that the opening of the oxirane ring and the radical addition to C-1′ or C-3′ must be a concerted process with configuration inversion at C-6. Thus, the ability of benzyl radicals **I** to form fused tricyclic β-lactams depends on the possibility of the original radical to reach the double bond and on the correct alignment of the (C-6-O) σ^* orbital with the enone π orbital.

The cyclization of the β-epoxides, i.e., isomers **1ab** and **1bb**, is not favored. Despite the possibility of reaching a conformation of the epoxide **1ab** in which the distance C-6−C-3′ would allow a radical attack, the orientation of the σ^* and π orbitals is not suitable for the conjugate addition. Also, the steric interactions between the benzene and the dioxolane rings prevent the cyclization process. In the isomer **1bb**, the distances between the reacting centers C-6 and C-1′ or C-3′ are always above 4.5 Å and an orientation appropriate for cyclization cannot be attained between the respective σ^* and π orbitals.

Conversely, it is possible for the isomers **1aa** and **1ba** to bring together the reacting centers with an alignment and distance appropriate for the cyclization. For these substrates, four diastereomers are possible but only one of them is formed for each isomeric epoxide.

The specific formation of the tribactam **2a** from the epoxide **1aa** should result by conjugated addition of the benzylic radical **I** on the easily accessible *Re*-face of C-3′ (Scheme 3). In contrast, the attack on the *Si*-face of C-3′ or C-1′ is strongly hindered by nonbonded interactions between the benzene and dioxolane rings. Likewise, the epoxide **1ba** led to the formation of the tribactam **8b** by attack of radical **I** on the *Si*-face of C-1′, less hindered than the *Re*-face of C-1′ or the *Si*-face of C-3′ (Scheme 3). The conjugate addition to the *Re*-face of C-3′ is less probable than for isomer **1aa** because of the steric effect between the dioxolane chain and the β-lactam ring. The diaxial β-elimination of the titanium-oxo moiety in the intermediate **III** should also favor the evolution of the titanium complex by addition to the *Si*-face of C-1′.

Last, it should be mentioned that the amines **7a** and **7b** are the minor reaction products (11−14%). In this case, the poor yields may be due to the low reactivity of the amide carbonyl group and the hindrance caused by the methoxyl group during the approach of the reacting centers. It is also observed that yields on the unsaturated monobactams **6** increase as the radicals **I** have more difficulties of cyclization, so the highest yields in deoxygenated products are found in the reactions of the β-epoxides **1ab** and **1bb**.

In conclusion, the Cp_2TiCl-promoted reaction of chiral epoxy-monobactams **1** has been shown as a new and short approach to the stereospecific synthesis of tricyclic β-lactams and, hence, to polyfunctionalized carbacephem antibiotics. We have also found that the generated benzyl radicals are prone to cyclization, even with amide and lactone carbonyl functional groups. This type of reaction has not been reported previously.

Experimental Section

General Procedure for the Preparation of Hemiketals 5a and 5b. To a solution of monobactams **4** (2.00 mmol) and $NaHCO_3$ (8.00 mmol) in 85:15 CH_3CN/H_2O (20.0 mL) was added [bis(trifluoroacetoxy)iodo]benzene (3.00 mmol), and the mixture was stirred at room temperature until the starting material disappeared. The reaction product was then concentrated to dryness, and the crude reaction products were purified by column chromatography on silica gel with 3% TEA in 7:3 hexane/ethyl acetate as an eluent.

5a. Isolated from the monobactam **4a** (1104 mg, 2.00 mmol) in 54% yield (418 mg, 1.08 mmol): R_f (3:7 hexane/ethyl acetate) 0.30; IR (film) υ 3420, 1769, 1659, 1452, 1385, 1256, 1215, 1118, 1050, 968, 845, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31, 1.37 (6H, 2s), 3.46 (3H, s), 3.73−4.31 (6H, m), 4.51−4.90 (6H, m), 5.30 (1H, s), 5.37 (1H, s), 5.71 (2H, s), 6.18−6.50 (2H, m), 6.83 (2H, d, J = 15.9 Hz), 7.26−7.51 (10H, m).

5b. Isolated from the monobactam **4b** (1363 mg, 2.50 mmol) in 75% yield (718 mg, 1.85 mmol): R_f (35:65 hexane/ethyl acetate) 0.32; IR (film) υ 3435, 1759, 1659, 1451, 1385, 1260, 1215, 1117, 1050, 970, 847, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29, 1.32 (6H, 2s), 3.48 (3H, s), 3.78−3.95 (2H, m), 4.00−4.29 (4H, m), 4.55−4.80 (6H, m), 5.41 (1H, br s), 5.77 (1H, d, J = 1.6 Hz), 5.92 (1H, s), 5.96 (1H, s), 6.22−6.41 (2H, m), 6.83 (2H, d, J = 15.9 Hz), 7.26−7.44 (10H, m).

Oxidation of 5 to Lactones 6. A solution of hemiketal **5** (1.00 mmol) and PDC (2.00 mmol) in CH_2Cl_2 (10.0 mL) was stirred at room temperature until the oxidation was finished (TLC, 20−24 h). The crude reaction product was filtered through celite, and the solvent was eliminated under reduced pressure. Then, the residue was dissolved in EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The solvents were eliminated under vacuum to give an oily residue, which was purified by column chromatography on silica gel with hexane/ethyl acetate mixtures as the eluent.

6a. Isolated from **5a** (418 mg, 1.08 mmol) in 100% yield (416 mg): R_f (3:7 hexane/ethyl acetate) 0.30; $[\alpha]_D^{25}$ +39 (c 1.0, $CHCl_3$); IR (film) υ 1761, 1643, 1406, 1217, 1144, 1065, 1065 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32, 1.42 (6H, 2s), 3.48 (3H, s), 3.69−4.10 (3H, m), 4.76−4.84 (2H, m), 5.21 (1H, dd, J = 5.0, 8.9 Hz); 6.24 (1H, dd, J = 8.9, 15.8 Hz), 6.89 (1H, d, J = 15.8 Hz), 7.25−7.44 (5H, m), 7.48 (1H, d, J = 1.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.9, 26.8, 58.9, 61.3, 66.8, 76.4, 81.0, 86.5, 110.5, 121.7, 126.9, 128.4, 128.7, 133.0, 136.1, 165.6, 166.9; MS (FAB) m/z (%) 386 (M^+ + 1, 13), 307 (12), 154 (95), 91 (48). HRMS (FAB) calcd for $C_{21}H_{24}NO_6$ (M^+ + 1) 386.1604, found 386.1561.

6b. Isolated from **5b** (718 mg, 1.85 mmol) in 100% yield (713 mg): R_f (4:6 hexane/ethyl acetate) 0.30; mp 158.5 °C (hexane/ethyl acetate); $[\alpha]_D^{25}$ −47 (c 1.0, $CHCl_3$); IR (KBr) υ 1780, 1757, 1645, 1458, 1377, 1138, 1063, 995 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32, 1.43 (6H, 2s), 3.48 (3H, s), 3.89−4.07 (2H, m), 4.11 (1H, dd, J = 6.1, 8.0 Hz), 4.80 (1H, d, J = 5.0 Hz), 4.84 (1H, dd, J = 2.0, 7.1 Hz), 5.22 (1H, dd, J = 5.0, 8.9 Hz), 6.24 (1H, dd, J = 8.9, 15.8 Hz), 6.89 (1H, d, J = 15.8 Hz), 7.26−7.52 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.0, 26.7, 58.9, 61.2, 66.6, 76.4, 81.0, 86.5, 110.5, 121.8, 125.9, 126.9, 128.4, 128.6, 132.6, 136.1, 137.9, 165.6, 166.6; MS (FAB) m/z (%) 386 (M^+ + 1, 4), 307 (17), 154 (100), 107 (22), 77 (23).

General Procedure for the Epoxidation of 6. To a solution of alkene **6** (1.00 mmol) in anhydrous CH_2Cl_2 was added m-CPBA (1.20 mmol), and the mixture was stirred at room temperature until the starting material disappeared. The epoxidation of **6a** (250 mg, 0.67 mmol) for 18 h with m-CPBA (163 mg, 0.90 mmol) gave, after column chromatography (65:35 hexane/ethyl acetate), epoxides **1aa** (120 mg, 44%) and **1ab** (140 mg, 53%). Likewise, the epoxidation of **6b** (750 mg, 1.95 mmol) for 18 h with m-CPBA (404 mg, 2.34 mmol) gave, after column chromatography (7:3 hexane/ethyl acetate), epoxides **1ba** (280 mg, 36%) and **1bb** (310 mg, 40%). For NMR data, see Supporting Information and discussion in the text.

1aa: R_f (1:1 hexane/ethyl acetate) 0.30; IR (film) υ 1763, 1647, 1406, 1304, 1263, 1217, 1148, 1065, 841, 750 cm^{-1}; MS (FAB) m/z (%) 402 (M^+ + 1, 5), 307 (15), 154 (100), 91 (46); HRMS (FAB) calcd for $C_{21}H_{24}NO_7$ (M^+ + 1) 402.1553, found 402.1575.

1ab: R_f (1:1 hexane/ethyl acetate) 0.33; IR (film) υ 1784, 1755, 1638, 1406, 1316, 1215, 1148, 1067, 841, 752 cm^{-1}; MS (FAB) m/z (%) 402 (M^+ + 1, 4), 307 (17), 154 (100), 91 (44); HRMS (FAB) calcd for $C_{21}H_{24}NO_7$ (M^+ + 1) 402.1553, found 402.1579.

1ba: R_f (6:4 hexane/ethyl acetate) 0.28; mp 136 °C (hexane/ethyl acetate); IR (KBr) υ 1763, 1692, 1574, 1416, 1304, 1262, 1144, 1069, 897, 849, 750 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{22}NO_7$ (M^+ − 1) 400.1396, found 400.1426.

1bb: R_f (6:4 hexane/ethyl acetate) 0.32; IR (film) υ 1771, 1647, 1404, 1383, 1256, 1217, 1150, 1067, 850, 752 cm^{-1}; MS (FAB) m/z (%) 424 (M^+ + 1, 11), 402 (3), 391 (2), 307 (9), 154 (100), 101 (66), 77 (50); HRMS (FAB) calcd for $C_{21}H_{24}NO_7Na$ (M^+ + Na) 424.1372, found 424.1399.

General Procedure for the Single-Electron-Transfer Process. A solution of epoxides **1** (165.6 mg, 0.32 mmol) in THF was added to a green suspension of Cp_2TiCl generated from Cp_2TiCl_2 (174.7 mg, 0.70 mmol) and Zn^0 (138.0 mg, 2.11 mmol) in THF (1.4 mL) at room temperature. After 4 h, the reaction was quenched with 10% v/v aqueous NaH_2PO_4 (5.0 mL) and the aqueous phase was separated and extracted with ethyl acetate. The combined organic extracts were filtered through celite, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 70% hexane/ethyl acetate) gave the products shown in Table 2.

2a: R_f (9:11 hexane/ethyl acetate) 0.28; $[\alpha]_D^{25}$ +21 (c 0.8, $CHCl_3$); IR (film) υ = 3488, 1792, 1763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31, 1.48 (6H, 2s), 2.80 (1H, ddd, J = 7.6, 2.4, 8.0 Hz), 3.60 (3H, s), 3.63 (1H, dd, J = 2.0, 4.8 Hz), 3.77 (1H, dd, J = 2.4, 2.9 Hz), 3.95 (1H, dd, J = 3.6, 8.0 Hz), 4.05 (1H, ddd, J = 7.6, 3.6, 6.4 Hz), 4.10 (1H, dd, J = 6.4, 8.0 Hz), 4.28 (1H, br s), 4.33 (1H, d, J = 7.6 Hz), 4.66 (1H, d, J = 4.8 Hz), 5.31 (1H, dd, J = 7.6, 8.0 Hz), 7.23 (2H, dd, J = 7.2, 7.6 Hz), 7.29 (1H, d, J = 7.6 Hz), 7.37 (2H, d J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.3, 42.3, 43.1, 50.8, 51.8, 59.8, 67.1, 70.1, 77.9, 82.4, 85.4, 110.3, 127.3, 128.1, 129.0, 139.8, 166.5, 169.2; MS (FAB) m/z (%) 404 (M^+ + 1, 12), 307 (22), 154 (100), 91 (24). HRMS (FAB) calcd for $C_{21}H_{26}NO_7$ (M^+ + 1) 404.1709, found 404.1683.

7a: R_f (13:7 hexane/ethyl acetate) 0.30; $[\alpha]_D^{25}$ −15 (c 0.6, $CHCl_3$); IR (film) υ 3356, 1761, 1717, 1659, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36, 1.47 (6H, 2s), 3.72 (3H, s), 3.89−3.94 (1H, m), 3.92 (1H, d, J = 3.2 Hz), 4.03 (1H, dd, J = 4.0, 8.8 Hz), 4.12 (1H, dd, J = 6.0, 8.8 Hz), 4.36 (1H, ddd, J = 3.2, 2.8, 7.6 Hz), 4.46 (1H, d, J = 7.6 Hz), 4.83 (1H, dd, J = 2.0, 7.6 Hz), 6.05 (1H, d, J = 2.0 Hz), 7.40−7.43 (3H, m), 7.48 (1H, d, J = 2.8 Hz), 7.71−7.73 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.7, 58.6, 59.2, 66.5, 76.9, 80.6, 87.0, 110.1, 127.2, 128.6, 129.6, 133.6, 134.3, 142.9, 149.1, 169.7, 201.2; MS (FAB) m/z (%) 386 (M^+ + 1, 16), 354 (12), 307 (8), 187 (60), 154 (88). HRMS calcd for $C_{21}H_{24}NO_6$ (M^+ + 1) 386.1604, found 386.1614.

7b: R_f (7:3 hexane/ethyl acetate) 0.28; $[\alpha]_D^{25}$ −32 (c 0.4, $CHCl_3$); IR (film) υ 3352, 1761, 1723, 1659, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37, 1.47 (6H, 2s), 3.71 (3H, s), 3.89 (1H, ddd, J = 8.0, 4.1, 6.2 Hz), 3.94 (1H, d, J = 3.2 Hz), 4.04 (1H, dd, J = 4.1, 8.9 Hz), 4.11 (1H, dd, J = 6.2, 8.9 Hz), 4.37 (1H, ddd, J = 3.2, 2.8, 8.0 Hz), 4.47 (1H, d, J = 8.0 Hz), 4.84 (1H, dd, J = 2.4, 8.0 Hz), 6.02 (1H, d, J = 2.4 Hz), 7.39−7.45 (3H, m), 7.47 (1H, d, J = 2.8 Hz), 7.69−7.75 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.7, 58.4, 59.2, 66.6, 77.3, 80.7, 87.1, 109.6, 110.2, 127.2, 128.7, 129.6, 134.3, 142.9, 149.3, 169.7, 201.2; HRMS (FAB) calcd for $C_{21}H_{24}NO_6$ m/z 386.1604, found 386.1610.

8b: R_f (3:7 hexane/ethyl acetate) 0.33; $[\alpha]_D^{25}$ −65 (c 1.5, $CHCl_3$); IR (film) υ 3439, 1767, 1684, 1067, 912, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37, 1.45 (6H, 2s), 3.67 (3H, s), 3.87 (1H, dd, J = 7.6, 4.4 Hz), 3.98 (1H, dd, J = 4.4, 8.4 Hz), 4.10−4.19 (2H, m), 4.89 (1H, d, J = 4.4 Hz), 5.07 (1H, dd, J = 2.0, 6.0 Hz), 5.24 (1H, dd, J = 2.0, 7.6 Hz), 5.90 (1H, d, J = 2.0 Hz), 7.34−7.44 (3H, m), 7.49 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 26.6, 57.9, 59.3, 62.2, 66.0, 76.9, 86.1, 88.3, 106.4, 110.2, 112.1, 127.0, 127.2, 128.3, 138.5, 132.9, 150.7, 164.4.

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Supporting Information Available: ^1H NMR and two-dimensional (COSY and/or HMQC) spectra for **1aa**, **1ab**, **1ba**, **1bb**, **2a**, **7a**, **7b**, and **8b** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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