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Synthesis of *epi*-Oxetin via a Serine-Derived 2-Methyleneoxetane

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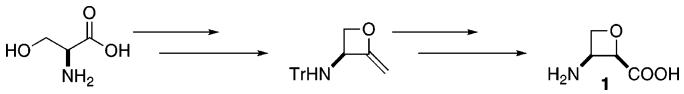

The unique reactivity of 2-methyleneoxetanes and 1,5-dioxaspiro[3.2]hexanes has been exploited for the synthesis of *epi*-oxetin (**26**), an oxetane-containing β-amino acid. While the preparation of the natural product oxetin (**1**) was the original goal, the unexpected diastereoselectivity of an precedented reduction provided the *epi*-oxetin framework. The methodology described herein should be amenable for the preparation of oxetin with a change in nitrogen protection.

Introduction

In 1984 β-amino acid **1** (Figure 1) was isolated from the culture filtrate of *Streptomyces* sp. OM-2317, a bacteria originating in a Japanese soil sample.[1] Due to its oxetane core, this novel compound was named oxetin. Structural determination via X-ray crystallography assigned an absolute stereochemistry of 2*R*,3*S*, which was later confirmed by the synthesis of the natural product by Omura and co-workers.[2] Their synthesis of oxetin, starting from D-glucose, provided oxetin and its three stereoisomers due to the nonstereoselective nature of several key steps.

Biological testing of oxetin revealed both antibiotic and herbicidal activity. Oxetin inhibited glutamine synthetase from *Bacillus subtilis* and spinach (*Spinacia oleracea*). Other noncompetitive glutamine antimetabolites, such as tabtoxin, are known to harm plants via inhibition of glutamine synthetase.[3] Moreover, oxetin exhibited antibacterial activity against *Bacillus subtilis*, *Piricularia oryzae*, and other microorganisms. Oxetin's three stereoisomers were found to be inactive.

A more concise synthesis utilizing the Paterno−Büchi reaction by Bach and Schröder was published in 1997.[4] Although this synthesis was shorter, it was racemic. Due to the oxetane core structure, we were interested in synthesizing oxetin via a 2-methyleneoxetane, which we have shown to be readily accessible from β-lactones.[5,6]

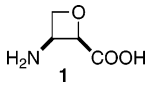

FIGURE 1. Structure of oxetin.

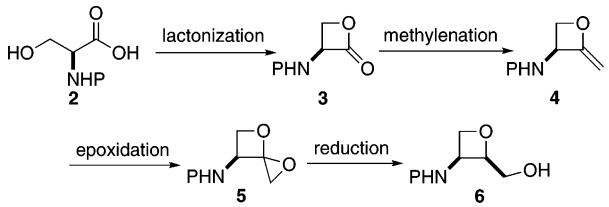

FIGURE 2. Proposed strategy for the synthesis of oxetin via 2-methyleneoxetane **4**.

Results and Discussion

Our initial strategy for the synthesis of oxetin is shown in Figure 2. The preparation of a variety of serine lactones (e.g., P = Boc,[7] Boc and allyl,[8] pthalimide,[9] CBz[10]) has been reported. We have previously reported the synthesis of serine-derived 1,5-dioxaspiro[3.2]hexane **5** (P = Boc) from the corresponding

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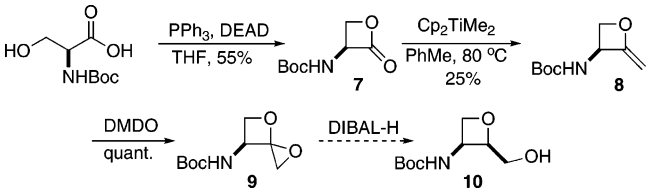
SCHEME 1



2-methyleneoxetane **4** (P = Boc).[11] On the basis of our previous studies on the reactivity of dioxaspirohexanes with DIBAL-H,[12] we anticipated that oxetane intact product **6** could be secured. Oxidation to the corresponding carboxylic acid and a final deprotection would yield oxetin (**1**).

Lactone **7** was prepared under the Mitsunobu conditions given in Scheme 1.[7] Methylenation with the Petasis reagent to form **8**, however, proceeded in modest yield despite numerous modifications in reaction conditions. In contrast, epoxidation with anhydrous, acetone-free dimethyldioxirane produced 1,5-dioxaspiro[3.2]hexane **9** in quantitative yield.

In 1999, we reported on the dichotomy of reactivity of 1,5-dioxaspiro[3.2]hexanes.[12] Although many nucleophiles gave α-functionalized-β-hydroxyketones, Lewis acidic reagents provided oxetane-intact products. Specifically, the reaction of **11** with DIBAL-H afforded predominantly oxetane **13** (Figure 3). Formation of **13** was rationalized by the coordination of the Lewis acid to the oxirane oxygen and participation of oxonium ion **12**. Subsequent hydride delivery was presumably favored on the less hindered face, leading to an 8:1 mixture of diastereomers.

We anticipated that the reduction of *N*-Boc-1,5-dioxaspiro-[3.2]hexane **9** would proceed with similar facial selectivity, providing the desired 2*R*,3*S* stereochemistry. After numerous attempts at the DIBAL-H reduction, no trace of alcohol **10** was observed. We speculated that the Boc carbonyl could be participating in stabilization of reaction intermediates. The failure of the reduction, coupled with the low-yielding methylenation step, prompted us to select an alternative nitrogen protecting group.

Campagne and Ghosez reported on an improved efficiency of RCM reactions of Boc-benzyl protected vinyl glycine derivatives over their Boc-protected counterparts.[13] Furthermore, these RCM reactions proceeded with even higher yields with the utilization of triphenylmethyl protection. Due to the potential difficulties and additional steps required to add and remove two nitrogen protecting groups, we examined *N*-trityl serine for the synthesis of oxetin.

N-Trityl serine (**14**), obtained in one step from L-serine, lactonized efficiently in the presence of the coupling agent BOP to yield **15**.[14] Methylenation of the *N*-trityl β-lactone **15** to methyleneoxetane **16** was both cleaner and higher yielding than was observed with the corresponding Boc-protected lactone **7**, and oxidation provided **17** (as a 2:1 mixture of diastereomers).

When dioxaspirohexane **17** was treated with 1 equiv of DIBAL-H (Table 1, entry 1), two diastereomers (2:1 ratio) resulted, but the isolated yield was low (~30%). With 2.5 equiv of DIBAL-H reduction of **17** gave diastereomers **18** and **19**

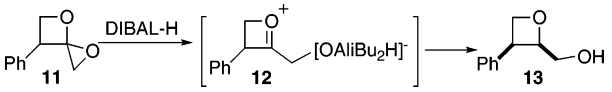


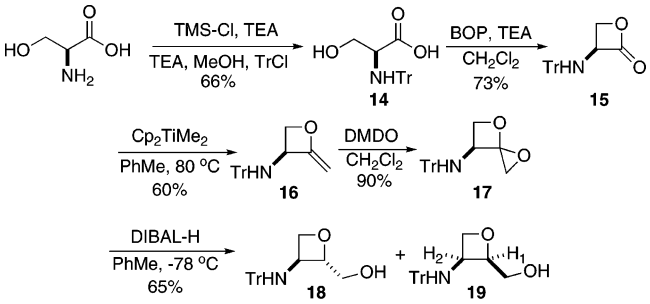
FIGURE 3. Formation of an aluminum-stabilized oxonium ion.

TABLE 1. Attempted Reduction Conditions for 17

entry	reducing agent	equiv	ratio of **18**:**19**[a]
1	DIBAL-H in hexanes	1.0	2:1
2	DIBAL-H in hexanes	2.5	2:1
3	DIBAL-H in hexanes	5	1.8:1
4	DIBAL-H in hexanes	10	1.7:1
5	DIBAL-H in DCM	2.5	
6	TMSCl, TEA, DIBAL-H	1.2[b]	2.6:1
7	$Mg(OTf)_2$, DIBAL-H	1.0	
8	$Mg(OTf)_2$, Et_3SiH	1.0	
9	$Zn(BH_4)_2$	1.1	3:1
10	$NaBH_3CN$	1.0	

[a] NMR ratios of crude reaction mixtures. [b] A similar outcome was seen with either 2 or 3 equiv of TMSCl.

SCHEME 2



(Table 1, entry 2), also as a 2:1 mixture, in a combined 65% yield. NOESY experiments provided the relative configuration of the diastereomers. Unexpectedly, minor isomer **19** clearly exhibited NOE between the hydrogens H_1 and H_2 (see Scheme 2 and the Supporting Information), while major isomer **18** did not. Although the overall reduction yield was good, the diastereoselectivity was low and favored the undesired isomer. Subsequently, a variety of reduction conditions were examined, as shown in Table 1, and none provided **19** as the major product (Table 1).

Reasoning that the DIBAL-H might be complexing with the nitrogen lone pair and subsequently delivering the hydride to the same face, a large excess of DIBAL-H (entries 3 and 4) was added to see if the excess reducing agent might compete to provide hydride delivery to the less hindered side. Only a slight improvement in the desired stereoselectivity was seen.

In a related strategy, a Lewis acid was first added to interact with the Lewis basic nitrogen prior to the addition of DIBAL-H with the goal of decreasing internal hydride transfer. With prior addition of 1.2 to 3 equiv of TMSCl in the presence of triethylamine (TEA), diastereoselectivity improved in the wrong direction! The addition of $Mg(OTf)_2$, however, did not give oxetane intact products.

Other reducing agents were also examined. Zinc borohydride gave **18** and **19** with a greater ratio of the undesired diastereomer. Dioxaspirohexane **17** was consumed in the presence of sodium cyanoborohydride and triethylsilane, but no alcohol

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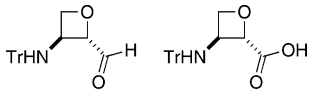
resulted. Surprisingly, a similar result was seen when DIBAL-H in dichloromethane (rather than hexanes) was used.

It has been reported that triphenylmethanol, as well as other molecules containing triaryl moieties, can act as inclusionary compounds.[15,16] Triphenylmethanol has extraordinary inclusion selectivity, allowing such molecules as methanol, DMSO, and DMF as guests in its crystal lattice. *N*-Triphenylmethyl moieties are also reported to act as "spacers", preventing host molecules from tightly packing, facilitating the incorporation of guest molecules into the crystal.[17] When extensive efforts to completely remove ethyl acetate from **18** or **19** failed, it seemed likely that **18** or **19** could be hosting ethyl acetate as a guest molecule.

A sample of **18** was washed with MeOH followed by solvent removal under vacuum. ^{1}H NMR (in CD_3OD) showed that the ethyl acetate was now replaced with MeOH. From this observation, we postulated that DIBAL-H could act as a guest in the aromatic pocket, subsequently delivering the hydride from the more hindered face. At this point, we decided to pursue the synthesis of *epi*-oxetin from **18** in order to develop methodology that could be later utilized in the formation of oxetin and oxetin derivatives.

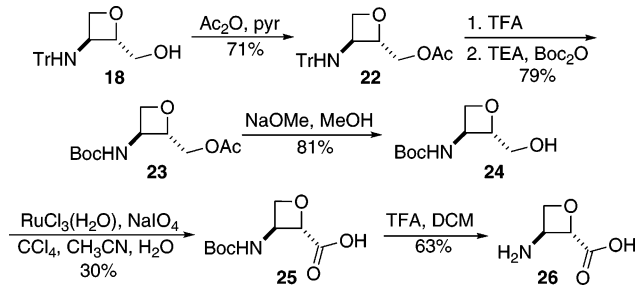
Direct oxidation of **18** to the carboxylic acid was problematic. A number of procedures, including PDC/DMF, ruthenium trichloride hydrate, and sodium periodate, failed to provide **21**. Attempted oxidations to aldehyde **20**, using Swern conditions, PCC, PDC/DCM, and TPAP/NMO, were also fruitless. By ^{1}H NMR, it was clear that the *N*-trityl group did not survive any of the oxidation conditions; therefore, we switched to another nitrogen protecting group.



20 **21**

A variety of approaches to trityl cleavage were pursued. While hydrogenolysis of **18** with Pd black[18] resulted in the recovery of starting material, TFA, $Yb(OTf)_3$,[19] and HCl,[20] yielded no oxetane intact products. Protection of **18** by acetic anhydride, followed by a one-pot TFA trityl deprotection-Boc reprotection, provided **23** in good yield. Following cleavage of the acetate group, oxidation to carboxylic acid **25** proceeded modestly using ruthenium trichloride hydrate and sodium periodate.[21] Boc deprotection using TFA rendered *epi*-oxetin (**26**) (Scheme 3). ^{1}H and ^{13}C NMR, as well as the optical rotation of **26**, agreed with literature values.[2]

SCHEME 3



Conclusions

Herein we have described the synthesis of *epi*-oxetin (**26**) in 10 steps, starting from the natural amino acid L-serine, via 2-methyleneoxetane **16**. It appears that, due to either the Lewis basic properties of the nitrogen or inclusionary attributes of the trityl group, the diastereoselectivity of the key reduction of dioxaspirohexane **17** proceeded in favor of the undesired alcohol **18**. Future work includes employing methodology described herein with alternative nitrogen protecting groups, including pthalimide or nitrogen double protection.

Experimental Section

Procedure for the Preparation of Dimethyldioxirane. Dimethyldioxirane (DMDO) was prepared and concentrated as described by Messegeur.[22] $NaHCO_3$ (240 g), acetone (260 mL), and water (350 mL) were charged into a 3 L round-bottomed flask with a large magnetic stir bar. The mixture was cooled with an ice bath and vigorously stirred. Oxone (450 g) was slowly added to the mixture, and vacuum was applied (80 mmHg). After 10 min, the ice bath was removed, and the reaction was allowed to warm to rt, where DMDO in acetone was trapped over 1 h into two receiving flasks in series maintained at −78 °C. The combined solutions were diluted with H_2O (220 mL), and extracted with cold CH_2Cl_2 (3 × 11 mL). The combined organic extracts were neutralized with phosphate buffer (pH 7, three times equal to the volume of organic extract), dried ($MgSO_4$), and filtered. The yellow CH_2Cl_2/DMDO solution was stored over 4 Å molecular sieves in the freezer. The concentration of DMDO was determined by ^{1}H NMR and was based upon the reaction between excess citronellic acid and DMDO. Concentrations vary from 0.3 to 0.5 M and have been shown to be >95% accurate.

Preparation of Dimethyltitanocene.[6] MeLi (1.4 M in Et_2O, 55 mL) was added dropwise over 30 min to a slurry of titanocene dichloride (10.0 g, 40.1 mmol) in toluene (80 mL) at −5 °C under N_2. The resulting mixture was then stirred at −5 °C for an additional hour and then brought to 0 °C. The reaction was then slowly quenched by the additional of a 6% NH_4Cl solution (75 mL). The aqueous layer was then extracted three times with Et_2O (3 × 100 mL). The organic layers were combined and washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), then dried ($MgSO_4$), filtered, and concentrated to approximately one-third the volume of toluene. ^{1}H NMR assay indicated 7.18 g (86%) of dimethyltitanocene. The deep red solution was diluted to 0.5 M with toluene and stored in the freezer.

***N*-Tritylserine (14).** L-Serine (3.15 g, 30.0 mmol) was suspended in CH_2Cl_2 (53 mL) under N_2. At rt, TMSCl (13.3 mL, 105 mmol) was added via syringe, and the mixture was heated at reflux for 1 h. The solution was allowed to cool to rt, and triethylamine (14.7 mL, 105 mmol) in CH_2Cl_2 (30 mL) was added slowly, whereupon

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the mixture became difficult to stir. The mixture was then heated at reflux for 45 min. Upon cooling to 0 °C, MeOH (1.8 mL) in CH_2Cl_2 (7.5 mL) was added, followed by the addition of triethylamine (4.2 mL, 30 mmol) and triphenylmethyl chloride (8.37 g, 30.0 mmol) in 2 portions over 15 min. The reaction was allowed to stir overnight. MeOH (6.0 mL) and triethylamine (4.2 mL) were then added, and the mixture was stirred for an additional 15 min. All solvents were removed under vacuum, and the crude acid was dissolved in EtOAc (150 mL) and washed with a 5% citric acid solution (3 × 75 mL) and then with H_2O (3 × 75 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated, yielding a yellow foam (85%). The crude acid was purified by precipitation from $CHCl_3$, and the product was isolated as a white solid (6.9 g, 66%):[14] ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) δ 7.44 (d, J = 7.6 Hz, 6H), 7.26 (m, 9H), 3.71(d, J = 11.1 Hz, 1H), 3.49 (s, 1H), 3.11 (m, 3H), 2.90 (dd, J = 4.3, 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD) δ 175.0, 144.7, 128.8, 128.4, 127.3, 72.1, 63.0, 58.7.

(*S*)-3-(Tritylamino)oxetan-2-one (15). *N*-Tritylserine (**14**) (1.75 g, 5.04 mmol) was suspended in CH_2Cl_2 (25 mL) under N_2 at rt. Triethylamine (2.0 mL, 14 mmol) was added, and the mixture became homogeneous. Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (3.12 g, 7.06 mmol) was added in two portions over 15 min and the solution was stirred for an additional hour. The reaction was then diluted with H_2O (25 mL) and stirred for an additional 20 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated, yielding a yellow solid. The crude solid was purified using flash column chromatography on silica gel (petroleum ether/EtOAc 85:15) to give lactone **15** (1.2 g, 73%) as a white solid: [14] $[\alpha]^{25}_D$ −70.4 (*c* 0.6, CH_2Cl_2); IR (KBr) 3322, 3063, 1816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.4 Hz, 6H), 7.30 (m, 9H), 4.65 (m, 1H), 3.55 (dd, J = 5.7, 5.7 Hz, 1H), 3.19 (dd, J = 5.1, 5.1 Hz, 1H), 2.76 (d, J = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 145.3, 128.5, 127.1, 70.9, 70.7, 64.7; MS (EI) *m*/*z* 243 ($^+$CPh$_3$) (100), 228, 165, 77.

(*S*)-2-Methylene-3-(tritylamino)oxetane (16). (*S*)-3-(Tritylamino)oxetan-2-one (**15**) (1.50 g, 4.58 mmol) was dissolved in a solution of dimethyltitanocene (0.5 M in toluene, 23 mL) and further diluted with toluene (20 mL). The reaction was then heated to 80 °C under N_2 in the dark and monitored by TLC for the disappearance of starting material (2−5 h). The cooled reaction mixture was added to petroleum ether (3 volumes), and the resulting suspension was stirred overnight. The orange precipitate was separated from the red filtrate using a pad of celite. The filtrate was concentrated in vacuo to approximately one-fourth the volume of toluene and purified by flash column chromatography on silica gel (petroleum ether/triethylamine/EtOAc 99:0.5:0.5). Methyleneoxetane **16** was obtained as a white solid (0.90 g, 60%): $[\alpha]^{25}_D$ −22.2 (*c* 2.4, CH_2Cl_2); IR (KBr) 3304, 3081, 1687, 1593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.15−7.29 (m, 9H), 4.42 (m, 1H), 4.12 (m, 1H), 3.95, (m, 1H), 3.88 (dd, J = 5.7, 5.7 Hz, 1H), 3.49 (dd, J = 5.5, 5.5 Hz, 1H), 2.50 (d, J = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 146.1, 128.9, 128.5, 126.9, 80.2, 79.5, 70.3, 55.3; MS (EI) *m*/*z* 243 ($^+$CPh$_3$) (100), 228, 215, 165, 77; HRMS (FAB) calcd for $C_{23}H_{22}NO$ (M^+ + H) *m*/*z* 328.1701, found 328.1714.

3-(Tritylamino)-1,5-dioxaspiro[3.2]hexanes (17). (*S*)-2-Methylene-3-(tritylamino)oxetane (**16**) (0.26 g, 0.78 mmol) was dissolved in CH_2Cl_2 (20 mL), and the solution was cooled to −78 °C under N_2. A solution of dimethyldioxirane (0.35 M in CH_2Cl_2, 2.7 mL) in CH_2Cl_2 was added in two portions over 15 min. The reaction was stirred at −78 °C for an additional 1 h, slowly allowed to warm to room temperature, and concentrated in vacuo. The resulting 2:1 mixture of diastereomers (**17**) was isolated as a white foam and used without further purification (0.25 g, 90%): IR (KBr) 3056, 2926, 1725, 1491, 1447 cm^{-1}: major diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.4 Hz, 6H), 7.22 (m, 9H), 4.45−4.25 (m, 2H), 3.12 (m, 1H), 2.81 (d, J = 8.9 Hz, 1H), 2.70 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 128.5, 128.1, 126.7, 95.1, 72.8, 70.8, 54.0, 50.2; minor diastereomer δ 7.43 (d, J = 7.4 Hz, 6H), 7.22 (m, 9H), 4.45−4.25 (m, 2H), 3.58 (t, J = 6.6 Hz, 1H), 2.86 (d, J = 4.0 Hz, 1H), 2.42 (d, J = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 128.5, 128.1, 126.8, 94.9, 70.1, 56.2, 49.0; MS (EI) *m*/*z* 274, 243, 197 (100), 165, 105, 77; HRMS (FAB) calcd for $C_{23}H_{22}NO_2$ (M^+ + H) 344.1651, found 328.1714.

2-Hydroxymethyl-3-tritylaminooxetanes 18 and 19. 3-(Tritylamino)-1,5-dioxaspiro[3.2]hexane (**17**) (0.39 g, 1.2 mmol) was diluted with dry toluene (25 mL), and the solution was cooled to −78 °C under N_2. A solution of DIBAL-H (1.0 M in hexanes, 2.9 mL, 2.9 mmol) was added dropwise via syringe over 20 min. The solution was stirred at −78 °C for 1 h. The reaction was quenched with MeOH (0.5 mL) at −78 °C and slowly brought to 0 °C, where it was quickly flashed on silica gel (petroleum ether/EtOAc 70:30) to avoid the formation of aluminum gels. After the evaporation of all solvents, the resulting oil was repurified on silica gel (petroleum ether/EtOAc 70:30). Two diastereomers, **18** and **19**, were isolated. The major diastereomer (2*S*,3*S*)-2-hydroxymethyl-3-tritylaminooxetane (**18**) was isolated as a white foam (0.20 g, 48%): $[\alpha]^{25}_D$ +24.0 (*c* 0.3, CH_2Cl_2); IR (KBr) 3396 (br), 3056, 2923, 1595 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (m, 6H), 7.13 (m, 9H), 4.50 (m, 1H), 3.73 (m, 2H), 3.62 (m, 1H), 3.36 (dd, J = 2.5, 12.7 Hz, 1H), 3.22 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) 148.0, 129.9, 129.2, 127.6, 93.1, 79.0, 71.6, 64.1, 51.8; MS (EI) *m*/*z* 244 ($^+$HC(Ph)$_3$) (100), 165, 152, 115, 77, 51; HRMS (FAB) calcd for $C_{23}H_{24}NO_2$ (M^+ + H) *m*/*z* 346.1807, found 346.1792. Minor diastereomer (2*R*,3*S*)-2-hydroxymethyl-3-tritylaminooxetane (**19**) was isolated as a cloudy oil (0.056 g, 14%): $[\alpha]^{25}_D$ −50.9 (*c* 1.7, CH_2Cl_2); IR (KBr) 3396 (br), 3056, 2922, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.6 Hz, 6H), 7.27 (m, 9H), 4.75 (m, 1H), 4.20 (dd, J = 7.5, 7.5 Hz, 1H), 4.11 (dd, J = 6.4, 6.4 Hz, 1H), 3.83 (m, 2H), 3.68 (d, J = 11.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 128.3, 128.0, 126.7, 87.6, 82.0, 70.4, 63.0, 50.9; MS (EI) *m*/*z* 244 ($^+$HC(Ph)$_3$) (100), 165, 152, 115; HRMS (FAB) calcd for $C_{23}H_{24}NO_2$ (M^+ + H) *m*/*z* 346.1807, found 346.1795.

(2*S*,3*S*)-Acetic Acid 3-(Tritylamino)oxetan-2-ylmethyl Ester (22). (2*S*,3*S*)-2-Hydroxymethyl-3-tritylaminooxetane (**18**) (0.21 g, 0.61 mmol) was dissolved in pyridine (5.0 mL) and stirred at rt under N_2. Acetic anhydride (0.10 mL, 0.90 mmol) and a catalytic amount of DMAP were added. Upon consumption of starting material (20−40 min), pyridine was removed in vacuo, and the resulting pale yellow oil was diluted with CH_2Cl_2 (10 mL). The solution was washed with 10% aqueous $CuSO_4$ (3 × 25 mL), H_2O (3 × 25 mL), and brine (3 × 25 mL), then dried ($MgSO_4$). Evaporation of all solvents yielded acetate **22** (160 mg, 71%) as a clear oil that was used without further purification: $[\alpha]^{25}_D$ +19.3 (*c* 1.2, CH_2Cl_2); IR (KBr) 2944, 2867, 1733 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (d, J = 1.3 Hz, 6H), 7.25 (t, J = 7.2 Hz, 6H), 7.17 (t, J = 7.2 Hz, 3H), 4.68 (m, 1H), 3.82 (m, 4H), 3.32 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 146.1, 128.5, 128.3, 126.9, 88.4, 78.6, 70.5, 65.3, 51.6, 21.0; MS (EI) *m*/*z* 244 ($^+$HCPh$_3$) (100), 183, 165, 105, 77; HRMS (FAB) calcd for $C_{25}H_{26}NO_3$ (M^+ + H) *m*/*z* 388.1913, found 388.1934.

(2*S*,3*S*)-Acetic Acid 3-*tert*-Butoxycarbonylaminoxetan-2-ylmethyl Ester (23). (2*S*,3*S*)-Acetic acid 3-(tritylamino)oxetan-2-ylmethyl ester (**22**) (120 mg, 0.31 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and MeOH (0.05 mL) under N_2 at rt. A solution of trifluoroacetic acid (0.1 mL) in CH_2Cl_2 (3 mL) was added via syringe in 0.5 mL portions until the starting material was consumed (30−120 min). Triethylamine (0.44 mL, 3.1 mmol) was diluted in CH_2Cl_2 (3 mL) and added slowly over 10 min. Di-*tert*-butoxycarbonyl dicarbonate (0.20 g, 0.94 mmol) was added, and stirring was continued overnight. Evaporation of all solvents yielded a yellow oil that was purified by flash column chromatography on silica gel (EtOAc/petroleum ether 30:70). The resulting Boc-protected acetate **23** was obtained as a clear oil (60 mg, 79%): $[\alpha]^{25}_D$ +15.4 (*c* 1.0,

CH_2Cl_2); IR (KBr) 3343, 1741, 1699, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.13 (d, $J = 6.1$ Hz, 1H), 4.72 (m, 3H), 4.38 (m, 2H), 4.19 (m, 1H), 2.11 (s, 3H), 1.44, (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 154.8, 86.9, 80.4, 75.3, 65.2, 47.2, 28.5, 21.0; MS (EI) *m*/*z* 172, 159, 116, 87, 57 (100). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.92; H, 7.85; N, 5.64.

(2*S*,3*S*)-3-*tert*-Butoxycarbonylamino-2-hydroxymethyloxetane (24). (2*S*,3*S*)-Acetic acid 3-*tert*-butoxycarbonylaminoxetan-2-ylmethyl ester (**23**) (0.15 g, 0.61 mmol) was dissolved in CH_2Cl_2 (5 mL). A solution of NaOMe in MeOH (0.5 M, 0.18 mmol, 0.37 mL) was added via syringe, and the solution was stirred under N_2 until the starting material was consumed (~30 min). Dowex resin (cation exchange resin, C-211, H^+ form) was added until the solution reached a pH of 7. The resin was filtered, and the remaining solvent was evaporated in vacuo. Purfication by flash column chromatography on silica gel (EtOAc/petroleum ether 50:50) yielded alcohol **24** (0.12 g, 81%) as a clear oil: $[\alpha]^{25}_D$ −5.2 (*c* 1.0, CH_2Cl_2); IR (KBr) 3374 (br), 2990, 1720, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (br s, NH), 4.65, (m, 3H), 4.44 (dd, $J = 6.4$, 6.4 Hz), 3.83 (dd, $J = 3.7$, 12.2 Hz, 1H), 3.77 (m, 1H), 2.98 (br s, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 90.0, 80.6, 74.4, 63.7, 47.4, 28.5; MS (EI) *m*/*z* 117, 87, 73, 57 (100); HRMS (FAB) calcd for $C_9H_{18}NO_4$ ($M^+ + H$) *m*/*z* 204.1236, found 204.1227.

(2S,3*S*)-*tert*-Butoxycarbonylaminooxetane-2-carboxylic Acid (25). (2*S*,3*S*)-3-*tert*-Butoxycarbonylamino-2-hydroxymethyloxetane (**24**) (0.067 g, 0.33 mmol) was added to a biphasic solution of CCl_4 (1.0 mL), CH_3CN (1.0 mL), and H_2O (1.5 mL) at rt. Sodium metaperiodate (0.29 g, 1.4 mmol) was added along with a catalytic amount of ruthenium trichloride hydrate (2 mg, 2 mol %) upon which the biphasic solution turned red. After 2 h, CH_2Cl_2 (10 mL) was added, and the phases were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was redissolved in ethyl acetate, filtered through a pad of celite to remove gray solids, and concentrated. The resulting crude oil was purified via flash column chromatography on silica gel (CH_2Cl_2/MeOH 98:2), providing carboxylic acid **25** as a clear oil (20 mg, 30%): $[\alpha]^{25}_D$ −61.2 (*c* 0.5, $CDCl_3$); IR (KBr) 3423 (br), 2918, 1627, 1466, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (br s, 1H), 5.10 (d, $J = 5.5$ Hz, 1H), 4.80 (m, 1H), 4.70 (m, 1H), 4.58 (dd $J = 6.0$, 5.7 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 156.5, 84.0, 82.6, 73.2, 49.3, 28.4; (EI) *m*/*z* 116, 87, 57 (100); HRMS (FAB) calcd for $C_9H_{16}NO_5$ ($M^+ + H$) *m*/*z* 218.1028, found 218.1037.

(2*S*,3*S*)-Aminooxetane-2-carboxylic Acid (26). (2*S*,3*S*)-*tert*-Butoxycarbonylaminooxetane-2-carboxylic acid (**25**) (0.036 g, 0.17 mmol) was added to dry CH_2Cl_2 (2.5 mL) under N_2. Trifluoroacetic acid (0.2 mL) was added, and the solution turned dark yellow. After the solution was stirred for 3 h, all solvents were removed, and the resultant orange oil was purified on a column of Dowex ion-exchange resin 50WX2-400. The column was washed with water and eluted with 0.5 M aqueous ammonia to yield *epi*-oxetin (**26**) (12 mg, 63%) as a pale yellow oil: $[\alpha]^{25}_D$ −13.6 (*c* 1.0, H_2O) [lit.[2] $[\alpha]^{25}_D$ −12.0 (*c* 1.0, H_2O)]; ^1H NMR (300 MHz, D_2O, 1,4-dioxane as an internal standard) δ 4.98 (d, $J = 5.7$ Hz, 1H), 4.76 (dd, $J = 8.0$, 8.0 Hz, 1H), 4.57 (dd, $J = 6.0$, 7.5 Hz, 1H), 4.27 (m, 1H); ^{13}C NMR (75 MHz, D_2O, 1,4-dioxane as an internal standard) δ 176.5, 83.5, 72.1, 49.5.

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Supporting Information Available: Copies of high-resolution ^1H and ^{13}C NMR spectra for those new compounds for which elemental analyses are not reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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