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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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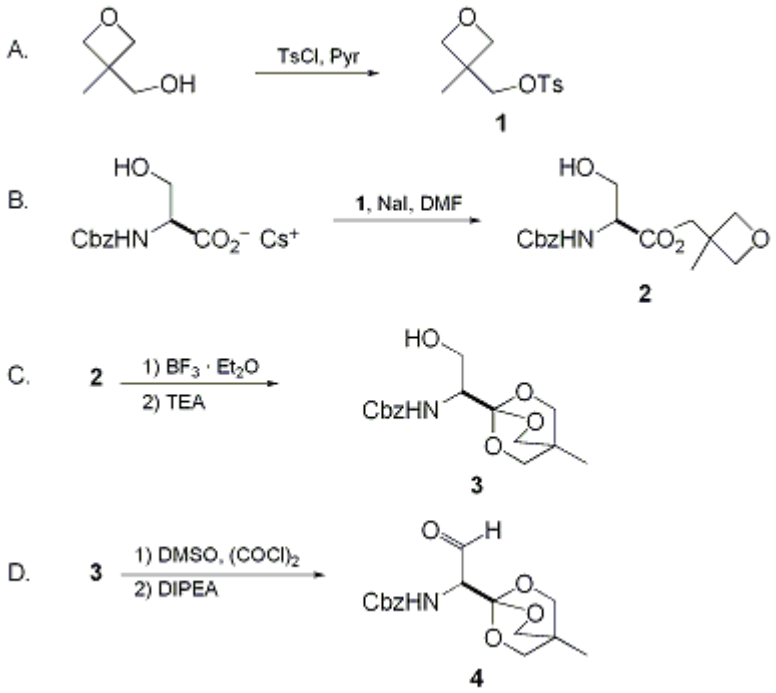
PREPARATION OF 1-[N-BENZYLOXYCARBONYL-(1S)-1-AMINO-2-OXOETHYL]-4-METHYL-2,6,7-TRIOXABICYCLO[2.2.2] OCTANE

[Carbamic acid, [1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-2-oxoethyl]-, phenylmethyl ester, (S)-]



Submitted by Nicholas G. W. Rose, Mark A. Blaskovich, Ghotas Evindar, Scott Wilkinson, Yue Luo, Dan Fishlock, Chris Reid, and Gilles A. Lajoie[1] .
Checked by Richard S. Gordon and Andrew B. Holmes.

1. Procedure

A. 3-Methyl-3-(toluenesulfonyloxymethyl)oxetane [Oxetane tosylate , (**1**)*]* . A dry, 1-L, round-bottomed flask is charged with p-toluenesulfonyl chloride (57.20 g, 0.30 mol) (Note 1) to which pyridine (250 mL) (Note 2) is added while stirring is carried out under nitrogen with a magnetic stir bar (Note 3). The reaction flask is placed inside a container to which an ice/water mixture may be added in the event that the reaction becomes too exothermic. 3-Methyl-3-oxetanemethanol (20.4 g, 0.2 mol) (Note 4) is added slowly and stirred for 1.5 hr. The mixture is slowly added to a vigorously (Note 3) stirred mixture of de-ionized water (700 mL) and crushed ice (700 g) in a 2-L Erlenmeyer flask and allowed to stir for an additional 0.5 hr. The white precipitate is collected on Whatman filter paper # 1 and washed with cold water (H_2O, Note 5). The product is dried under high vacuum and/or phosphorus pentoxide (P_2O_5) to obtain the white powder of oxetane tosylate **1** (39.8-44.60 g, 78-87%) (Note 6).

B. N-Benzyloxycarbonyl-L-serine 3-methyl-3-(hydroxymethyl)oxetane ester [Cbz-Ser oxetane ester, (**2**)*]* . Cbz-L-Ser (11.36 g, 0.047 mol) (Note 7) and cesium carbonate (Cs_2CO_3, 9.19 g, 0.028 mol, 0.6 equiv) (Note 8) are combined in a 500-mL, round-bottomed flask and dissolved in H_2O (100 mL). The water is removed under reduced pressure and the resulting oil is lyophilized for 12 hr to give a white foam. To this foam are added oxetane tosylate **1** (12.65 g, 0.049 mol) and sodium iodide (NaI, 1.41 g, 9.8 mmol, 0.2 equiv) (Note 9), which is taken up in dimethylformanide (DMF, 400 mL) (Note 10) and the solution is stirred with a magnetic stir bar at 25°C under argon (Ar) for 48 hr. The DMF is removed

under reduced pressure (0.5 mm, bath temperature 50°C) and the resulting solid is dissolved in a two-phase mixture by sequential treatment with alternating aliquots of ethyl acetate (EtOAc, 600 mL total) and H_2O (200 mL total). The organic phase is separated and washed with aqueous 10% sodium bicarbonate ($NaHCO_3$, 2 × 100 mL) (Note 11) and saturated aqueous sodium chloride (NaCl, 1 × 100 mL), dried over magnesium sulfate ($MgSO_4$), and evaporated on a rotary evaporator. The solvent is removed under reduced pressure to yield a yellow oil that is recrystallized from diethyl ether to yield colorless, rod-like crystals in 70-72% yield (10.6-10.9 g) (Note 12).

C. 1-[N-Benzyloxycarbonyl-(1S)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane [Cbz-L-Ser OBO ester, (**3**)*]* . In a 500-mL, round-bottomed flask, Cbz-Ser oxetane ester **2** (11.85 g, 36.6 mmol) (Note 13) is dissolved in dry dichloromethane (CH_2Cl_2, 450 mL) (Note 14) and cooled to 0°C under Ar. Boron trifluoride etherate ($BF_3 \cdot Et_2O$, 0.23 mL, 1.83 mmol) (Note 15) is diluted in dry CH_2Cl_2 (5.0 mL) and added by syringe to the reaction flask. The solution is stirred with a magnetic stir bar at 25°C under Ar for 6 hr, at which point TLC indicates that the reaction is over. Triethylamine (Et_3N, 1.28 mL, 9.15 mmol) (Note 16) is added and the reaction is stirred for an additional 30 min before being concentrated to a thick oil. The crude product is redissolved in EtOAc (400 mL) and washed with aqueous 3% ammonium chloride (NH_4Cl, 2 × 250 mL) (Note 17), aqueous 10% $NaHCO_3$ (1 × 250 mL), saturated aqueous NaCl (1 × 250 mL), dried ($MgSO_4$), and evaporated to dryness. The reaction yields a colorless thick oil, (14.2 g, 95% yield). The clear colorless oil is crystallized from EtOAc/hexane to give (9.7-11 g, 82-93% yield) of shiny crystals (Notes 18-20).

D. 1-[N-Benzyloxycarbonyl-(1S)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, [Cbz-L-Ser(ald) OBO ester, (**4**)*]* . Cbz-Ser OBO ester **3** (9.10 g, 28.0 mmol) (Note 21) is dissolved in dry CH_2Cl_2 (80 mL) (Note 14) under Ar and cooled to −78°C in a 100-mL, round-bottomed flask labeled flask 1. Oxalyl chloride (3.9 mL, 45 mmol, 1.61 equiv) (Note 22) is added to dry CH_2Cl_2 (120 mL) (Note 14) in a separate 250-mL, round-bottomed flask (flask 2) under Ar, and cooled to −78°C. Dry dimethyl sulfoxide (DMSO, 7.0 mL, 90 mmol, 3.21 equiv) (Note 23) is added to the oxalyl chloride solution (flask 2) and the mixture is stirred under Ar (magnetic stir bar) at −78°C for 15 min. The alcohol solution **3** (in flask 1) is transferred slowly by cannula to flask 2 over a period of 45 min and then rinsed with dry CH_2Cl_2 (50 mL) (Note 14). The resulting cloudy white mixture is stirred for 1.5 hr at −78°C. Diisopropylethylamine (DIPEA, 24.27 mL, 0.14 mol, 5.0 equiv) (Note 24) is added and the solution is stirred for 30 min at −78°C and 10 min at 0°C. Ice-cold CH_2Cl_2 (250 mL) is added and the solution is washed with ice-cold aqueous 3% NH_4Cl (3 × 250 mL), aqueous 10% $NaHCO_3$ (1 × 250 mL), saturated aqueous NaCl (1 × 250 mL), dried ($MgSO_4$), and evaporated to dryness on a rotary evaporator. The reaction yields 8.4-8.77 g (92-96%) of a slightly yellowish solid that may be used without further purification (Notes 25, 26, 27).

2. Notes

1. p-Toluenesulfonyl chloride (>97%) was purchased from Aldrich Chemical Company, Inc., (checkers) or Fluka Chemicals (submitters) and used without further purification.
2. Pyridine (>99%) was purchased from Fisher Scientific, UK (checkers) or Fisher Scientific Company (submitters) and used without further purification.
3. The checkers found that vigorous stirring was essential.
4. 3-Methyl-3-oxetanemethanol (98%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
5. The checkers cooled 250 mL of distilled water in a refrigerator for this purpose.
6. The submitters obtained 49.1 g (96%). The product has the following physical and spectral characteristics: mp 59-60°C or 61-62°C; the submitters observed mp 49.5-51°C; (lit.[2] mp 49.5-51°C); TLC (3:2 v/v, hexane:ethyl acetate) R_f (Merck kieselgel) = 0.42; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.31 (s, 3 H), 2.46 (s, 3 H), 4.11 (s, 2 H), 4.35 (d, 2 H, J = 6.3), 4.35 (d, 2 H, J = 6.3), 7.37 (d, 2 H, J = 8.2), 7.81 (d, 2 H, J = 8.2) ; ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 20.6, 21.6, 39.3, 74.3, 78.9, 128.0, 130.0, 132.7, 145.1 ; IR (cast from $CHCl_3$) cm^{-1}: 2958, 2877, 1531, 1364, 1226, 1223, 1189, 1177 ; HRMS (ES, M + Na^+) *m/z* Calcd for $C_{12}H_{16}O_4Na$: 279.0667. Found: 279.0656 ; Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.2; H, 6.3; N. Found: C, 56.3; H, 6.4.
7. The checkers purchased Cbz-L-Serine from Nova Biochem while the submitters purchased this from Advanced Chemtech ; in both cases the material was used without further purification.

8. Cesium carbonate (99%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
9. Sodium iodide (99%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
10. DMF (99.8%) was purchased from BDH and stored over activated 4Å molecular sieves (8-12 Mesh, purchased from Acros Organics) before use.
11. The $NaHCO_3$ solution was prepared and used immediately.
12. The submitters recrystallized the product from ethyl acetate and hexanes to obtain a 78% yield. The checkers obtained crude product **2** in 85-94% yield. They found the recrystallization of **2** difficult and preferred diethyl ether as solvent. The crude product was initially dissolved in diethyl ether (ca. 50 mL) and left open to the atmosphere to reduce the volume to about 15 mL. The yield is based on the recovery of solid from two crops. The checkers found that the use of diethyl ether , although time consuming, was a more reliable procedure for recrystallization. The chemical properties of **2** are as follows: mp 58-60°C (Et_2O) (69-71°C from EtOAc-hexane) (submitters and lit.[2] 70-70.5°C from EtOAc-hexanes); sample recrystallized from Et_2O $[\alpha]_D^{20}$ −8.6° (EtOAc, *c* 1.0) sample recrystallized from EtOAc-hexanes $[\alpha]_D^{20}$ −8.3° (EtOAc, *c* 1.0); the submitters reported $[\alpha]_D^{20}$ −8.5° (EtOAc, *c* 1.04); TLC (2:1, EtOAc:hexane), R_f = 0.34; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.28 (br s, 3 H), 3.01 (t, 1 H, J = 6.0), 3.80-3.93 (br m, 1 H), 4.04-4.13 (br m, 2 H), 4.38-4.56 (m, 6 H), 5.12 (s, 2 H), 5.89 (d, 1 H, J = 7.9), 7.30-7.40 (br m, 5 H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.7, 39.6, 56.4, 63.3, 67.1, 68.9, 79.4, 128.1, 128.2, 128.5, 136.1, 156.2, 170.7 ; IR (cast from $CHCl_3$) cm^{-1}: 3329, 2958, 2877, 1714, 1527, 1214, 1062, 976, 752 ; HRMS (ES, M + Na^+) *m/z* Calcd for $C_{16}H_{21}NO_6Na$: 346.1267. Found: 346.1257 . Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.4; H, 6.6; N, 4.3. Found: C, 59.5; H, 6.6; N, 4.4.
13. The checkers obtained the required quantity of ester **2** by combining the product from two runs in Step B. Alternatively, in several trial experiments, the checkers used the crude ester **2** as a starting material with no appreciable decrease in yield of compound **3**.
14. Dichloromethane is freshly distilled from CaH_2.
15. Boron trifluoride diethyl etherate (redistilled) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
16. Triethylamine (99%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
17. The checkers found the work-up lengthy as the phases took extended periods to separate (15 min). Significant emulsion formation (with product loss) on work-up was observed if aqueous solutions were marginally more concentrated (see Note 11).
18. Care must be taken not to expose product **3** to aqueous acid conditions for prolonged periods of time since ring opening of the OBO will occur. Thus care must be taken upon both addition of $BF_3 \cdot Et_2O$ to **2** and upon work-up, hence the sodium bicarbonate wash after the 3% NH_4Cl extraction. The diol that is formed upon acid-catalyzed hydrolysis of the OBO also crystallizes out making purification of the desired product **3** impossible.
19. The checkers also prepared racemic 1-[N-benzyloxycarbonyl-(1±)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane using the identical procedure (50% over 2 steps from racemic Cbz-serine purchased from Aldrich Chemical Company, Inc.). The enantiomeric ratio of the crystalline (S)-**3** enantiomer (Note 20) was > 99.5:0.5 as determined by comparison with racemic **3** by courtesy of Mr. Eric Hortense (GlaxoSmithKline, Stevenage). Chiral HPLC (25 cm Chiracel OD-H, Column No ODHOCE-IF029, mobile phase ethanol/heptane 1:4 v/v, UV detector at 215 nm, flow rate 1.0 mL/min at room temperature) afforded the (S)-**3** enantiomer with a retention time of 8.1 min while the (R)-**3** enantiomer had a retention time of 11.0 min.
20. The submitters recrystallized the sample from EtOAc-hexanes and obtained a yield of 93%. The checkers' yield is based on combined product from two successive crops, although additional product was observed in the remaining mother-liquor (2 g of crude material) which could be used, as obtained, for subsequent reactions. The physical and spectroscopic properties of **3** are as follows: mp 104-106°C (material isolated by column chromatography alone); mp 110-112°C $[\alpha]_D^{20}$ −24.6° (EtOAc, *c* 1.0) (after a single crystallization from EtOAc/hexane); mp 119-121°C $[\alpha]_D^{20}$ −24.1° (EtOAc, *c* 0.8) (after two recrystallizations) with all samples exhibiting analytical purity by TLC analysis; the submitters reported mp 103.5-105°C; $[\alpha]_D^{20}$ −24.8° (EtOAc, *c* 1.00); TLC (3:1 EtOAc:hexane), R_f = 0.37; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.81 (s, 3 H), 2.57 (m, 1 H), 3.61-3.95 (m, 9 H), 5.10-5.18 (m, 2 H), 5.33 (d, 1 H, J = 8.8), 7.29-7.38 (m, 5 H) ; ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 14.2, 30.5, 55.2, 61.9, 66.9, 72.7, 108.4,

128.1, 128.2, 128.5, 136.4, 156.3 ; IR (cast from $CHCl_3$) cm^{-1}: 3019, 2966, 2881, 1717, 1519, 1216 ; HRMS (ES, M + Na^+) *m/z* Calcd for $C_{16}H_{21}NO_6Na$: 346.1267. Found: 346.1260 . Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.4; H, 6.55; N, 4.3. Found: C, 59.2; H, 6.6; N, 4.2. Chiral HPLC of **3** displayed a single enantiomer (R_t=8.1 min) (Note 19). It is essential that $CDCl_3$ used for NMR samples containing the ortho ester be prefiltered through basic alumina to remove traces of acid.

21. The checkers obtained the required quantity of alcohol **3** by combining the product from two runs in step C.

22. Oxalyl chloride (98%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification. Amounts of reagents for the Swern oxidation have been optimized as reported. Alternative amounts reduce both yield and % ee.

23. DMSO (dimethyl sulfoxide) (99.8%) stored in an Aldrich Sure/Seal bottle was purchased from Aldrich Chemical Company, Inc. , and used without further purification.

24. DIPEA (diisopropylethylamine, redistilled 99.5%) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.

25. The submitters obtained 8.68 g (96%). The aldehyde **4** should be used immediately after preparation. It cannot be purified by chromatography. The checkers observed the following physical and spectroscopic properties of **4**: $[\alpha]_D^{20}$ (EtOAc, *c* 1.0) fell in the range −36° to −62.0° and was considered an unreliable estimate of enantiomeric purity (see Note 26); the submitters obtained $[\alpha]_D^{20}$ −99.3° (EtOAc, *c* 1.03) (lit. 8); TLC (3:1 EtOAc:hexane), R_f = 0.60; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.83 (s, 3 H), 3.94 (s, 6 H), 4.60 (d, 1 H, J = 8.9), 5.08-5.14 (m, 2 H), 5.38 (d, 1 H, J = 9.2), 7.30-7.38 (m, 5 H), 9.69 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 14.2, 30.9, 63.3, 67.2, 72.9, 107.2, 128.1, 128.5, 136.2, 156.2, 195.6 ; IR (cast from $CHCl_3$) cm^{-1}: 2947, 2883, 1723(br), 1517, 1218 . HRMS (ES, M + Na^+) *m/z* Calcd for $C_{16}H_{19}NO_6Na$: 344.1440. Found: 346.1106 . Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.75; H, 6.0; N, 4.4. Found: C, 59.4; H, 6.1; N, 4.3.

26. To confirm the enantiomeric integrity of aldehyde **4**, and in view of the variability of the specific rotation, the checkers reduced aldehyde **4** to the alcohol **3**. Aldehyde **4** (6.9 g, 21.3 mmol) was dissolved in THF/EtOH (60 mL, 1:1), and the solution was stirred with a magnetic stir bar in a 100-mL round-bottomed flask at −20°C. Sodium borohydride (0.8 g, 22.2 mmol) (Note 26) was added as a suspension in water (2 mL), and the mixture was stirred for 1 hr. The organic solvents were removed and the residue was subsequently redissolved in EtOAc (100 mL). The organic phase was washed with aqueous 3% NH_4Cl (2 × 100 mL), aqueous 10% $NaHCO_3$ (1 × 100 mL) and saturated aqueous NaCl solution. This was dried ($MgSO_4$) and the solvent was removed (rotary evaporator) to afford alcohol **3** (6.5 g, 20.2 mmol, 95%) as a white solid. This was recrystallized as described in Step C (6.0 g). Chiral HPLC analysis of the recrystallized product, under the previously described conditions (Note 19), showed **3** having an enantiomeric ratio 99.5:0.5. The mother-liquors (0.5 g) from the crystallization of **3** contained an enantiomeric ratio > 85:15 of the (S)-and (R)-enantiomers respectively. These figures would correspond to an enantiomeric ratio of 98.4:1.6 for the as prepared Cbz-L-Ser(ald) OBO ester **4**, assuming no loss of material. The submitters determined the enantiomeric purity of Cbz-Ser(ald) OBO ester by chiral shift ^1H NMR studies. Cbz-Ser(ald) OBO ester **4** (10 mg) was dissolved in benzene-d_6 . $Eu(hfc)_3$ (100 µL, 50 mg/mL in benzene-d_6) was added to obtain the ^1H NMR spectrum at 250 MHz. The purity was observed to be 97-99% ee.

27. Sodium borohydride was purchased from Avocado , and used without purification.

Waste Disposal Information

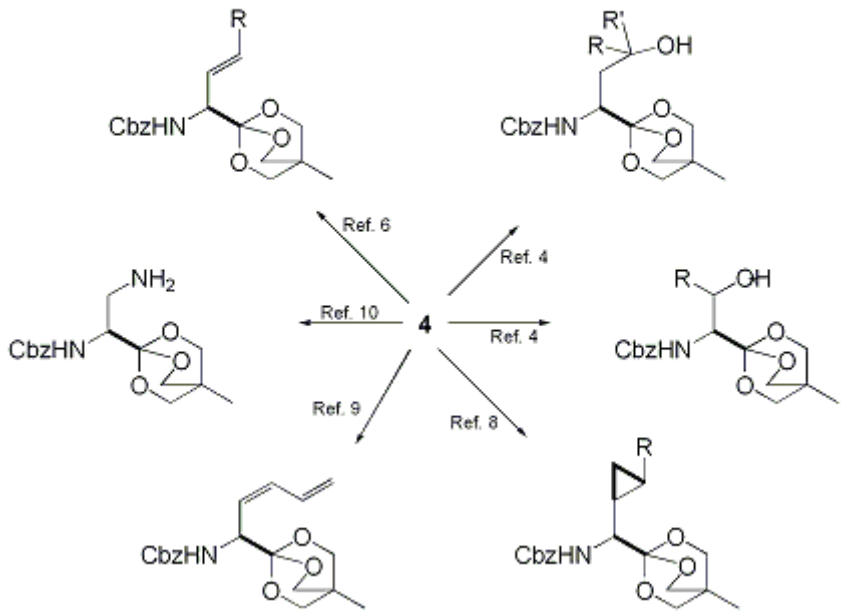
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The nonproteinogenic α-amino acids represent an important group of natural products because of their varied biological properties.[2] One approach to the synthesis of these compounds is through elaboration of the chiral pool of 19 natural α-amino acids. Serine aldehyde derivatives are perhaps the most popular chiral synthons for the synthesis of nonproteinogenic α-amino acids; the Garner aldehyde has been especially popular in that regard.[3] The submitters have developed an alternative chiral serine aldehyde synthon **4** that is both more facile in preparation and prepared in higher yields (70% over 3 steps).[4] However, the greatest benefit exists in the fact that conversion to the free α-amino acid proceeds

through deprotection of the intermediate, unlike Garner's aldehyde that requires further oxidation to achieve the α-amino acid, and may suffer from racemization.[5] The conversion of the α-carboxylic acid to the OBO protecting group reduces the acidity of the α-proton, preventing racemization in both olefination[6] and nucleophilic[4,7 8 9 10] addition homologation reactions to the aldehyde **4**. The procedure described here provides aldehyde **4** determined to be 97-99% enantiomerically pure by chiral shift ^{1}H NMR studies and HPLC analysis.[7] Conversion to the free amino acid can be achieved by acid hydrolysis to yield products typically >98% enantiomerically pure.[4] Examples of the use of 1-[N-benzyloxycarbonyl-(1S)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2] oxetane **4** as a chiral synthon for natural product synthesis are shown in Scheme 1.

Scheme 1



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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-[N-Benzyloxycarbonyl-(1S)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane:
Carbamic acid, [1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-2-oxoethyl]-, phenylmethyl ester, (S)- (14); (183671-34-3)

3-Methyl-3-(toluenesulfonyloxymethyl)oxetane:
3-Oxetanemethanol, 3-methyl-, 4-methylbenzenesulfonate (11); (99314-44-0)

p-Toluenesulfonyl chloride (8);
Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

Pyridine (8, 9); (110-86-1)

3-Methyl-3-oxetanemethanol:
3-Oxetanemethanol, 3-methyl- (9); (3143-02-0)

N-Benzyloxycarbonyl-L-serine 3-methyl-3-(hydroxymethyl)oxetane ester:
L-Serine, N-[(phenylmethoxy)carbonyl]-, (3-methyl-3-oxetanyl)methyl ester (14); (206191-42-6)

Cesium carbonate:
Carbonic acid, dicesium salt (8, 9); (534-17-8)

N-(Benzyloxycarbonyl)-L-serine:
L-Serine, N-[(phenylmethoxy)carbonyl]- (9); (1145-80-8)

Sodium iodide (8, 9); (7681-82-5)

N,N-Dimethylformanide: CANCER SUSPECT AGENT:
Formamide, N,N-dimethyl- (8, 9); (68-12-2)

1-[N-Benzyloxycarbonyl-(1S)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7,trioxabicyclo[2.2.2]octane:
Carbonic acid, [(1S)-2-hydroxy-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)ethyl]-, phenylmethyl ester (14); (206191-44-8)

Boron trifluoride etherate:
Ethyl ether, compd. with boron fluoride (BF_3) (1:1) (8);
Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

Triethylamine (8);
Ethanamine, N,N-diethyl- (9); (121-44-8)

Oxalyl chloride: HIGHLY TOXIC: (8);
Ethanedioyl dichloride (9); (79-37-8)

Dimethyl sulfoxide:
Methyl sulfoxide (8);
Methane, sulfinylbis- (9); (67-68-5)

N,N-Diisopropylethylamine:
Triethylamine, 1,1'-dimethyl- (8);
2-Propanamine, N-ethyl-N-(1-methylethyl)- (9); (7087-68-5)