from methanol/ethyl acetate to give 2-deoxy-2-fluoro-D-glucose: 80 mg (40%); mp 157–168 °C (lit. mp[23] 160–165 °C). This melting point was unchanged on mixing with authentic 2-deoxy-2-fluoro-D-glucose.

(c) The foam was treated with boron tris(trifluoroacetate) (5 mL; 1 M in TFA acid) for 5 min at room temperature. The TFA was evaporated, and the residue was dissolved in water and desalted with Dowex MR-3. Evaporation and crystallization gave 2-deoxy-2-fluoro-D-glucose (130 mg, 70%).

(23) Adamson, J.; Foster, A. B.; Hall, L. D.; Johnson, R. N.; Hesse, R. H. *Carbohydr. Res.* **1970**, *15*, 351.

**Registry No.** 1 (isomer 1), 86747-78-6; 1 (isomer 2), 86747-79-7; 2 (isomer 1), 86747-80-0; 2 (isomer 2), 86747-81-1; 3, 65530-26-9; 4, 86783-81-5; 5, 86747-82-2; 6, 86747-83-3; 7, 66183-24-2; 8, 86747-85-5; 10, 39110-57-1; 11, 86783-82-6; methyl 2-bromo-2-deoxy-β-D-glucopyranoside, 2880-98-0; 2-bromo-2-deoxy-D-glucose tetraacetate, 86783-83-7; methyl 4,6-*O*-benzylidene-α-D-mannopyranoside-2,3-*O*-disulfuryl chloride, 86747-86-6; methyl β-D-mannopyranoside, 22277-65-2.

# A Simple and Efficient Synthesis of Chiral Acetic Acid of High Optical Purity

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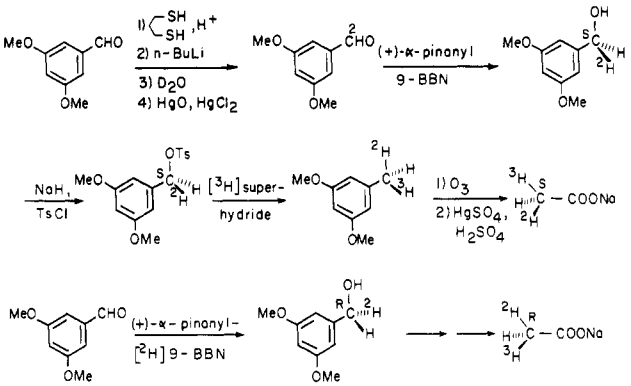
*Received February 4, 1983*

(*R*)- and (*S*)-[2-$^2$H,2-$^3$H]acetic acid of high chiral purity was synthesized in over 50% radiochemical yield. Reduction of 3,5-dimethoxy-[7-$^2$H]benzaldehyde with optically pure (+)-α-pinanyl-9-BBN and reduction of the unlabeled aldehyde with deuterated (+)-α-pinanyl-9-BBN gave 3,5-dimethoxy-(7*S*)- and -(7*R*)-[7-$^2$H]benzyl alcohol, respectively. Conversion to the tosylate and displacement with tritiated Superhydride gave 3,5-dimethoxy-(7*S*)- and -(7*R*)-[7-$^2$H,7-$^3$H]toluene, which was ozonized to produce *S* and *R* chiral acetic acid. Within the limits of detection, all the reaction steps proceeded completely (>98%) stereospecifically.

Chiral acetic acid, i.e., (*R*)- and (*S*)-[2-$^2$H,2-$^3$H]acetic acid has been synthesized by several enzymatic and chemical routes and by combinations of chemical and enzymatic reaction sequences.[1] An efficient synthesis should allow the generation of material of high chiral purity and high specific activity, the chiral purity of intermediates should be readily monitored, and radioactivity should be introduced late in the reaction sequence from an easily handled source of tritium. Most of the published routes do not meet one or more of these criteria. With this in mind we developed a new synthesis along the route outlined in Scheme I.

The general approach involved the sequential conversion of an aldehyde group into a stereospecifically deuterated hydroxymethyl group and then into a chiral methyl group[2-5] followed by oxidation to give chiral acetic acid. Dimethoxybenzaldehyde was selected as the starting material to facilitate the final oxidation step; the 3,5-substituted compound was chosen over the 3,4- and 2,4-isomers because the latter substitution significantly increased the reactivity of the benzylic position, producing very unstable benzyl tosylates. Conversion to the dithiane,[6] generation of the anion, quenching with $D_2O$, and treatment with mercuric oxide/mercuric chloride[4] produced the deuterated aldehyde (>98% $^2$H) in 65% overall yield. Reduction of this aldehyde with (+)-α-pinanyl-9-borabicyclo[3.3.1]nonane (-BBN)[7] gave 3,5-dimethoxy-(7*S*)-[7-$^2$H]benzyl alcohol (83% yield, >98% $^2$H). An aliquot of this material was converted to the (−)-camphanic acid ester and analyzed by proton NMR spectroscopy in the presence of shift reagent.[8] The absence of any detectable signal for the benzylic *pro-S* proton indicated that the material

Scheme I




contained a high (estimated ≳ 95%) enantiomeric excess of the *S* isomer. The optical purity of the product depends only on the degree of deuteration and the optical purity of the α-pinene used to generate the α-pinanyl-9-BBN; the reduction itself is completely stereospecific within the limits of detection. Optically pure (+)-α-pinene (100% ee) was prepared from commercial material (92% ee) by a

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(2) The same general principle has been used before, e.g., by Lüthy et al.,[3] by Golding et al.,[4] and by Caspi and co-workers,[5] in different forms of implementation.

(3) Lüthy, J.; Retey, J.; Arigoni, D. *Nature (London)* **1969**, *221*, 1213–1215.

(4) Golding, B. T.; Ioannou, P. V.; Eckhard, I. F. *J. Chem. Soc., Perkin Trans.* 1 **1978**, 774–780.

(5) Caspi, E.; Shapiro, S.; Piper, J. *Tetrahedron* **1981**, *37*, 3535–3543.

(6) Seebach, D. *Synthesis* **1969**, 17–36.

(7) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352–2355.

(8) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274–275.

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0022-3263/83/1948-3510$01.50/0 

modification of the procedure described by Brown and co-workers.[9]

The corresponding *R* alcohol can be obtained in a number of ways. One simple option involves the substitution of (−)-α-pinene for the (+) enantiomer in the reduction step. An alternative that we implemented consists of reduction of the unlabeled aldehyde with deuterated (+)-α-pinanyl-9-BBN (92% $^2H$, prepared from $NaB^2H_4$[10]). A third possibility that we also implemented involves inversion of the configuration of the *S* alcohol via alkaline hydrolysis of the tosylate (data not shown). Within the limits of detection by NMR, this process is completely stereospecific.

A sample of the *S* alcohol was converted to the tosylate by treatment with NaH and TsCl, and the tosylate (51% yield) was reduced with tritiated $LiAlH_4$ to give (*S*)-3,5-dimethoxy-[7-$^2H$,7-$^3H$]toluene in 9% radiochemical yield.[4] Aliquots of this product were converted to acetic acid under a variety of different conditions to develop an optimal set of parameters. Direct Kuhn–Roth oxidation[11] of the crude dimethoxytoluene produced acetic acid (69%), which upon chirality analysis by the method of Cornforth et al.[12] and Arigoni and co-workers[3] gave an *F* value of 40.5, corresponding to 33% ee *S* isomer.[13] After purification of the toluene derivative by preparative-layer chromatography (silica gel, *n*-hexane/ether, 4:1), Kuhn-Roth oxidation gave acetic acid of *F* = 35.4 (50% ee *S*). Better results were obtained when the purified dimethoxytoluene was ozonized and the distillate from the reaction subjected to oxidation (to destroy contaminating formic acid) with Kuhn-Roth oxidation mixture (65% yield, *F* = 24, corresponding to 90% ee *S*) or $HgSO_4/H_2SO_4$[14] (75% yield, *F* = 22 or 95.5% ee *S*). Hence, ozonolysis followed by oxidation with $HgSO_4/H_2SO_4$ was chosen as the optimal conditions.

Both the 3,5-dimethoxy-(7*R*)-[7-$^2H$]benzyl alcohol (92% $^2H$) and the 7*S* isomer (>98% $^2H$) were converted to the tosylate. In view of the low radiochemical yield of the $LiAlH_4$ reduction, the two tosylates were reduced with tritiated Superhydride[15] (lithium triethylboro[$^3H$]hydride, 10 mCi each) to give, after preparative-layer chromatography, the two enantiomers of 3,5-dimethoxy[7-$^2H$,7-$^3H$]toluene in radiochemical yields of 81% and 73%, respectively. Tritiated Superhydride can be readily prepared from [$^3H$]LiH and triethylborane.[16,17] Ozonolysis and oxidation with $HgSO_4/H_2SO_4$ gave acetic acid (71% yield, *F* = 76.5 ± 1 or 91.4 ± 3.4% ee *R* isomer) from the 7*R* enantiomer of the dimethoxytoluene whereas the 7*S* material produced acetic acid of *F* = 21 ± 1 (100 ± 3.4% ee *S* isomer) in 70% yield.

The sequence outlined here provides a convenient and highly efficient chemical route for the synthesis of chiral acetic acid. Tritium is introduced late in the reaction sequence from a very convenient source, resulting in a high overall radiochemical yield (51–57% based on tritiated Superhydride). The chiral purity of the acetic acid is very high. Even in the case of the *R* isomer, the close correspondence of the chiral purity of the product (91.4% ee) and the deuterium content of the deuterated reagent used (92% $^2H$) indicates that within the limits of detection every reaction step in the sequence is completely stereospecific. This is powerful testimony of the synthetic utility of suitably selected boron hydrides in carrying out highly stereospecific processes.

## Experimental Section

**3,5-Dimethoxy-[7-$^2H$]benzaldehyde.** Dry HCl gas was passed for 20 min through a gently stirred, ice-cooled solution of propane-1,3-dithiol (433 mg, 4 mmol) and 3,5-dimethoxybenzaldehyde (664 mg, 4 mmol) in 7 mL of chloroform. Stirring was continued for 18 h at room temperature, and the solution was then washed successively with water, 10% NaOH, and water. Drying over $Na_2SO_4$, removal of the solvent, and recrystallization from $MeOH/CHCl_3$ gave the dithiane (776 mg, 75.8% yield, mp 96.5–97.5 °C).

To a solution of the dithiane (151 mg, 0.59 mmol) in 3 mL of dry tetrahydrofuran was added 0.275 mL of a 2.36 M solution of *n*-butyllithium in hexane over a period of 10 min at -70 °C under an argon atmosphere. After stirring for 1 h at −70 °C, 0.12 mL of $^2H_2O$ (99.8% $^2H$) was added at once with vigorous stirring. After being stirred for 2 h at room temperature, the reaction mixture was evaporated in vacuo, and the residue was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give, after recrystallization from $MeOH/CHCl_3$, 148 mg (97.6%) of the deuterated dithiane. The deuteration at the benzylic position was complete within the limits of detection (>98%) as judged by the absence of the signal at δ 5.10 in the proton NMR spectrum.

To a suspension of 192 mg of the deuterated dithiane in 8 mL of $MeOH/H_2O$ (9:1) was added red mercuric oxide (244 mg) and mercuric chloride (448 mg) under an argon atmosphere. The mixture was refluxed with vigorous stirring for 2 h at 80–85 °C; insoluble material was then filtered off and washed with chloroform. The filtrate and washings were combined and concentrated in vacuo; the residue was dissolved in $CHCl_3$, and the solution was washed with water, dried over $MgSO_4$, and evaporated. Preparative-layer chromatography (silica gel, $CHCl_3$) of the residue gave the deuterated 3,5-dimethoxybenzaldehyde (110 mg, 88.1% yield).

**3,5-Dimethoxy-(7*S*)-[7-$^2H$]benzyl Alcohol.** To a dry, 50-mL flask closed with a septum was added 9-BBN solution in dry tetrahydrofuran (0.552 M, 5.31 mL, 2.93 mmol) and (+)-α-pinene ($[\alpha]_{23}$ +51.5° (neat), 0.498 mL, 3.14 mmol) under an argon atmosphere. The mixture was stirred and gently refluxed for 2 h and then cooled to 0 °C. Deuterated 3,5-dimethoxybenzaldehyde (441 mg, 2.64 mmol) was added, and the mixture was stirred for 15 h at room temperature and then refluxed for 1 h. After cooling to room temperature, 0.1 mL of acetaldehyde was added, and after 15 min of stirring, the solvent was evaporated on an aspirator. The pinene was then removed by evaporation at 40 °C by using an oil pump. Argon was admitted to the flask, followed by addition of 3 mL of dry ether. After cooling to 0 °C, 2-aminoethanol (0.177 mL, 2.93 mmol, distilled over $CaH_2$) was added, and the mixture was stirred for $^1/_2$ h. The precipitate formed was removed by filtration and washed with ether, and the combined ether solutions were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by preparative-layer chromatography (silica gel, $CHCl_3$) gave 372 mg (83.4%) of (7*S*)-[7-$^2H$]benzyl alcohol. The proton NMR spectrum of the (−)-camphanic acid ester of this material (5 mg) in $CDCl_3$ (0.6 mL) recorded in the presence of $Eu(dpm)_3$ (8.0 mg) showed only a singlet for the benzylic *pro-R* hydrogen. The nonlabeled ester under similar conditions showed doublets (*J* = 12.2 Hz) at δ 5.78 ($H_R$) and 5.84 ($H_S$).

**3,5-Dimethoxy-(7*R*)-[7-$^2H$]benzyl Alcohol.** This compound was prepared analogously by reduction of unlabeled aldehyde (441

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(12) Cornforth, J. W.; Redmond, J. W.; Eggerer, H.; Buckel, W.; Gutschow, C. *Eur. J. Biochem.* **1970**, *14*, 1–13.

(13) For a discussion of the analytical methodology, the definition of the *F* value, and the calculation of enantiomeric excess (ee), see ref 1b.

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(15) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669–1671.

(16) Pearce, C. J.; Coates, R. M., personal communication: see ref 17. We thank Drs. Pearce and Coates for providing $^3H$ Superhydride and use of their facilities for these reductions.

(17) Coates, R. M.; Hedge, S.; Pearce, C. J. In "Application of Isotopically labeled Compounds"; Duncan, W. P., Susan, A. B., Ed.; Elsevier: Amsterdam, 1983, p 429.

mg, 2.64 mmol) with [9-$^2$H]-9-BBN (0.628 M solution in THF, 4.67 mL, 2.93 mmol) and (+)-α-pinene (0.498 mL, 3.14 mmol). The product (425 mg, 95.3%) upon conversion of an aliquot to the (-)-camphanic acid ester showed a signal for the benzylic *pro-S* hydrogen and a small signal (doublet, 0.05–0.1 H) for the *pro-R* hydrogen.

**3,5-Dimethoxy-[7-$^2$H]benzyl Tosylate.** To a suspension of NaH in mineral oil (87 mg, 60% dispersion, 2.1 mmol) in 8 mL of dry ether was added 333 mg (2.0 mmol) of 3,5-dimethoxy-[7-$^2$H]benzyl alcohol under argon. After being stirred for 15 h at 50 °C, the mixture was cooled to −60 °C, and a solution of *p*-toluenesulfonyl chloride (381 mg, 2.0 mmol) in 2 mL of dry ether was added dropwise with stirring. The mixture was stirred for 1 h at −30 to −10 °C and then for 2 $^1/_2$ h at 4 °C. Insoluble material was filtered off and washed with a small amount of dry ether. The combined ether solution was cooled to −60 °C to give colorless needles of the tosylate (330 mg, 51.1%).

**3,5-Dimethoxy-[7-$^2$H,7-$^3$H]toluene. A. By Reduction with [$^3$H]LiAlH$_4$.** To a solution of 3,5-dimethoxy-(7*S*)-[7-$^2$H]benzyl tosylate (161 mg, 0.50 mmol) in 5 mL of dry ether was added $LiAlH_4$ (1.0 mg) at 0 °C under argon, followed after several minutes by [$^3$H]$LiAlH_4$ (1.0 mg, 5.0 mCi). After stirring for 3 h at room temperature, excess $LiAlH_4$ (25 mg) was added and stirring was continued for 3 h. Excess reagent was decomposed with water at 0 °C, and 1 N HCl was added to dissolve the precipitate. The mixture was extracted with ether, and the ether phase was washed with 5% $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated in vacuo to give crude 3,5-dimethoxy-(7*S*)-[7-$^2$H,7-$^3$H]toluene (455 μCi), which was purified by preparative-layer chromatography (silica gel, *n*-hexane/ether, 4:1) with almost quantitative recovery of radioactivity; radiochemical yield 9.1%.

**B. By Reduction with Supertritide.** To a solution of 3,5-dimethoxy-(7*S*)-[7-$^2$H]benzyl tosylate (138 mg, 0.428 mmol) in dry THF (0.4 mL) was added Superhydride (Aldrich; 43 μL of a 1 M solution in THF, 0.043 mmol) at room temperature under argon, followed, after 10 min of stirring, by $^3$H Superhydride (286 μL of a 1 M solution in THF, 0.286 mmol, 10 mCi). Stirring was continued for 1$^1/_2$ h, excess nonlabeled Superhydride (526 μL, 0.526 mmol) was then added followed by stirring for another 2 h. Excess reagent was destroyed with water, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by preparative-layer chromatography (silica gel, $CHCl_3$) to give 3,5-dimethoxy-(7*S*)-[7-$^2$H,7-$^3$H]-toluene (7.34 mCi, 0.42 mmol, 73% radiochemical yield). Under identical conditions the *R* isomer was obtained from 3,5-dimethoxy-(7*R*)-[7-$^2$H]benzyl tosylate in 81% radiochemical yield.

**Sodium (*R*)- and (*S*)-[2-$^2$H,2-$^3$H]acetate.**[18] To a solution of 3,5-dimethoxy-(7*S*)-[7-$^2$H,7-$^3$H]toluene (0.42 mmol, 7.34 mCi) in 2 mL of *n*-pentane was added $SiO_2$ (4.5 g, 100 mesh), and the solvent was evaporated in vacuo. The resulting $SiO_2$ carrying the labeled material was stirred for 4 h at −78 °C under a stream of ozone. After standing at room temperature for 1 h, the ozonolysis was repeated for 4 h at −78 °C. The mixture was then warmed to 4 °C, 10 mL of water was added, and after the mixture stood at 4 °C overnight, it was subjected to steam distillation, replacing the water as necessary. The distillate (250 mL) was neutralized with 0.1 N NaOH and evaporated to dryness. The residue (5.77 mCi) was dissolved in 90 mL of water, mixed with 1.8 g of $HgSO_4$ and 3 mL of concentrated $H_2SO_4$, and subjected to steam distillation. Neutralization of the distillate and evaporation to dryness gave sodium (*S*)-[2-$^2$H,2-$^3$H]acetate (0.30 mmol, 5.16 mCi) in 70% radiochemical yield. The *F* value of this material was determined to be 21.

Similary, 3,5-dimethoxy-(7*R*)-[7-$^2$H,7-$^3$H]toluene (0.42 mmol, 8.09 mCi) gave sodium *R*-[2-$^2$H,2-$^3$H]acetate (5.78 mCi) of *F* = 76.5 in 71.4% radiochemical yield.

**Acknowledgment.** We thank Professor R. M. Coates and Dr. C. J. Pearce, University of Illinois, Urbana, for providing the tritiated Superhydride. They as well as Professor H. C. Brown, Purdue University, are also thanked for allowing us to use some of their facilities. Financial support of this work by the U.S. Public Health Service (NIH Grant GM 18852) and the American Cancer Society is gratefully acknowledged. T.M.Z. is the recipient of a postdoctoral fellowship from the National Cancer Institute.

**Registry No.** Propane-1,3-dithiol, 109-80-8; 3,5-dimethoxybenzaldehyde, 7311-34-4; 2-(3,5-dimethoxyphenyl)-1,3-dithiane, 57009-72-0; 2-(3,5-dimethoxyphenyl)[2-$^2$H]-1,3-dithiane, 86728-49-6; 3,5-dimethoxy[7-$^2$H]benzaldehyde, 86728-50-9; 3,5-dimethoxy-(7*S*)-[7-$^2$H]benzyl alcohol, 86728-51-0; (+)-α-pinanyl-9-borabicyclo[3.3.1]nonane, 64106-79-2; 3,5-dimethoxy-(7*S*)-[7-$^2$H]-benzyl alcohol (-)-camphanate, 86728-52-1; (+)-α-(pinan[2-$^2$H]-3-yl)-9-borabicyclo[3.3.1]nonane, 70738-23-7; 3,5-dimethoxy-(7*S*)-[7-$^2$H]benzyl tosylate, 86747-48-0; 3,5-dimethoxy-(7*S*)-[7-$^2$H,7-$^3$H]toluene, 86728-53-2; 3,5-dimethoxy-(7*R*)-[7-$^2$H,7-$^3$H]toluene, 86728-54-3; 3,5-dimethoxy-(7*R*)-[7-$^2$H]benzyl tosylate, 86747-49-1; sodium (*S*)-[2-$^2$H,2-$^3$H]acetate, 62678-90-4; sodium (*R*)-[2-$^2$H,2-$^3$H]acetate, 62678-94-8.

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# Marine Toxins of *Latrunculia magnifica*

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*Received November 15, 1982*

Latrunculins A (1) and B (2) are the major extractable toxins of *Latrunculia magnifica*, constituting up to 0.35% of the dry weight of the sponge. The structure of the compounds was determined by detailed spectral analysis, some minor chemical transformations, and X-ray crystallography. The latrunculins are the first-known 2-thiazolidinone-bearing marine macrolides. They were found to cause major alterations in specific cytoskeletal proteins. A retrosynthesis of the new compounds is suggested.

Among the shallow-water coral reefs of the northern Red Sea, many sponge species grow below or beneath coral plates and rocks and, if artificially exposed, are immediately devoured by various fish. Only a few sponge species grow exposed, and among them, the most prominent are colonies of the branching red-colored *Latrunculia magnifica* (Keller). Colonies of *L. magnifica* have never been observed to be damaged or eaten by fish.[1] When squeezed manually, these sponges exude a reddish fluid accompanied by a strong odor. In the sea this "juice" causes fish to flee immediately. Squeezing *L. magnifica* into an aquarium

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