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Article

A New Approach to the Synthesis of Pulo'upone Side Chain

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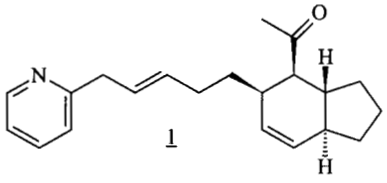
A síntese da cadeia lateral do produto natural Pulo'upona foi realizada utilizando-se uma nova metodologia envolvendo a (E)-3-bromo-1-propen-tributilestanana 3 obtida a partir do álcool propargílico.

The synthesis of Pulo'upone side chain was accomplished by a new and efficient methodology using the (E)-3-bromo-1-propen-tributylstannane 3 obtained from propargyl alcohol.

Keywords: *Pulo'upone, (E)-3-bromo-1-propen-tributylstannane*

Introduction

Pulo'upone 1, isolated[1] from the cephalaspidean mollusk *Philinopsis speciosa*, has been an interesting target[2,3,4] for organic synthesis since it is an uncommon pyridine derivative substituted at C-2 by a bicyclic C16-polyketide.



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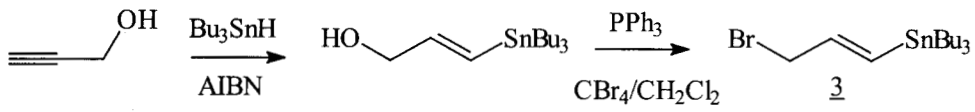
A number of different approaches to construct the side chain of this natural compound and its attachment to the hydrindene moiety has been published[2,3,4]. During a collaborative joint research program we developed a new strategy for intramolecular annulation leading to hydrindenone systems[5,6]. In this communication we present a new approach to assemble the side chain of pulo'upone using (E)-3-bromo-1-propen-tributylstannane 3 as the central unit to link the pyridine and hydrindene moieties as outlined below.

The (E)-3-bromo-1-propen-tributylstannane 3 was prepared using a two step protocol from propargyl alcohol[7,8]. This synthon contains suitable functionalities to join the intermediate 2 and the pyridine portion. Albeit (E)-3-tri-n-butylstannyl-prop-2-en-1-ol has been used as an important intermediate in organic synthesis[9], as far as we know, the bromo derivative was introduced the first time by us[10]. Recently other authors[11] reported the use of (Z) and (E)-3-chloro-1-propen-tributylstannane in the synthesis of pharmacological active compounds.

Scheme 1 shows the coupling of the model compound 2[6] with bromo vinyl stannane 3. After several functional group manipulations, coupling with 2-picoline lead to a diastereomer of pulo'upone 1'.

Coupling[12] of the anion of the sulfone 2 (1.1 eq. of n-BuLi, THF, 3.9 eq. of HMPA, -78 °C, 30 min) with the (E)-3-bromo-1-propen-tributylstannane 3 (1.5 equiv, 60



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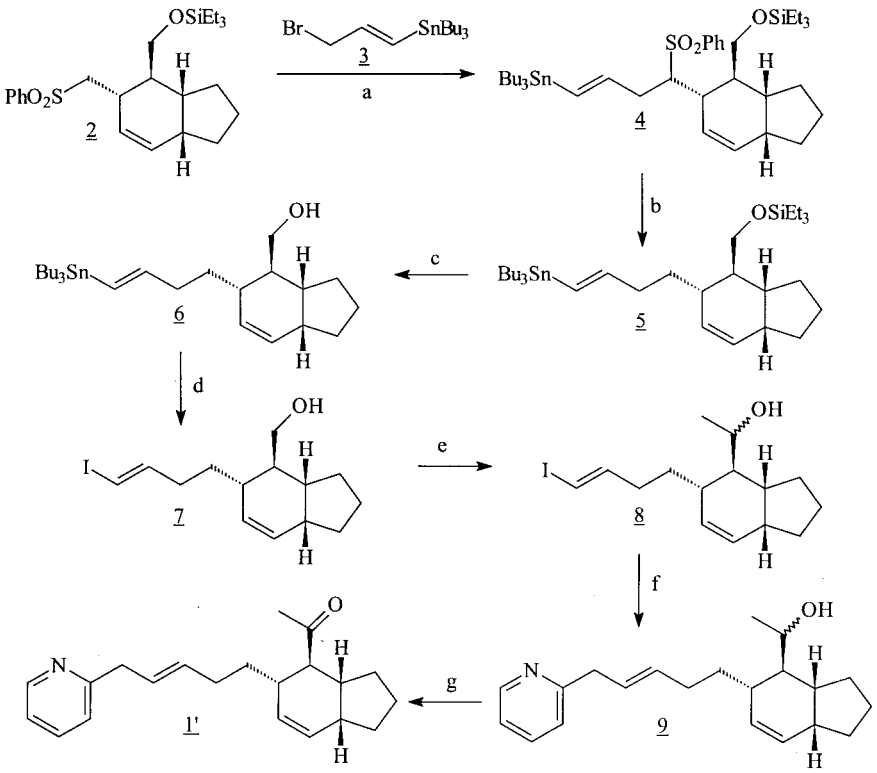

Scheme 1. a) n-BuLi, THF, HMPA, -78 °C, 3, 42%; b) 6% Na(Hg), Na_2HPO_4, MeOH, 0 °C, 76%; c) Bu_4NF, THF, 90%; d) I_2, CH_2Cl_2, -78 °C to 0 °C, 88%; e) $(COCl)_2$,DMSO, Et_3N, THF, -78 °C to -35 °C; 5.0 eq. of MeMgBr, 70%; f) 2-picoline, n-BuLi, THF, 0 °C; CuCN, THF, -78 °C, 83%; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C, 82%.

min, -78 °C) gave the (E)-vinylstannyl sulfone 4 (42% yield) along with recovered starting material (35% yield). Desulfonylation[13] of compound 4 was performed using 6% Na(Hg) sodium amalgam in methanol and sodium hydrogen phosphate (4 equiv) at -20 °C; the mixture was left to warm up to room temperature affording the (E)-vinylstannane 5 in 76% yield.

Deprotection of the hydroxyl group was done with an excess of tetrabutylammonium fluoride (TBAF), affording the alcohol 6 in 90% yield. Treatment of 6 with 1.1 eq. of iodine[14] in methylene chloride gave pure (E)-vinyliodide 7 in 88% yield.

Homologation of compound 7 by Ireland's one pot Swern-Grignard procedure[15] provided the alcohol 8 as a mixture of diastereomeric carbinols in 70% overall yield. Treatment of this mixture with the cuprate derived from 2-picoline[16] provided the compound 9 in 83% yield. Swern oxidation[17] of 9 afforded (1') a diastereomer of pulo'upone, in 82% yield.

Experimental

All operations were carried out under a nitrogen atmosphere with oven-dried glassware. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR Spectrophotometer. ^{1}H-NMR spectra and ^{13}C-NMR spectrum were obtained on a Bruker WM-360 FT NMR or at Bruker AM-300 FT NMR using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. High resolution mas spectra (HRMS) were determined on a VG 70-250S instrument. Column chromatography was performed using Merck Silica Gel 60 (230-400 mesh).

Preparation of (E)-3-tri-n-butylstannyl-prop-2-en-1-ol

A mixture of propargyl alcohol (4.82 g, 86 mmol), tri-n-butyltin hydride (30.1 mL, 112 mmol) and 2,2'-azo-bis(2-methyl propionitrile) as a catalyst, was stirred at 80 °C for 2 h. The reaction mixture was distilled under reduced pressure (125-127 °C and 0.075 mmHg), affording the desired (E)-3-tri-n-butylstannyl-prop-2-en-1-ol 15 g (50% yield)[7,8]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.75-0.95 (m,15H); 1.20-1.35 (m, 6H); 1.40-1.54 (m,6H); 4.10-4.20 (m,2H); 6.05- 6.25 (m,2H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 9.52; 13.59; 27.30; 29.09; 66.26; 128.29; 147.11; IR (film) 3310, 2924, 1603, 1464, 1376, 1292, 1180, 991, 874, 667 cm^{-1}.

Preparation of (E)-3-bromo-1-propen-tributylstannane 3

To a mixture of (E)-3-tri-n-butylstannyl-prop-2-en-1-ol (2.0 g, 5.8 mmol) and triphenylphosphine (2.3 g, 8.7 mmol) in methylene chloride (23 mL) at -20 °C, was added carbon tetrabromide (2.9 g, 8.7 mmol). The mixture was allowed to warm up to room temperature and stirred for 5 h and then

concentrated under reduced pressure to afford an oil. Hexane (15 mL) was added and the resulting precipitate was removed by filtration, affording a colorless solution which was concentrated under reduced pressure. The crude residue was chromatographed on silica gel by eluting with hexane to afford 1.3 g (55% yield) of (E)-3-bromo-1-propen-tributylstannane 3.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85-0.95 (m,15H); 1.25-1.40 (m,6H); 1.42-1.51 (m,6H); 3.95 (d, J= 6.6 Hz, 2H); 6.10 (dd, J_1=6.6 Hz, J_2=18.6 Hz, 1H); 6.28 (d, J=18.6 Hz,1H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 9.64; 13.65; 27.21; 29.01; 35.68; 135.03; 143.10; IR (film) 2955, 2923, 2870, 1591, 1463, 1438, 1376, 1171, 1120, 1072, 983, 876 cm^{-1}.

Alkylation of Sulfone 2

To a mixture of sulfone 2 (1.0 g, 2.38 mmol) in tetrahydrofuran (5 mL) at -78 °C under nitrogen, was added a solution of 2.9 M n-butyllithium in hexanes (0.90 mL, 2.62 mmol). After 30 min., hexamethylphosphoramide (1.6 mL, 9.20 mmol) was added, and the resulting mixture stirred for another 30 min. The bromide 3 (1.5 g, 3.70 mmol) was added and the reaction mixture stirred for 1 h at -78 °C. The reaction was quenched by addition of H_2O (5 mL) and extracted with ether. The extract was dried (Na_2SO_4), and the solvent evaporated under reduced pressure to afford a colorless oil. The crude product was chromatographed on silica gel by eluting with 20:1 hexane-ethyl acetate affording the (E)-vinylstannyl sulfone 4 (750 mg, 42%) and the starting material (350 mg, 35%).

Desulfonylation of (E)-Vinystannyl Sulfone 4

A mixture of compound 4 (600 mg, 0.80 mmol) in dry methanol (15 mL), sodium amalgam 6% (4 g, excess) and sodium hydrogen phosphate (1.46 g, 10.28 mmol) was stirred for 30 min at room temperature. Water (20 mL) was added and the resulting mixture was extracted with ether. The ether extract was dried (Na_2SO_4), and concentrated under reduced pressure to afford an oil. Chromatography on silica gel using hexane for elution afforded compound 5 (371 mg, 76%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.60 (q, J= 8.0 Hz, 6H); 0.90-1.05 (m,24H); 1.15-1.40 (m,9H); 1.40-1.60 (m,8H); 1.60-1.75 (m,2H); 1.75-1.90 (m,2H); 2.00-2.40 (m,4H); 2.45-2.60 (m,1H); 3.57 (dd, J_1= 10.1 Hz, J_2= 4.0 Hz, 1H);3.69 (dd, J_1= 10.1 Hz, J_2= 4.0 Hz, 1H); 5.55-5.75 (m,2H); 5.75-6.10 (m,2H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 4.69; 6.78; 9.62; 13.57; 24.67; 27.24; 29.17; 31.07; 33.16; 33.28; 35.03; 35.87; 37.77; 39.52; 42.65; 63.42; 127.10; 129.61; 130.51; 149.99; IR (film) 2954, 1598, 1459, 1415, 1378, 1238, 1102, 1009, 869, 786, 738 cm^{-1}; HRMS (EI, 70eV) calculated for $C_{28}H_{53}OSi^{120}Sn$ $(M-C_4H_9)^+$ 553.2903, found 553.2888.

Preparation of (E)-Vinylstannyl 6

To a solution of compound 5 (548 mg, 0.9 mmol) in tetrahydrofuran (10 mL), was added tetrabutylammonium fluoride (706 mg, 2.7 mmol) and stirred for 2 h at room temperature. This solution was concentrated under reduced pressure affording an oil which was chromatographed on silica gel by eluting with 20:1 hexane-ethyl acetate to give the compound 6 400 mg (90% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.80-0.95 (m,15H); 1.15-1.40 (m,9H); 1.40-1.60 (m,9H); 1.60-1.75 (m,2H); 1.76-1.95 (m,2H); 2.10-2.40 (m,4H); 2.32-2.45 (m,1H); 3.60-3.85 (m,2H); 5.59 (dt, J_1= 10.0 Hz, J_2= 2.0 Hz, 1H); 5.68 (dt, J_1= 10.0 Hz, J_2= 3.21 Hz, 1H); 5.80-6.10 (m,2H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 9.66; 13.58; 24.65; 27.24; 29.17; 30.96; 33.03; 33.23; 34.93; 35.47; 37.79; 39.53; 42.66; 63.64; 127.69; 129.82; 130.16; 149.60; IR (film) 3330, 3012, 2924, 1597, 1457, 1375, 1183, 1071, 991, 914, 869, 663 cm^{-1}; HRMS (EI, 70eV) calculated for $C_{22}H_{39}OSn$ $(M-C_4H_9)^+$ 439.2018, found 439.2022.

Preparation o (E)-Vinyl-iodide 7

A mixture of (E)-vinylstannyl 6 (400 mg, 0.81 mmol), iodine (1.0 g, excess) and methylene chloride (10 mL) at -78 °C, was stirred for 3 to 4 h until the temperature rose to -50 °C. The organic phase was washed with saturated sodium thiosulfate and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford an oil which was chromatographed on silica gel by eluting with 20:1 hexane-ethyl acetate affording (E)-vinyl-iodide 7 (235 mg, 88% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10-1.30 (m,3H); 1.30-1.55 (m,3H); 1.55-1.75 (m,2H); 1.76-1.95 (m,2H); 1.96-2.20 (m,4H); 2.28-2.45 (m,1H); 3.55-3.80 (m,2H); 5.45-5.60 (m,1H); 5.65-5.75 (m,1H); 6.00 (d, J= 14.34 Hz 1H); 6.40-6.60 (m,1H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 24.68; 30.82; 32.21; 32.86; 33.02; 35.07; 37.30; 39.47; 42.27; 63.12; 74.49; 129.32; 130.26; 146.52; IR (film) 3334, 3011, 2942, 1605, 1449, 1210, 1064, 942 cm^{-1}; HRMS (CI, NH_3) calculated for $C_{14}H_{21}OINH_4$ $(M+NH_4)^+$ 350.0977, found 350.0981.

Preparation of Compound 8

To a stirred solution of oxalyl chloride (27.5 μL, 0.32 mmol) in tetrahydrofuran (1.0 mL), at -78 °C under nitrogen, was added dimethyl sulfoxide (23.4 μL, 0.33 mmol). The solution was allowed to warm up to -35 °C, stirred for 3 min., then cooled to -78 °C. After the addition of the alcohol 7 (100 mg, 0.3 mmol) and tetrahydrofuran (0.5 mL), the reaction mixture was allowed to warm up to -35 °C and kept at that temperature for 15 min., triethylamine (0.21 mL, 1.52 mmol) was added and the reaction mixture was allowed to warm to room temperature, then cooled again to -78 °C. After dropwise addition of 3 M methyl magnesium bromide in tetrahydrofuran (0.5 mL, 1.51

mmol), the reaction mixture was stirred at -50 °C for 1 h, cooled to -78 °C, then carefully quenched with ethanol (0.25 mL) and a solution of NH_4Cl/NH_4OH (4:1 v/v; 0.5 mL). After addition of a larger amount of the solution of NH_4Cl/NH_4OH (4:1 v/v; 20 mL), the resulting mixture was extracted with ether. The ether extracts were dried (Na_2SO_4) and concentrated at reduced pressure to afford an oil which was chromatographed on silica gel by eluting with 10:1 hexane: ethyl acetate affording compound 8 (73.1 mg, 70% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10-1.20 (m,3H); 1.30-1.70 (m,9H); 1.75-1.90 (m,1H); 1.95-2.20 (m,4H); 2.35-2.45 (m,1H); 3.70-3.90 (m,1H); 5.55 (m,2H); 5.90-6.10 (m,1H); 6.40-6.60 (m,1H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 20.44; 21.26; 23.65; 24.28; 31.59; 32.28; 32.87; 33.10; 33.78; 33.99; 34.12; 34.57; 34.92; 35.13; 37.05; 37.18; 37.57; 38.79; 45.96; 46.47; 71.24; 71.48; 74.63; 128.83; 129.12; 130.97; 131.18; 146.37; 146.49; IR (film) 3368, 2942, 1605, 1450, 1208, 1063, 943 cm^{-1}; HRMS (CI, NH_3) calculated for $C_{15}H_{23}OINH_4$ $(M+NH_4)^+$ 364.1138, found 364.1137.

Preparation of Compound 9

The 2-picoline anion was previously prepared by addition of 2.9 M n-butyllithium in hexanes(725 μL, 2.10 mmol) to picoline (208 μL, 2.10 mmol) in tetrahydrofuran (2 mL) at room temperature. The resulting solution was cannulated to a suspension of copper cyanide (94 mg, 1.05 mmol) in tetrahydrofuran (2 mL) cooled at -78 °C, under nitrogen atmosphere. Addition of vinyl-iodide 8 (120 mg, 0.35 mmol) at -78 °C afforded a mixture that was stirred for 1 h. After addition of 5 mL of a solution of NH_4Cl/NH_4OH (4:1 v/v, the resulting mixture was extracted with ether, dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford an oil. The crude product was chromatographed on silica gel by eluting with 3:1 hexane: ethyl acetate to afford the desired coupled compound 9 (90 mg, 83%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23-1.07 (m,3H); 1.70-1.28 (m,8H); 1.90-1.70 (m,1H); 2.15-1.90 (m,5H); 2.20-2.50 (m,1H); 3.50 (d, J= 6.3 Hz, 1H); 3.70-3.85 (m,1H); 5.46-5.69 (m,4H); 7.08 (t, J= 6.4 Hz, 1H); 7.14 (d, J= 7.8 Hz, 1H); 7.57 (t, J= 7.4 Hz, 1H); 8.49 (d, J= 4.6 Hz, 1H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 20.65; 20.92; 23.64; 24.17; 30.36; 30.58; 31.62; 32.32; 32.97; 33.17; 34.25; 35.07; 35.76; 36.03; 37.23; 37.44; 38.80; 41.64; 45.98; 46.68; 71.32; 71.42; 121.02; 122.66; 127.47; 129.57; 129.72; 130.49; 130.79; 132.84; 136.31; 149.25; 160.91; IR (film) 3355, 3008, 1655, 1593, 1473, 1371, 1106, 968, 632 cm^{-1}; HRMS (EI, 70eV) calculated for $C_{21}H_{29}ON$ 311.2249, found 311.2249.

Preparation of compound 1'

To a stirred solution of oxalyl chloride (21 μL, 0.24 mmol) in tetrahydrofuran (1.0 mL) cooled to -78 °C, under nitrogen atmosphere, was added dimethyl sulfoxide (17.5 μL, 0.25 mmol). The reaction mixture was allowed to warm up to -35 °C, stirred for 3 min, then cooled again to -78 °C. After the addition of the alcohol 9 (70 mg, 0.225 mmol) in tetrahydrofuran (0.5 mL), the resulting reaction mixture was allowed to warm up to -35 °C. After 15 min the reaction mixture was treated with triethylamine (0.16 mL, 1.14 mmol), quenched by the addition of a solution of NH_4Cl/NH_4OH (4:1 v/v; 10 mL) and the resulting mixture extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford an oil which was chromatographed on silica gel by eluting with 4:1 hexane: ethyl acetate affording the diastereomer 1' of pulo'upone (57 mg, 82%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10-2.10 (m,10H); 2.10 (s,3H); 2.10-2.40 (m,4H); 3.48 (d, J= 6.5, 2H); 5.70-5.40 (m,3H); 5.76 (dt, J_1= 3.30 Hz, J_2= 9.97 Hz, 1H); 7.05-7.10 (m,1H); 7.12 (d, J= 7.84 Hz, 1H); 7.56 (m, J_1= 1.8 Hz, J_2=7.68 Hz, J_3= 7.68 Hz, 1H); 8.49 (d, J= 4.0 Hz, 1H); ^{13}C-NMR (75.46 MHz, $CDCl_3$) δ 24.31; 28.95; 29.24; 30.30; 32.30; 33.07; 37.53; 39.84; 40.53; 41.64; 56.93; 120.96; 122.54; 127.76; 128.65; 129.84; 132.13; 136.22; 149.23; 160.80; 213.11; IR (film) 2943, 1702, 1590, 1433, 1357, 1223, 971, 755 cm^{-1}; HRMS (EI, 70eV) calculated for $C_{21}H_{27}ON$ 309.2093, found 309.2093.

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References

1. Coval, S.J.; Scheeuer, P.J. *J. Org. Chem.* **1985**, *50*, 3025-3026.
2. Burke, S.D.; Piscopio, A.D.; Buchanan, J.L. *Tetrahedron Lett.* **1988**, *23*, 2757-2760.
3. Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T.R.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 5885-5888.
4. Sugahara, T.; Iwata, T.; Yamaoka, M.; Takano, S. *Tetrahedron Lett.* **1989**, *30*, 1821-1824.
5. Marino, J.P.; Long, J.K. *J. Amer. Chem. Soc.* **1988**, *110*, 7916-7917.
6. Marino, J.P.; Stengel, P.J.; Simonelli, F.; Ferreira, J.T.B., manuscript in preparation.
7. Ensley, H.E.; Buescher, R.R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404-408.
8. Slagle, J.D.; Huang, T.T.S.; Franzus, B. *J. Org. Chem.* **1981**, *46*, 3526-3530.
9. Bansal, R.; Cooper, G.F.; Corey, E.J. *J. Org. Chem.* **1991**, *56*, 1329-1332.

10. Simonelli, F. PhD Thesis 1992, presented at the Departamento de Química, Universidade Federal de São Carlos, São Carlos, Brazil.
11. Goodman, M.M.; Kung, M-P.; Kabalka, G.W.; Kung, H.F.; Switzer, R. *J. Med. Chem.* **1994**, *37*, 1535-1542.
12. Birkinshaw, T.N.; Holmes, A.B. *Tetrahedron Lett.* **1987**, *28*, 813-816.
13. Trost, B.M.; Arndt, H.C.; Strege, P.E.; Verhoeven, T.R. *Tetrahedron Lett.* **1976**, *39*, 3477-3478.
14. Jung, M.E.; Light, L.A. *Tetrahedron Lett.* **1982**, *23*, 3851-3854.
15. Ireland, R.E.; Norbeck, D.W. *J. Org. Chem.* **1985**, *50*, 2198-2200.
16. Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron* **1984**, *40*, 5005-5038.
17. Mancuso, A.J.; Huang, S.L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.

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