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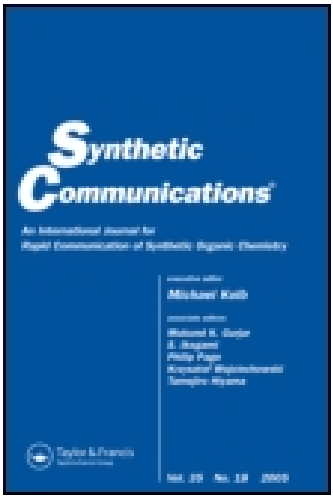

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Publication details, including instructions for authors and subscription information:
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Synthesis of 3-Alkyl-6-bromo-4,5-E-hexenoate

Mark W. Embrey [a], Thorsten E. Fisher [a] & John S. Wai [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories West Point, Pennsylvania, 19486, USA

Published online: 21 Aug 2006.

To cite this article: Mark W. Embrey, Thorsten E. Fisher & John S. Wai (1996) Synthesis of 3-Alkyl-6-bromo-4,5-E-hexenoate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:18, 3431-3442, DOI: 10.1080/00397919608003748

To link to this article: http://dx.doi.org/10.1080/00397919608003748

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SYNTHETIC COMMUNICATIONS, 26(18), 3431-3442 (1996)

SYNTHESIS OF 3-ALKYL-6-BROMO-4,5-*E*-HEXENOATE

Mark W. Embrey, Thorsten E. Fisher, and John S. Wai*

Department of Medicinal Chemistry, Merck Research Laboratories
West Point, Pennsylvania 19486, USA.

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Abstract: Two complementary routes for the preparation of 3-alkyl-6-bromo-4,5-*E*-hexenoate are reported.

Recently we undertook a systematic study of replacing polar, proteolytically susceptible peptide linkages with *trans*-olefin, alkane, ketomethylene, cyclopropane, and cyclobutane isosteres. The crucial synthetic intermediates required for one of the studies are 3-alkyl-6-bromo-4,5-*E*-hexenoates (alkyl = methyl, phenylethyl, benzyl), either in the racemic or enantiomerically pure form. Literature searches did not reveal any precedent for their preparations. Here we report two efficient, complementary routes for their synthesis.

Retrosynthetic analysis of the target molecule **1** was based on two well established methodologies (Scheme 1). The first employs ortho ester Claisen rearrangement of secondary allylic alcohol **2** to the corresponding

* To whom correspondence should be addressed

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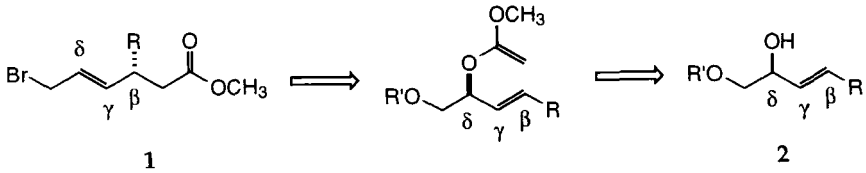
Scheme 1



hexenoate. The reaction transposes stereochemistry from the δ- to β-carbon, and migrates the *trans* olefin to the γ,δ-position in a specific manner. The second makes use of a Sharpless kinetic resolution to resolve racemic secondary allylic alcohol **2**. The undesired enantiomer is selectively epoxidized to provide the required isomer with excellent enantiomeric purity.

Since the protecting group for the primary hydroxy group in allylic alcohol **2** has to survive in acidic medium at 140 °C for the ortho ester Claisen rearrangement to proceed, and must be selectively deprotected in the presence of an ester moiety, we employed a *tert*-butyldiphenylsilyl (TBDPSi) protecting group. As such, reaction of *tert*-butyldiphenylsilyl-oxyacetaldehyde **3**[1] with *trans* 1-lithio-1-propene[2] in diethyl ether provided the required racemic secondary allylic alcohol **2a** (Scheme 2). Treatment of **2a** with stoichiometric amounts of (+)-diisopropyl tartrate and titanium isopropoxide, and a half equivalent of *tert*-butyl hydroperoxide at -20 °C in dichloromethane, provided the enantiomerically enriched S alcohol[3]. ^{1}H NMR ($CDCl_3$) of the Mosher ester of a sample of the enriched alcohol revealed only one methoxy signal at δ 3.59 versus a pair of signals for that of the racemic alcohol at δ 3.59 and 3.55. This indicated that the enriched alcohol was at least 96% enantiomerically

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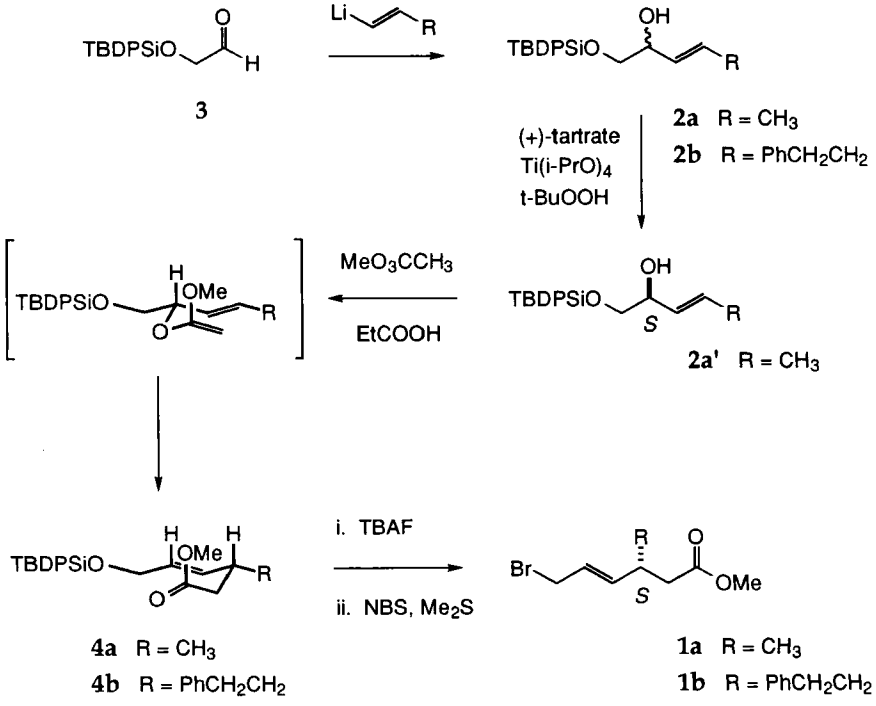
pure. The absolute stereochemistry assigned is based on Sharpless's established examples.[3] Enriched allylic alcohol **2a'** was then treated with trimethyl orthoacetate in the presence of propionic acid at 140 °C for 30 min.[4] The rearrangement proceeds, presumably via a chair-like transition state (Scheme 2), to provide stereospecifically methyl 3(*S*)-methyl-6-*tert*-butyl-diphenylsilyloxy-4,5-*E*-hexenoate (**4a**). The olefinic protons exhibited a coupling constant of 15.4 Hz, which is consistent with the assigned *E* configuration. Silyl group deprotection[5] and bromination[6] of the resultant primary allylic alcohol provided the bromide **1a** in good yield.[7,8]

Scheme 2



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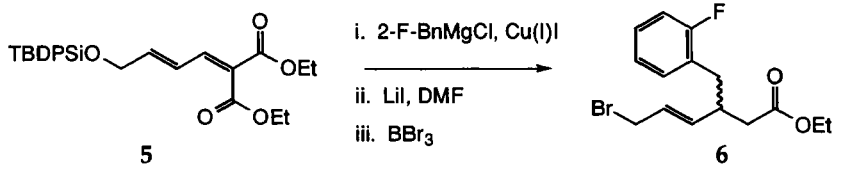
Similarly, the corresponding methyl 3-phenylethyl-6-bromo-4,5-*E*-hexenoate (**1b**) was prepared. The required *trans* 1-lithio-4-phenyl-1-butene was obtained by transmetallation of *trans* 1-tri-*n*-butylstannyl-4-phenyl-1-butene with *n*-butyllithium.[9]

Employing the route just described, preparation of a 3-benzyl derivative such as **6** would be problematic. The required *trans* 1-lithio-2-benzylethene is anticipated to equilibrate to 3-lithio-3-phenyl-1-propene. Recently Kasatkin *et. al.* reported that, in the presence of a catalytic amount of copper(I) iodide, Grignard reagent added to diethyl *E*-(2-butenylidene)malonate predominately in an 1,4-manner.[10] Adapting to our need, diethyl *E*-(4-*tert*-butyldiphenylsilyloxy-2-butenylidene)-malonate (**5**)[11,12] was prepared and treated with 2-fluorobenzylmagnesium chloride in the prescence of 5% of copper(I) iodide (Scheme 3). The 1,4-addition product was then mono-decarboxylated,[10] and the resultant allyl silyl ether was brominated[13] to provide **6** in racemic form.

Scheme 3



5 6

In conclusion, we have developed efficient routes for the preparation of optically highly enriched 3-methyl and 3-phenylethyl-6-bromo-4,5-*E*-hexenoates,[7] and a racemic 3-benzyl-4,5-*E*-hexenoate. These bromides have been used successfully to N-alkylate lactams and amides.

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Experimental

1-*tert*-Butyldiphenylsilyloxy-2(*S*)-hydroxy-3,4-*E*-pentene (2a').

To a suspension of lithium metal (2.2 g of 30% dispersion in mineral oil, equivalent to ~0.67 g lithium; washed four time with anhydrous ether) in diethyl ether (26 mL, freshly distilled from sodium benzophenone ketal) at -35 °C under an atmosphere of argon, *trans* 1-bromo-propene (2.34 g, 19 mmol) was added dropwise. After stirring at -35 °C for 3 h, the resultant mixture was drawn into a 50 mL gas tight syringe. The mixture was then injected into a flame dried flask through a Teflon syringe filter (25 mm diameter, 0.45 μm pore size). The clear colorless filtrate was cooled to -78 °C, and a solution of *tert*-butyldiphenylsilyloxyacetaldehyde (**3**)[1] (4.12 g, 13.8 mmol) in ether (10 mL) was added. The resultant mixture was stirred at 0 °C overnight, quenched with addition of dilute aq. HCl, and extracted with ether. The extract was washed with brine (3 times), dried (MgSO4), filtered and concentrated *in vacuo* to provide 4.4 g (94%) of racemic 1-*tert*-butyl-diphenylsilyloxy-2-hydroxy-3,4-*E*-pentene (**2a**) as clear colorless oil. The oil was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.39 (m, 6 H), 5.73 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.38 (ddd, *J* = 15.4, 6.8, 1.5 Hz, 1H), 4.18 (br m, 1H), 3.64 (dd, *J* = 10.0, 3.7 Hz, 1 H), 3.51 (dd, *J* = 10.0, 8.1 Hz, 1H), 2.63 (br s, 1 H), 1.66 (d, *J* = 6.6 Hz, 3H), 1.07 (s, 9H).

To a cold (-20 °C) mixture of the above racemic allylic alcohol **2a** (20.38 g, 59.8 mmol), (+)-diisopropyl tartrate (16.8 g, 71.8 mmol), freshly activated powdered 3Å molecular seives (3.5 g), and anhydrous methylene chloride (430 mL) under an atmosphere of dry argon, titanium(IV) isopropoxide (17.7 mL, 59.8 mmol) was added. The resultant slurry was stirred at -20 °C

for 0.5 h. Then a solution of *tert*-butylhydroperoxide (7.2 mL, 5 M) in isooctane was added. The reacting mixture was stirred at -20 °C for 18 h, treated with a solution of iron(II) sulfate and citric acid, and then Celite®. The resultant slurry was filtered. The filtrate was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to column chromatography on silica gel, eluted with 15% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided **2a'** (8.85 g, 86.8% recovery of the required enantiomer). A sample of the optically enriched allylic alcohol and the racemic alcohol were separately treated with Mosher acid chloride. Only one diastereomer was observed with the ^1H NMR spectrum of the Mosher ester derived from the enriched sample, suggesting that the enriched allylic alcohol is at least 96% enantiomerically pure. Anal. Calcd. for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 74.11; H, 8.53.

Methyl 3(*S*)-methyl-6-bromo-*E*-4,5-hexenoate (1a).

The allylic alcohol **2a'** (9.6 g, 28 mmol), *n*-propionic acid (21 g, 28 mmol), trimethyl orthoacetate (280 mL) was immersed into an oil bath of 140 °C for 30 min. Distillate was collected (~90 mL). The resultant product mixture was concentrated *in vacuo* and the residue subjected to column chromatography on silica gel eluting with 5% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided 5.3 g (48%) of methyl 3(*S*)-methyl-6-*tert*-butyldiphenylsilyloxy-*E*-4,5-hexenoate (**4a**) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.39 (m, 6 H), 5.59 (dd, J = 15.4, 5.4 Hz, 1 H), 5.53 (dt, J = 15.4, 4.1 Hz, 1 H), 4.15 (br d, J = 3.4 Hz, 2 H), 3.65 (s, 3 H), 2.68 (m, 1 H), 2.30 (m, 2 H), 1.45 (s, 9 H), 1.03 (d, J = 7 Hz, 3 H). A solution of **4a** (1.6 g, 4 mmol) in THF (20 mL) was treated

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with a solution of tetra-*n*-butylammonium fluoride (10 mL, 1 M) at room temp. for 1 h. The reaction mixture was concentrated onto silica gel and loaded directly onto a column of silica gel and eluted with 2% methanol in chloroform. Collection and concentration of appropriate fractions provided 0.50 g (87%) of methyl 3(*S*)-methyl-6-hydroxy-*E*-4,5-hexenoate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (br m, 2 H), 4.16 (br t, *J* = 5 Hz, 2 H), 3.67 (s, 3 H), 2.71 (br m, 1 H), 2.3 (m, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H).

To a suspension of N-bromosuccinimide (0.52 g, 2.9 mmol) in CH_2Cl_2 (10 mL) at 0 °C, dimethyl sulfide (0.25 mL, 3.4 mmol) was added dropwise over a period of 10 min. The resultant yellow slurry was cooled to -25°C and a solution of the above primary allylic alcohol (0.35 g, 2.2 mmol) in dichloromethane (2 mL) was added. The reaction mixture was stirred at 0 °C for 3 h., diluted with pentane, and washed with ice cold water and brine. The organic extract was filtered through a plug of silica gel (0.8 g) eluting with dichloromethane. Concentration of the eluent provided 0.34 g (98%) of methyl 3(*S*)-methyl-6-bromo-*E*-4,5-hexenoate (**1a**) as semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (br m, 2 H), 3.93 (m, 2 H), 3.67 (s, 3 H), 2.72 (m, 1 H), 2.33 (dd, *J* = 14.9, 6.9 Hz, 1 H), 2.29 (dd, *J* = 14.9, 6.9 Hz, 1 H), 1.06 (d, *J* = 6.8 Hz, 3 H); Anal. Calcd. for $C_8H_{13}O_2Br$: C, 43.46; H, 5.93. Found: C, 43.76; H, 5.53.

1-*tert*-Butyldiphenylsilyloxy-2-hydroxy-6-phenyl-3,4-*E*-hexene (2b).

A mixture of 4-phenyl-1-butyne (4.0 g, 31 mmol), tri-*n*-butyltin hydride (11.6 g, 40 mmol), AIBN (0.5 g), and benzene (60 mL) was heated under reflux for 5 h. The resultant mixture was concentrated *in vacuo*. The residue was subjected to column chromatography. Collection and concentration of appropriate fractions provided a 85:15 mixture of *trans* 1-

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tri-*n*-butyl-stannyl-4-phenyl-1-butene and its regioisomer. A cold (-78 °C) solution of the mixture of *trans* 1-tri-*n*-butylstannyl-4-phenyl-1-butene (9.33 g, 22 mmol) in anhydrous THF (freshly distilled from sodium benzophenone ketal) was treated with a solution of *n*-butyllithium in hexanes (7.6 mL, 2.5 M, 19 mmol, 0.85 equiv). The mixture was stirred at -78 °C for 1 h, and at -50 °C for 1 h. The resultant solution was cooled back to -78 °C, and treated with a solution of *tert*-butyldiphenylsilyloxyacetaldehyde in THF. The resultant mixture was stirred at 0 °C overnight and worked up as described for **2a**.

Ethyl 6-bromo-3-(2-fluorobenzyl)-*E*-4,5-hexenoate (6).

To a cold (-50 °C) solution of diethyl (4-*tert*-butyldiphenylsilyloxy-*E*-2,3-butenylidene)-malonate[1, 11, 12] (6.24 g, 13.36 mmol) in anhydrous ether (36 mL, freshly distilled from sodium benzophenone ketal) under an atmosphere of argon, was added copper(I) iodide (127.6 mg, 0.67 mmol) followed by dropwise addition of 2- fluorobenzylmagnesium chloride [10 mL, approx. 15.8 mmol, prepared by dropwise addition of 2-fluorobenzyl chloride (3.0 mL, 25.2 mmol) to magnesium metal (729.5 mg, 30.0 mmol) in anhydrous ether (16 mL) under an atmosphere of argon. The resultant solution was stirred for 1 hour before use]. The reaction mixture was warmed to room temp. over 3.5 hours and then quenched with 8% aq. HCl and extracted with ether (3 times). The organic extracts were washed with 5% $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with 25% ether in hexane. Collection and concentration of appropriate fractions provided 3.09 g (40%) of diethyl (4-*tert*-butyldiphenylsilyloxy-1-(2- fluorobenzyl)-*E*-2,3-butenyl)malonate. ^1H NMR

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(300 MHz, $CDCl_3$) δ 7.60 (m, 4H), 7.38 (m, 6H), 7.15 (m, 2H), 7.00 (m, 2H), 5.70 (dd, *J* = 15.3, 9.3 Hz, 1H), 5.46 (dt, *J* = 15.3, 4.6 Hz, 1H), 4.18 (m, 4H), 4.02 (d, *J* = 4.6 Hz, 2H), 3.43 (d, *J* = 8.3 Hz, 1H), 3.15 (m, 1H), 2.88 (dd, *J* = 13.4, 4.9 Hz, 1H), 2.77 (dd, *J* = 13.4, 9.0 Hz, 1H), 1.25 (m, 6H), 1.01 (s, 9H).

A mixture of diethyl (4-*tert*-butyldiphenylsilyloxy-1-(2- fluorobenzyl)-*E*-2,3-butenyl)malonate (3.09 g, 5.36 mmol) and LiI (2.17 g, 16.2 mmol) in DMF (23 mL) was heated at 150 °C for 10 hours. Water (95 μL, 5.3 mmol) was added after five hours, and LiI (0.85 g, 6.35 mmol) was added after seven hours. The product mixture was concentrated *in vacuo* and the residue partitioned between ether and water. The organic extracts were washed with water, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with 15% ether in hexane. Collection and concentration of appropriate fractions provided 1.04 g (39%) of ethyl 6-*tert*-butyldiphenyl-silyloxy-3-(2-fluorobenzyl)-*E*-4,5-hexenoate. ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.39 (m, 6H), 7.16 (m, 2H), 7.01 (m, 2H), 5.62 (dd, *J* = 15.4, 7.6 Hz, 1H), 5.50 (dt, *J* = 15.4, 4.4 Hz, 1H), 4.09 (m, 6H), 2.91 (m, 1H), 2.71 (d, *J* = 7.3 Hz, 2H), 2.39 (dd, *J* = 15.1, 6.1 Hz, 1H), 2.31 (dd, *J* = 15.1, 8.2 Hz, 1H), 1.22 (t, 3H), 1.03 (s, 9H).

To a cold (0 °C) solution of ethyl 6-*tert*-butyldiphenyl-silyloxy-3-(2-fluoro-benzyl)-*E*-4,5-hexenoate (940 mg, 1.86 mmol,) in anhydrous methylene chloride (5 mL), a solution of boron tribromide (2.2 mL, 1 M) in methylene chloride was added over a period of three minutes. The reaction was stirred at room temp. for 45 min., diluted with ether, and quenched with saturated aq $NaHCO_3$. The ethereal extract was washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting

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with 15% ether in hexane. Collection and concentration of appropriate fractions provided 330 mg (54%) of ethyl 6-bromo-3-(2-fluorobenzyl)-*E*-4,5-hexenoate (**6**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (m, 4H), 5.64 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.86 (d, *J* = 6.6 Hz, 2H), 2.90 (m, 1H), 2.73 (d, *J* = 7.1 Hz, 2H), 2.37 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); Anal. Calcd. for $C_{15}H_{18}O_2BrF$: C, 54.73; H, 5.51. Found: C, 54.64; H, 5.73.

Acknowledgments: We would like to thank Drs. S. D. Young and G. D. Hartman for encouragement, and our analytical group for elemental analysis.

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References and footnotes

1. Shiao, M.-J.; Yang, C.-Y.; Lee, S.-H.; Wu, T.-C. *Synth. Commun.* **1988**, *18*, 359. The reported procedure was adapted to provide large quantity of the silyloxyacetaldehyde **3** without chromatography. To a cold (-78 °C) solution of *tert*-butyldiphenylsilyl chloride (89.2 g, 325 mmol) and DMAP (3.97 g, 32.5 mmol) in THF (530 mL) stirred with a mechanical stirrer, a solution of solketal (40.3 mL, 324 mmol) and triethylamine (50 mL, 359 mmol) in THF (30 mL) was added dropwise over a period of 40 min. The reaction was allowed to warm to room temp and stirred overnight. The white slurry was filtered and the white solid washed with hexane (five times). The combined filtrate was concentrated, and the residue triturated with hexane, and was then filtered. The filtrate was concentrated *in vacuo* to provide 124 g of the crude silyl ether as clear colorless viscous oil. Without further purification, a solution of the above silyl ether (26.7 g, 72 mmol) and aq. HCl (72 mL, 2 M) in THF (360 mL) was stirred at room temp

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overnight. The resultant mixture was concentrated *in vacuo* to remove most of the THF. The residue was diluted with ethyl acetate, and washed successively with sat. $NaHCO_3$ and brine. The organic extract was dried ($MgSO_4$), filtered, concentrated *in vacuo*, triturated with hexane, and cooled to 0 °C. The white solid was filtered, washed with ice-cold hexanes, stored *in vacuo* overnight, to provide 22 g (93%) of analytical pure 1-*tert*-butyldiphenylsilyloxy-2,3-propanediol. Oxidation to the aldehyde **3** was carried out as reported.

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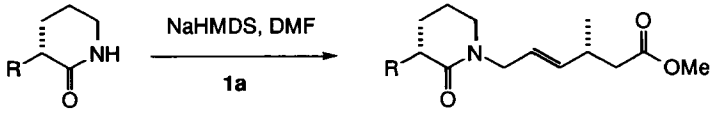
7. Reaction of an optically pure lactam with bromide **1a** led to a single diastereomer. The ^1H NMR spectrum of which showed only a set of signals for the allylic protons (CH=CHC**H**$_2$N), versus the two sets observed with products derived from alkylation with racemic **1a**.[8] This indicated that the enantiomerically enriched **1a** was >96% optically pure.



8. Racemic **1a** was prepared in a similar manner with omission of the kinetic resolution step. Furthermore, a much cheaper mixture of *trans*

and *cis* 1-bromo-1-propene could be used instead of the more costly pure *trans* 1-bromo-1-propene. After the Claisen rearrangement, no spectroscopic difference was observed between products derived from pure *trans* propene versus those from the *trans/cis* mixture.

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(Received in the USA 31 March 1996)

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