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Enantiospecific Routes to 3,4 Disubstituted Azetidinones

Michael Kahn[1] and Kagari Fujita

University of Illinois at Chicago
Department of Chemistry M/C 111
Box 4348
Chicago, Illinois 60680

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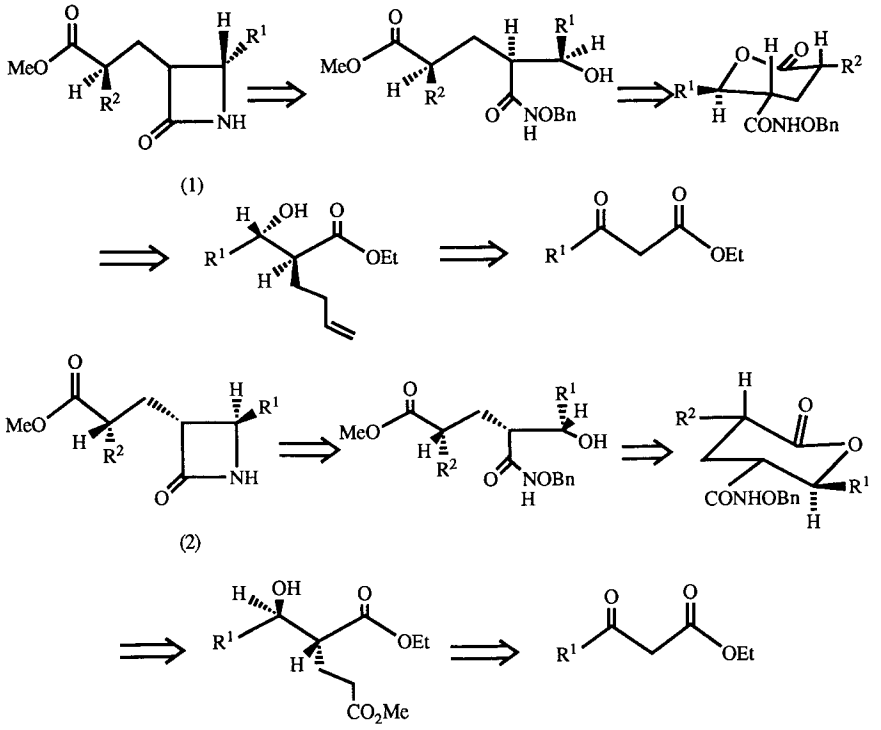
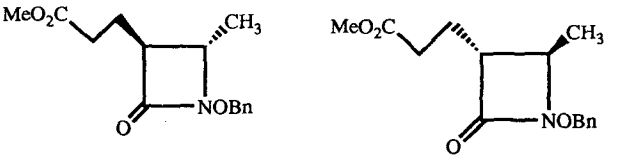
Abstract: Enantiospecific routes to 3,4 disubstituted azetidinones are outlined which commence with readily available β-ketoester precursors.

During the course of our investigations of the synthesis of β-turn mimetics,[2] we required a facile enantiospecific entry into (3S), (4S) and (3R), (4R) substituted azetidinones of type 1 and 2, to provide access to mimetic structures of both the natural (L) and unnatural (D) configurations.[3] We have investigated two conceptually analagous routes in this regard. Both proceed from readily available β-ketoester precursors, and rely on an enzymatic reduction to generate the required stereogenicity. The retrosynthetic strategies are outlined in Scheme 1.

Scheme 1



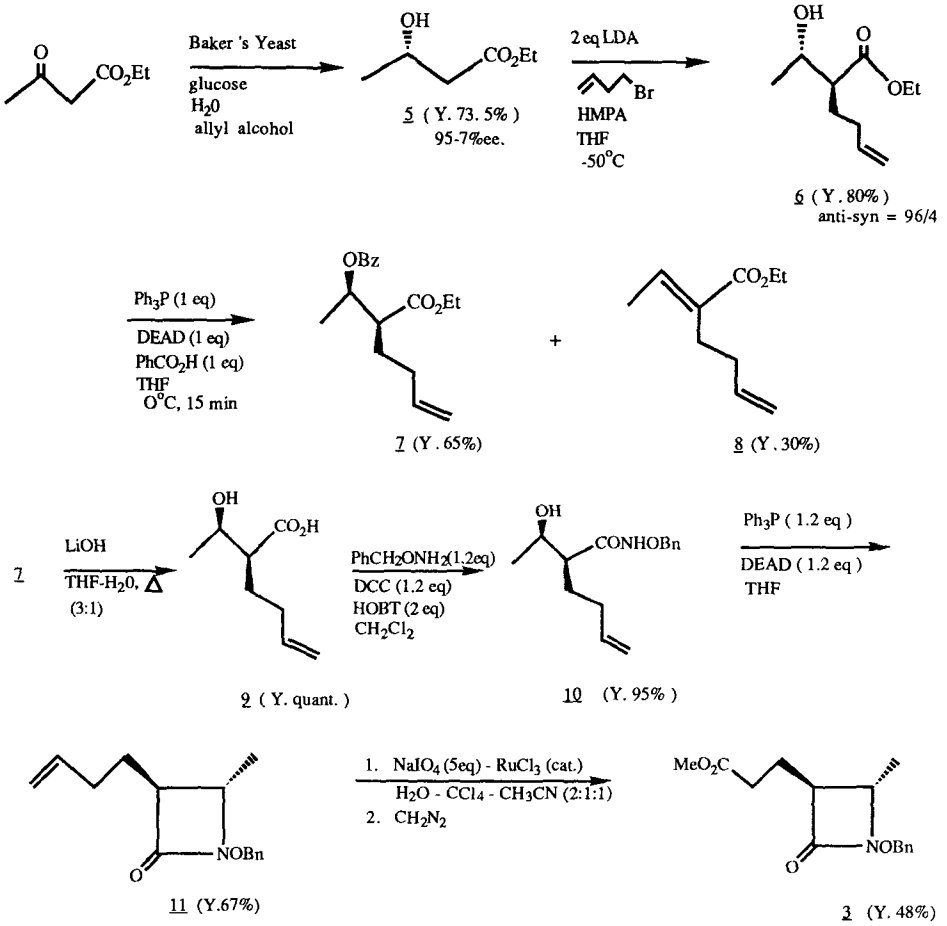
This strategy allows for the ready assemblage of the azetidinone intermediates in either enantiomeric form from a common precursor. In the event, we wish to report a key feasibility study in this regard involving the syntheses of both (3S), (4S) and (3R), (4R)-1-benzyloxy-3-methylcarbonylethyl-4-methyl-azetidin-2-one (3 and 4 respectively).



(3) (4)

The synthesis of 3 (Scheme 2) begins with the well known baker's yeast reduction of ethylacetoacetate [4] to provide S-ethyl-3-hydroxybutanoate 5, which was subsequently

Scheme 2

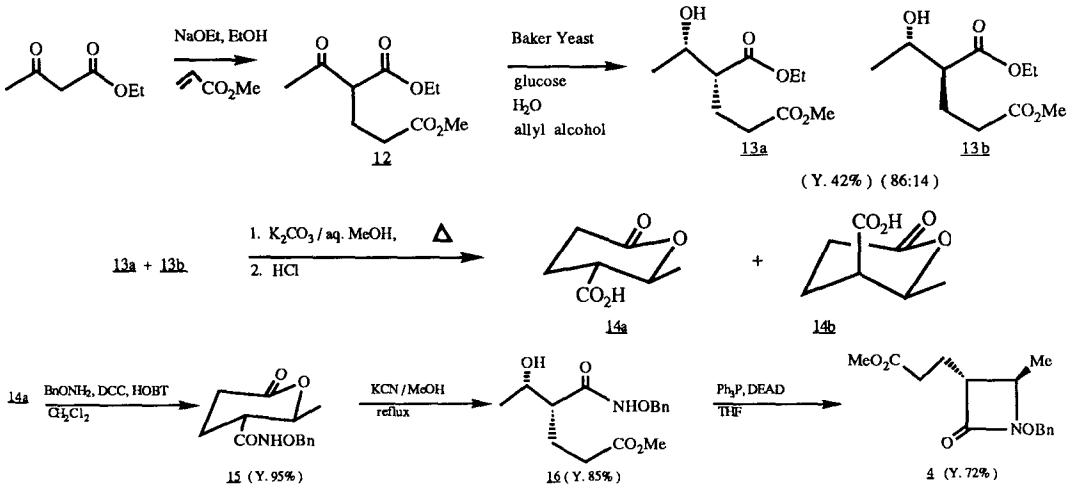


alkylated with 4-bromobutene using the Frater protocol,[5] to provide 6. Mitsonobu inversion[6] provided 7 along with by-product 8 which were readily separable by flash chromatography. Hydrolysis and subsequent hydroxamic acid formation proceeded smoothly to afford 10, which was converted to azetidinone 11 using the procedure of Miller.[7] Oxidative cleavage of the olefin[8] and esterification provides 3.

The synthesis of 4 (Scheme 3) commences with the Michael addition of ethylacetoacetate to methyl acrylate to provide 12.[9] The yeast reduction of 12, as anticipated from literature precedence[10] provided an 86:14 ratio of

diasteriomeric alcohols 13a and 13b, both in greater than 99% enantiomeric excess.[11] Saponification and lactonization provided 14a and 14b which were readily separated at this stage by flash chromatography. The major diasteriomer 14a was carried on in an analogous fashion to that previously outlined to provide 4.

Scheme 3



Several points should be emphasized. The enantiospecificity achieved as determined by ^{19}F NMR spectra of the derived Mosher esters[12] is exceedingly high (>95% for 5 and >99% for 13a). Both syntheses commence with readily available β-keto ester precursors. Finally, the intermediate lactones of type 15 provide not only a mechanism for differentiation of the two ester functionalities, but also via alkylation a method for the stereocontrolled introduction of the R^2 substituent.[13] In summary, an efficacious, versatile, highly enantiospecific route to key intermediates for the construction of β-turn mimetic precursors is outlined.

Experimental

Synthesis of S-ethyl-hydroxybutanoate (5)

To a 1L. round bottomed flask was added H_20(400ml.), baker's yeast(40g.) and glucose(20g.). The suspension was stirred vigorously for 1h. at which time allyl alcohol(0.4ml.) was added. After an additional 1h. ethyl acetoacetate (2.60g., 20mmol.) was added and the suspension was stirred for 14h. Celite(3g.) was added and the mixture was filtered through celite. The aqueous phase was saturated with NaCl and extracted with $CHCl_3$ (500ml. x 10). The organic phase was dried over $MgSO_4$, evaporated and the residue was purified on Si-gel to provide 1.94g. (73.5%) of 5 as a colorless oil.

The product was derivatized as its R-MTPA ester (MTPACl, pyridine, DMAP, rt.) and analyzed by ^{19}F-nmr (376.4MHz, $CDCl_3$) and HPLC(Si-gel 60-254, 5μM, 5 x 250 (mm. x mm.), solvent gradient; hexane: iso-PrOH 100/0 ---- hexane: iso-PrOH 90/10 during 20 mins.)

by HPLC:	Retention time		
	8.30 mins.	97.5	95% ee.
	10.10 mins.	2.5	

400 MHz pmr ($CDCl_3$, TMS, δ, ppm.)

1.22(d,3H, J=6.16Hz), 1.27(t,3H, J=7.1Hz), 2.41(dd,1H, J=8.66, 16.49Hz), 2.49(dd,1H, J=3.55, 16.49Hz), 3.09(S,1H, OH), 4.16(qr, 2H, J=7.1Hz), 4.18(dd.qr, 1H, J=3.55, 8.66Hz(for d), 6.16Hz(for qr)

100MHz cmr ($CDCl_3$, TMS, δ, ppm.)

14.11, 22.35, 42.69, 60.62, 64.18, 172.93

IR ($CHCl_3$, $cm.^{-1}$)
3400, 2960, 2940, 1735

Synthesis of 2S, 1'S-ethyl-2-(1'hydroxyethyl)-5-hexenoate (6)

5(1.69g;12.8mmol.) was treated with 2eq. of LDA(24.8mmol.) in THF at -50°C for 1h. 4 bromobutene (3.35g.;24.8mmol.) and HMPA(10.8ml.; 62mmol.) were added to the reaction mixture at -50°C. The mixture was stirred to ambient temp. and then overnight. 6N HCl (5ml.) was added, the mixture was extracted with $CHCl_3$, and the organic phase was dried, concentrated and the residue purified on Si-gel to afford 1.84g. (80%) of 6 as a pale yellow oil.

400 MHz pmr ($CDCl_3$, TMS, δ, ppm.)
1.25(d,3H,J=6.4Hz), 1.28(t,3H,J=7.16Hz), 1.56-1.72(m,1H), 1.74-1.88(m,1H), 2.38 2.45(m,2H), 2.52(ddd,1H,J=0.5,7.68,8.40Hz), 3.05(s,1H,OH), 3.94 d.qr,1H,J=7.68Hz (for d), 6.4Hz (for q)), 4.20(qr,2H,J=7.16Hz), 5.10(dd,1H,J=3.08,17.09Hz), 5.76(dddd,1H,J=5.92,7.44,10.2, 17.09Hz)

100MHz cmr ($CDCl_3$, δ, ppm.)
14.04, 22.33, 28.40, 32.35, 51.91, 60.52, 68.30, 115.23, 132.47, 172.78

IR ($CHCl_3$, cm^{-1})
3400, 2940, 2860, 1735, 990, 910

Synthesis of 2S, 1'R-ethyl-(1'-benzoyloxyethyl)-5-hexenoate (7)

To a solution of 6 (404mg.; 2.17mmol.) at 0° was added, Ph_3P (triphenylphosphine) (569mg.; 2.17mmol.) $PhCO_2H$ (265mg.; 2.17mmol.) and DEAD (diethylazodicarboxylate) (378mg.; 2.17mmol.). After 15min., H_20(0.5ml.) was added and the solvent was evaporated. The residue was purified on Si-gel to yield 400mg. (65%) of 7, along with 110mg. (30%) of elimination product 8.

Spectral data for 7

400MHz pmr ($CDCl_3$, TMS, δ, ppm)
1.26 (d, 3H, J=7.2Hz), 1.39 (d, 3H, J=6.2Hz), 1.62-1.74 (m, 1H), 1.82-1.93 (m, 1H), 2.01-2.09 (m,1H), 2.10-2.21 (m, 1H), 2.76 (ddd, 1H, J=5.92, 7.06, 7.44Hz), 4.16 (qr, 2H, J=7.2Hz), 5.01 (dd, 1H, J=3.08, 10.2Hz), 5.08 (dd, 1H, J=3.08, 17.09Hz), 5.37 (d.qr, 1H, J=6.2Hz(for qr), 7.06Hz (for d)), 5.78 (dddd, 1H, J=5.92, 7.44, 10.2 17.0Hz) 7.39-7.42 (m, 2H), 7.51-7.58 (m, 1H), 8.1-8.6 (m, 2H)

100MHz cmr (CDCl, TMS, ppm.)
13.85, 17.50, 27.55, 29.55, 49.95, 60.55, 71.04, 115.50, 128.32, 128.85, 129.55, 130.55, 132.95, 134.52, 137.41, 165.70, 172.92

Synthesis of 2S, 1'R-2-(1'-hydroxyethyl-5-hexenoic acid (9)

A solution of 7 (950mg.; 5.1mmol.) and LiOH (322mg.; 7.7mmol.) in THF (15ml.) and H_20 (5ml.) was refluxed for 12 h. The solution was cooled to 0°C and was acidified with 6N HCl (2ml.). The mixture was evaporated and the residue was purified on Si-gel to provide 751mg. (93%) of 9 as an oil.

400MHz pmr ($CDCl_3$,TMS, δ, ppm.)
1.24(d, 3H, J=6.44Hz), 1.53-1.72(m, 1H), 1.73-1.89(m, 1H), 1.96-2.10(m, 1H), 2.10-2.22(m, 1H), 2.54(ddd, 1H, J=4.52, 4.84, 11.2Hz), 4.09(d.qr, 1H, J=4.84Hz (for d), 6.44Hz(for qr)), 5.02(dd, 1H, J=3.08, 10.2Hz), 5.07(dd, 1H, J=3.08, 17.09Hz), 5.81(dddd, 1H, J=5.92, 7.44, 10.2, 17.09Hz), 7.50 (br.s, 2H, COOH, OH)

100MHz cmr ($CDCl_3$), δ, ppm.)
20.29, 26.52, 31.65, 51.57, 68.19, 115.30, 137.64, 179.54

IR (CHCl, cm^{-1})
3400, 3010, 1710, 1650

Synthesis of 2S, 1'R-N-benzyloxy-2(1'hydroxyethyl)-5-hexenoic hydroxamate (10)

To a solution of 9(193mg.;1.22mmol.) and 0-benzylhydroxylamine(165mg.;1.34mmol.), in CH_2Cl_2 was added DCC (dicyclohexylcarbodimide) (276mg.;1.34mmol.) and HOBT (1thydroxybenzotriazole) (330mg.; 2.44

mmol.). The reaction mixture was stirred overnight and solvent removed in vacuo. The residue was purified on Si-gel to give 305mg. (95%) of 10 as a white crystalline solid (mp 103-5°C)

400MHz pmr ($CDCl_3$, TMS, δ, ppm)

1.24 (d, 3H, J=6.4Hz), 1.49-1.62(m, 1H), 1.62-1.72 (m,1H), 1.78-1.98 (m, 2H), 2.48 (ddd, 1H, J=4.12, 4.55, 11.2Hz), 2.57 (br.s, 1H, OH), 4.01 (d. qr, 1H, J=4.55Hz (for d), 6.4Hz (for qr)), 4.86 (d, 1H, 11.5Hz), 4.93, (d, 1H, J=11.5Hz), 5.02 (dd, 1H, J=3.08, 10.2Hz), 5.09 (dd, 1H, J=3.08, 17.09Hz), 5.81 (dddd, 1H, J=5.92, 7.44, 10.2, 17.1Hz), 7.28-7.54 (m, 5H)

100MHz cmr ($CDCl_3$, δ, ppm.)

19.63, 25.49, 31.49, 48.88, 68.20, 78.12, 115.03, 128.46, 128.64, 129.09, 135.17, 137.83, 172.23

IR ($CHCl_3$, cm^{-1})

3420, 3040, 1680, 1520, 1480, 1425, 1020, 990, 925

Synthesis of 3S, 4S-1-benzyloxy-3 (3-butenyl)-4-methylazetidin-2-one (11)

A solution of 10 (315mg.; 1.2mmol.), Ph_3P (367mg.; 1.4mmol.) and DEAD (243 mg.; 1.4mmol.) in THF was stirred for 15 h. The solvent was removed in vacuo and the residue was purified on Si-gel to yield 198mg. (67%) of 10 as a colorless oil.

400MHz pmr ($CDCl_3$, TMS, δ, ppm.)

1.18 (d, 3H, J=6.08Hz), 1.52-1.62 (m, 1H), 1.72-1.84 (m, 1H), 2.04-2.14 (m, 2H), 2.42 (ddd, 1H,J=2.05Hz for trans-β-lactam ring coupling), 3.24 (d, qr, 1H, J=2.05 (for d), 6.08Hz (for qr)), 4.92 (d, 1H,J=12Hz), 4.95 (d, 1H, J=12Hz), 5.04 (dd, 1H, J=3.1, 10.2Hz), 5.09 (dd, 1H, 3.1, 17.10Hz), 5.72 (dddd, 1H, J=5.92, 7.44, 10.2, 17.1Hz), 7.30-7.48 (m, 5H)

100MHz cmr ($CDCl_3$, δ, ppm)

17.25, 25.55, 32.08, 51.69, 78.18, 117.18, 128.56, 128.58, 128.96, 129.28, 129.33, 134.15, 135.47, 165.75

Synthesis of 3S, 4S-1-benzyloxy-3-methoxycarbonylethyl-4-methylazetidin-2-one (3)

11 (44mg.;0.18mmol.) and $NaIO_4$(192mg.;0.9mmol.) were suspended in a mixture of H_2O-CCl_4-CH_3CN (2:1:1 total 4ml.). A catalytic amount of $RuCl_3$ was added and the suspension was vigorously stirred overnight. AcOEt(20ml.) and a small amount of activated charcoal was added and the suspension was filtered through celite. Water(5ml.) was added and the organic phase was separated. The aqeous phase was extracted with AcOEt and the combined organic phase was dried over $MgSO_4$ and the solvent removed in vacuo. To the residual oil was added Et_2O(5ml.) and MeOH(1ml.). An ethereal solution of diazomethane was added and the solution was stirred for 2h. The solvent was removed and the residual oil was purified on Si-gel to provide 24mg. (48%) of 3 as an oil.

400MHz pmr ($CDCl_3$, TMS, δ, ppm.)

1.18(d,3H,J=6.44Hz), 1.72-1.86(m,2H), 2.46(ddd,1H,J=2.08Hz,4.1Hz,9.98Hz), 2.38-2.51(m, 2H), 3.23 (d.qr,1H,J=2.08Hz (for d), 6.44Hz (for q),3.64 (s,3H), 4.92(d,1H,J=11.3Hz), 4.96(d,1H,J=11.3Hz), 7.32-7.48(m,5H)

100MHz cmr ($CDCl_3$, TMS, δ, ppm.)

20.14, 22.28, 31.77, 41.10, 51.61, 68.12, 77.34, 127.92, 128.30, 128.37, 135.20, 168.23, 174.24

phenyl ring appears as 4 carbons underlined

IR ($CDCl_3$, cm^{-1})

2940, 1780, 1735, 1640, 1470, 1380, 1250, 1110

MS (EI, m/z)

203 (3.65%, M^+-74 [CH_3COOCH_3]), 149 (29.9%, right half), 137.2 (5.4% bottom half), 129 (29.8%, left half +1), 91.2 (C_7H_7)

Synthesis of 4R, 5S-methyl-4-ethoxycarbonyl-5-hydroxyhexanoate (13a) and 4S, 5S-methyl-4-ethoxycarbonyl-5-hydroxyhexanoate (13b)

In a 1L. round bottomed flask was placed H_2O(400ml.), baker's yeast (Fleishmann's) and glucose (20g.).

The mixture was stirred for 1h. and allyl alcohol (0.4ml.) was added. After an additional 1h., 12(4.32g.;20mmol.) was added to the mixture and stirred overnight. The mixture was filtered through celite. The aqueous solution was extracted with $CHCl_3$ (500ml. x 10) dried over $MgSO_4$, and evaporated. The residue was purified on Si-gel to afford a mixture of 13a and 13b 1.83g. (42%) as colorless oils.

13a, 13b mixture

400MHz pmr ($CDCl_3$, TMS, δ, ppm)

1.22* (d, J=6.6Hz), 1.23 (t, 3H, J=7.32Hz), 1.25* (d, J=6.16Hz), 1.99 (qn, 2H, J=7.04Hz), 2.30-2.50 (m,3H), 3.68 (s, 3H), 3.93** (d.qr, J=5.87, 6.16Hz), 4.02** (d.qr, J=4.99, 6.16Hz), 4.18 (qr, 2H, J=7.32Hz)

*total 3H **total 1H

IR ($CHCl_3$, cm^{-1})

3030, 1730, 1520, 1422

MS (EI, m/z) 187 (M^+ -MeO)

Synthesis of 5R, 6S-5-carboxy-6-methyl-3,4,5, 6-tetrahydropyran-2-one (14a) [and 5S,6S,5-carboxy-6-methyl-3,4,5, 6-tetrahydropyran-2-one (14b)]

The mixture of alcohols 13a and 13b(1.79g.,8.3mmol.) was dissolved in a solution of K_2CO_3(2.29g., 16.6mmol.) and 80% aq. MeOH (50ml.). The solution was refluxed for 12h., cooled to 0°C and acidified to pH 2 with 6N HCl and concentrated in vacuo to a volume of ca. 10ml. The solution was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$, evaporated and the residue was purified on Si-gel to yield 858mg (66%) of 14a and 123mg. (9.5%) of 14b.

Spectral data for 14a white crystalline solid mp 117-8°C.

400MHz pmr (CD_3OD, δ, ppm.)

1.47 (d, 3H, J=9.95Hz), 2.16-2.24 (m, 2H), 2.51-2.67 (m, 2H), 2.68-2.76 (m, 1H), 4.63 (d.qr, 1H, J=7.30Hz (for d), 9.95z (for t), 9.50 (br.s, 1H)

100MHz cmr (CD_3OD, δ, ppm.)

20.37, 22.29, 27.98, 45.02, 76.58, 171.31, 176.70

IR ($CHCl_3$, $cm.^{-1}$)

3035, 1735, 1720, 1520, 1425

14b colorless oil

400MHz pmr ($CDCl_3$, TMS, δ, ppm.)

1.27(t,3H,J=7.3Hz), 1.39(d,2H,J=6.48Hz), 2.04-2.24(m,2H), 2.48-2.58(m,1H), 2.69-2.79(m,1H), 2.88 (ddd,1H,J=3.81, 4.11, 5.87Hz), 4.14(qr,2H,J=7.3Hz), 4.71(d.qr,J=4.11Hz(for d), 6.48Hz(for t)

100MHz cmr ($CDCl_3$, δ, ppm.)

14.12, 18.17, 19.98, 27.22, 42.16, 61.16, 75.38, 170.63, 171.02

IR ($CHCl_3$, $cm.^{-1}$)

1735, 1650, 1610, 1475, 1390, 1095

MS (EI, m/z)

186 (M^+), 171 (M^+-CH_3), 158 (M^+ -C_2H_5)

Synthesis of 5R, 6S-5, N-benzyloxycarbonyl-6-methyl-3,4,5, 6-tetrahydropyran-2-one (15)

Under an argon atmosphere, 15 (455mg.,2.88mmol.) and 0-benzylhydroxylamine (372mg.,3.02mmol.) were dissolved in CH_2Cl_2(10ml.). DCC (653mg.,3.17mmol.) and HOBT (777mg., 5.76mmol.) were added. The reaction mixture was stirred overnight and concentrated in vacuo. The residue was purified on Si-gel to afford 720mg. (95%) of 15 as a colorless oil.

400MHz, pmr, ($CDCl_3$, TMS, δ, ppm.)

1.24 (d, 2H, J=6.75Hz), 1.88-1.98 (m, 2H), 2.57-2.69 (m,2H), 2.88-2.97 (m, 1H), 4.44 (d.qr, 1H, J=6.75Hz

(for q), 7.3Hz (for d)), 5.03 (s, 2H), 7.34-7.54 (m, 5H)

100MHz cmr ($CDCl_3$, TMS, δ, ppm.)

16.82, 19.42, 32.19, 49.34, 66.26, 78.28, 128.27, 128.36, 128.61, 128.92, 129.93, 133.71, 168.08, 170.55

IR ($CHCl_3$, $cm.^{-1}$)

3010, 2980, 2930, 1747, 1702, 1650, 1570, 1460, 1180, 1095

Synthesis of 4R, 5S-methyl-4-N-benxyloxycarbonyl-5-hydroxyhexanoate (16)

A solution of 15(300mg.,1.08mmol.) and KCN(2.6mg.,0.04mmol.) in dry MeOH(20ml.) was refluxed for 14h. The solution was cooled, evaporated and partitioned between H_2O and $CHCl_3$. The organic phase was dried over $MgSO_4$, evaporated and the residue was purified on Si-gel to afford 270mg.(85%) of 16 as a pale yellow oil.

400MHz pmr ($CDCl_3$, TMS, δ, ppm.)

1.16(d,3H,J=6.2Hz), 1.88-2.08(m,2H), 2.32-2.41(m,2H), 2.43(d.t,1H,J=6.2Hz(for t), 6.7HZ(for d)), 3.62 (s,3H), 3.94(d.qr,1H,J=6.2Hz(for qr), 6.7Hz(for d)), 4.85(d,1H,J=11Hz), 4.92(d,1H,J=11Hz), 7.29-7.55 (m,5H)

IR ($CHCl_3$, $cm.^{-1}$)

3420, 3040, 1735, 1680, 1520, 1480, 1425, 1020, 925

MS (EI, m/z)

173 (M^+-C_6H_5ONH)

Synthesis of 3R, 4R-1-benzyloxy-3-methoxycarbonylethyl-4-methyl-azetidin-2-one (4)

To a solution of 16(75mg.,0.25mmol.) and Ph_3P(80mg.,0.305mmol.) in THF(3ml.) was added DEAD (53mg., 0.305mmol.). The reaction was stirred overnight. The solution was evaporated and the residue was purified on Si-gel to provide 50mg. (72%) of 4 as a colorless oil.

400MHz pmr ($CDCl_3$, TMS, δ, ppm.)

1.18(d,3H,J=6.44Hz), 1.72-1.86(m,2H), 2.46(ddd,1H,J=2.08Hz,4.1Hz,9.98Hz), 2.38-2.51(m,2H), 3.23 (d.qr,1H,J=2.08Hz(for d), 6.44Hz(for q), 3.64(s,3H), 4.92(d,1H,J=11.3Hz), 4.96(d,1H,J=11.3Hz), 7.32 7.48(m,5H)

100MHz cmr ($CDCl_3$, TMS, δ, ppm.)

20.14, 22.28, 31.77, 41.10, 51.61, 68.12, 77.34, 127.92, 128.30, 128.37, 135.20, 168.23, 174.24

IR ($CDCl_3$, $cm.^{-1}$)

2940, 1780, 1735, 1640, 1470, 1360, 1250, 1110

MS (EI, m/z)

203 (3.65%, M^+--74 [CH_3COOCH_3]), 149 (29.9%, right half), 137.2 (5.4% bottom half), 129 (29.8%, left half +1), 91.2 (C_7H_7)

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1. Recipient of a Dreyfus Young Faculty Grant (1985-1990), Searle Scholars Award (1986-1989), Presidential Young Investigators Award (1987-1992), American Cancer Society Junior Faculty Fellowship (1987-1990), American Heart Association Established Investigators Award (1990-1995) and an American Cyanamid Award.
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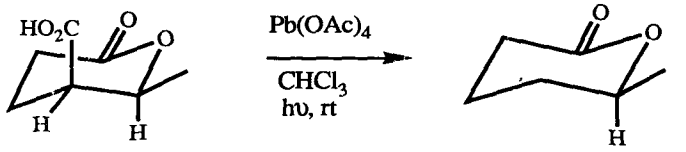
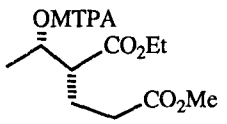
11. The absolute configuration of the reduction product was confirmed in the following manner:



$[\alpha]_D^{25} = -48.0°$ (C = 0.01 EtOH)

14b

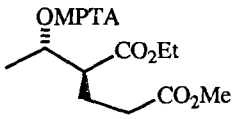
Lit $[\alpha]_D = -51^0$ Hardegger, E., Rieder, W., Walser, A. and Kugler, F. (1966) *Helv. Chim. Acta*, **49**, 1283.
Spectral data for MTPA derivatives



17

MeO- (400MHz pmr) 3.429 ppm (only one isomer)
CF_3- (376.4 MHz^{19} F-nmr) 4.748 ppm (only one isomer)

Thus the optical purity of 3a was found to be 100%ee.



18

MeO- (400MHz pmr) 3.426 ppm (only one isomer)
CF_3- (376.4 MHz^{19} F-nmr) 4.687 ppm (only one isomer)

12. Dale, J.A., Dull, D.L., and Mosher, H.S. (1969) *J. Org. Chem.* **34**, 2543.
13. Preliminary investigations in this regard appear promising, M. Kahn and K. Fujita unpublished results.