International Journal of Advance Research in Science and Engineering
Vol. No.5, Issue No. 05 , May 2016
www.ijarse.com
IJARSE
ISSN 2319 - 8354

SYNTHESIS OF C32-C42 FRAGMENT OF ETNANGIEN

A Bal Reddy[1], J S Yadav[2]

[1,2] Centre for Semio Chemical Division,

CSIR-Indian Institute of Chemical Technology, Hyderabad-500607, (India)

ABSTRACT

The stereoselective synthesis of C32-C42 fragment of etnangien has been achieved from propane diol and propargyl bromide. The synthesis proceeds in 18 steps using Sharpless epoxidation, epoxide opening with Gilman reagent, 1,4-syn aldol and syn reduction.

Key Words: Etnangien, Sharpless Epoxidtion, Methyl Gilman Reagent, Syn Aldol and Syn Reduction

I INTRODUCTION

A macro polyketide etnangien was isolated[1] by the group of Ho¨fle in 2007 from stains (So ce750, So ce1045) of myxobacterium *Sorangium cellulosum*. Entnagien shows potent antibiotic activity in both in vitro and in vivo assays over a broad range of Gram-positive bacteria by inhibition of RNA-polymerase. Entnagien and its analogue methyl ester shows no cross-resistance to rifamyicine, it retains retroviral activity against DNA polymerase. It has low cytotoxicity against mammalian cell that promotes the development of the synthesis of etnangien. The salient features of etnangien; it is 22-membered macrolactone, 12 sterogenic centers with polyunsaturated side chain. In 2009 Menche group reported the first total synthesis of etnangien[2].

As a part of our longstanding interest in the synthesis of bioactive natural products, we have taken up the synthesis of C32-C42 fragment of etnangien, highlighting Sharpless epoxidation and opening with Gilman reagent, *syn* aldol, 1, 3-acetonide protection are the key reactions. Several reports were on synthesis of etnangien using different conditions[2] and strategy such as asymmetric aldol and dyssymmetrization. We report herein the synthesis of C32-C42 fragment of etnangien.

II RESULTS AND DISCUSSION

The retro synthesis of C32-C42 fragment **2** of etnangien can be prepared from 1, 4-syn aldol[3] reaction between ethyl ketone **4** and aldehyde **3** followed by syn reduction and 1,3-acetonide protection of diol. The aldehyde could be

prepared from asymmetric proprgylation[4] with oxazolidinone **12** and propargyl bromide followed by reduction with DIBAL-H. The fragment **4** can prepared from allyl alcohol **5** by sharpless epoxidation and opening with methyl Gilman reagent.

Fig 1: Retro Synthetic Analysis

Fig 2: Synthesis of Fragment 4

Reagents and conditions: i) 4A^{o}MS, D (-)-DIPT, Ti(O*i*Pr)$_4$, 4.0 M TBHP, DCM, -20 °C 80%. ii) CH_3MgBr, CuI, THF, -20 °C. 65%. iii) TBS-Cl, imidazole, 0 °C-RT, 88%. iv) HF-pyridine, THF, 25 °C, 86%. v) IBX, DMSO, DCM, RT 90%. vi) EtMgBr, THF, 0 °C, 92%. vii) Dess-Martin periodinane, DCM, 90%.

The synthesis of C32-C42 fragment began from propane diol and propargyl bromide. The synthesis of compound **4** achieved from compound **5** by Sharpless epoxidation[5] with D- (-) DIPT at -20 °C to gave epoxy alcohol **6** in 80% yield, which on opening with methyl Gilman[6] reagent -20 °C resulted 1,3-diol **7** with 65% yield. The 1,3-diol **7** treated with TBS-Cl and imidazole in DCM produced disillylated compound **8,** the resulted compound **8** treated with HF-Pyridine[7] in THF at 25 °C gives mono TBS alcohol **9** in 80% yield. Alcohol **9** oxidation with IBX gave aldehyde **10** in 90% yield. The aldehyde **9** on reacts with ethyl magnesiumbromide at 0 °C followed by oxidation with Dess-Martien Periodinane gave ethyl ketone **4** in overall 82% yield.

The compound **13** prepared via asymmetric propargylation with propargyl bromide and oxazolidinone **12** using LDA and HMPA at -78 °C furnished methylpentenyl-oxazolidinone **13** with 75% yield. On treatment of compound **13** with sodium borohydride in THF:H_2O at RT obtained 78 % yield of methylpent-4-yn-1-ol **14.** Trans vinyl iodo obtained by reduction[8] with DIBAL-H at 50 °C and treatment with iodine at 0 °C gave 65% of trans vinyliodo **15**. The iodo alcohol oxidation with IBX at room temperature yielded aldehyde **3** in 86 %.

Fig 3: Synthesis of Aldehyde 3

Reagents and conditions: i) LDA, HMPA, propargyl bromide, THF, -78 °C, 75%. ii) $NaBH_4$, THF: H2O, RT, 78%. iii) DIBAL-H, I_2, THF, 0-55 °C, 65%. iv) IBX, DMSO, DCM, RT 86%.

Fig 4: Coupling of aldehyde 3 ethyl ketone 4.

Reagents and conditions*:* i) $TiCl_4$, DIPEA, DCM, -78 °C, 65%. ii) DIBAL-H, THF, 0 °C, 55%. iii) 2,2-DMP, *p*-TsOH, DCM, 91%.

The compound **4** treated with $TiCl_4$ and diisopropylethylamine in DCM at -78 °C followed by addition of aldehyde **3** gave 1,4-*syn* aldol product **16** with 65 % yield. The compound **16** reduction with $Zn(BH_4)_2$ give *syn* diol which on reacts with 2,2-DMP and *p*-TsOH afforded the target fragment **2** with an overall 50% yield .

III EXPERIMENTAL

3.1 ((2R,3R)-3-(2-(benzyloxy)ethyl)oxiran-2-yl)methanol (6):

D-(-)-Diisopropyl tartrate (0.76 g, 3.24 mmol), Ti(O*i*Pr)4 (0.92 g, 3.24 mmol) and 4.0M soln. of *t*-BuOOH (10.81 mL,43.24 mmol) were sequentially added to a stirred mixture of molecular sieves (4 Å 3.0 g) in CH_2Cl_2 (45 mL) at - 20 °C, and the mixture was stirred for 30 min at - 20 °C. To this mixture, added a solution of compound **5** (4.5 g, 21.62 mmol) in CH_2Cl_2 (25 mL) at - 20 °C. The mixture was stirred at - 20 °C for 12 h, and reaction was filtered through celite pad and washed with CH_2Cl_2 (15 mL), reaction was quenched with H_2O (0.92 mL) and 30% NaOH (0.46 mL). Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (15 mL). Organic layers were combined and washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified on silica gel column chromatography eluting with 15% ethyl acetate in hexanes afforded epoxy alcohol **6** as colorless oil (3.88 g, 17.3 mmol) in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.20 (m, 5H), 4.52 (s, 3H), 3.97-3.82 (d, *J* = 12.8, 1H), 3.68-3.56 (t, *J* = 6.04 3H), 3.15-3.08 (m, 1H), 2.98 (s, 1H), 2.01-1.75 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 128.4, 127.7, 73.1, 66.9, 61.8, 58.6, 53.8, 32.1.

3.2 (2S,3R)-5-(benzyloxy)-2-methylpentane-1,3-diol (7):

To a stirred mixture of cuprous iodide (1.53 g, 8.0 mmol) and anhydrous THF (60 mL) added a solution of methylmagnesium bromide 2M in THF (26.7 mL, 53.4 mmol) at -20 °C, and the solution was stirred for 30 min at -

20 °C. To this mixture epoxy alcohol **6** (6.0 g, 26.6 mmol) in THF (30 mL) was added at -20 °C and the mixture was stirred at -20 °C for additional 3.0 h. The reaction was quenched with saturated NH_4Cl. The product was extracted with diethyl ether (4 x 60 mL), the organic extracts layers were combined and washed with saturated NH_4Cl and brine, dried over sodium sulfate and concentrated under vacuum. The crude was dissolved in methanol (120 mL) and water (30 mL), added $NaIO_4$ (1.89 g, 8.9 mmol) and stirred for 6 h. Methanol was removed under vacuum, water (150 mL) was added and compound was extracted with DCM (3 x 75 mL). The organic layers were combined and concentrated in *vacuo, crude* was purified on silica column chromatography eluting with 50% ethyl acetate in hexanes obtained compound **7** as colorless oil (3.88 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.20 (m, 5H), 4.52 (s, 2H), 3.90 (bs, 1H), 3.82-3.58 (m, 5H), 3.41 (bs,1H), 1.88-1.80 (m, 2H), 1.77-170 (m, 1H), 0.86 (d, *J* = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 128.4, 127.8, 127.6, 77.4, 73.4, 69.4, 67.6, 40.0, 34.2, 13.8.

3.3 (2S,3R)-5-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentan-1-ol (9):

HF-Pyridine solution (32 mL) was added to a stirred solution of compound **8** (5.8 g, 12.8 mmol) in THF (100 mL) and pyridine (32 mL) in plastic vessel at 0 °C, and the reaction was stirred at RT for 18h. The reaction was quenched with saturated $NaHCO_3$ sol. (200 mL) at 0 °C. The mixture was extracted with ethyl acetate (3 x 100 mL), organic extracts were combined and washed with brine, dried over Na_2SO_4. Organic layer was concentrated under reduced pressure, crude was purified by flash column chromatography afford colorless oil **9** (3.8 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 4.49 (s, 2H), 3.92-3.85 (m, 1H), 3.78-3.68 (m, 1H), 3.52 (t, *J* = 6.4, 3H), 2.62-2.53 (m, 1H), 1.87 (d, *J* = 6.4, 2H), 1.80-1.72 (m, 1H), 0.99 (d, *J* = 7.2, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1 128.3, 127.6, 73.4, 73.2, 72.4, 65.44, 39.2, 25.8, 18.0, 11.6, -4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 3, -5.01

3.4 (4R,5R)-7-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-4-methylheptan-3-one (4)

To a stirred solution of aldehyde **10** (3.1g, 9.21 mmol) at 0 °C was added freshly prepared EtMgBr (11.0 mL, 1.0M) and the reaction mixture was stirred at 0 °C for 2 h. The mixture was quenched with sat. NH_4Cl (25 mL), and extracted with ethyl acetate (3 x 50 mL). Combined the extracts and dried over Na_2SO_4 and concentrated under vacuum. The crude was dissolved in dry DCM (40 mL) , this solution was added to a suspension of Dess–Martin periodinane (4.69 g, 11.05 mmol) and $NaHCO_3$ (1.86 g, 22.1 mmol) in DCM (20 mL) at 0 °C, the reaction was stirred at 0 °C for 2 h. The mixture was diluted with DCM (20 mL), mixture was washed with sat. $NaHCO_3$ (2 x 100 mL). The organic layer was dried on Na_2SO_4, and concentrated under vacuo. Crude was purified on silica column by eluting with 10% ethyl acetate in hexanes obtained thick oil **4** (3.0 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 4.49 (s, 2H), 4.11 (dd, *J* = 11.1, 5.7, 1 H), 3.56 (t, *J* = 6.8, 2H), 2.75 (qn, *J* = 7.0, 1H), 2.47 (q, *J* = 7.2, 2H), 1.86-1.64 (m, 2H), 1.01 (d, *J* = 7.0, 3H), 1.00 (t, *J* = 7.2, 3H), 0.84 (s, 9H), 0.04 (s, 3H), -0.01 (s, 3H).

3.5 (R)-4-benzyl-3-((S)-2-methylpent-4-ynoyl)oxazolidin-2-one (13):

To a stirred solution of *N*,*N*-diisopropylamine (8.23 mL, 53.46 mmol) in THF (45 mL) at 0 °C added (1.6 M in hexanes) *n*-butyllithium (30.4 mL, 48.6 mmol). The mixture was stirred at 0 °C for 30 min and cooled to -78 °C, added HMPA (6 mL) and (R)-4-benzyl-3-propionyloxazolidin-2-one **12** (8.0 g, 34.73 mmol) in THF (20 mL). The reaction mixture was stirred at -78 °C for 45 min, added propargyl bromide (10.32 g, 86.8 mmol) into the mixture, the mixture was stirred at -78 °C for 18 h. The reaction was quenched with saturated NH_4Cl (40 mL) an water (40mL), organic layer was separated and aqueous layer extracted with ethyl acetate (2 x 80 ml). Combined organic extracts and washed with sat. NaCl solution (50 mL), dried over sodium sulfate and concentrated under vacuo. Pure product was obtained by column chromatography by eluting with 30 % ethyl acetate in hexanes afforded oil **13** (5.15 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H), 7.29 (d, *J* = 7.3, 1H), 7.23 (d *J* = 6.7, 2H), 4.73-4.68 (m, 1H), 4.24-4.16 (m, 2H), 3.96 (dd, *J* = 13.5, 6.8, 1H), 3.30 (dd, *J* = 13.4, 3.2, 1H), 2.79 (dd, *J* = 13.4, 9.5, 1H), 2.63 (dd, *J* = 6.7, 2.6, 1H), 2.63 (dd, *J* = 6.5, 2.6, 1H), 2.03, (t, *J* = 2.6), 1.29 (d, *J* = 6.9, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 153.0, 135.1, 129.4, 128.9, 127.3, 81.28, 70.1, 66.1, 55.3, 37.9, 37.2, 22.6, 16.5

3.6 (S,E)-5-iodo-2-methylpent-4-en-1-ol (15)

(S)-2-methylpent-4-yn-1-ol **14** (1.2 g, 12.22 mmol) in THF (3mL) into a solution of DIBAL-H (1.0 M in hexane, 36.6 mL, 36.6 mmol) at RT. The reaction mixture was heated to 55 °C for 1 h. The mixture was cooled to -78 °C, added a solution of iodine (9.4 g, 37.0 mmol) in THF (20 mL), the mixture was allowed to RT and stirred for 1 h at RT. Poured, the mixture into 2 M HCl solution (30 mL) and extracted with diethyl ether (3 x 50 mL). Organic extract were combined and washed with saturated NaCl solution (50 mL), dried over sodium sulfate and concentrated in vacuo, purification on silica gel eluting with 20 % ethyl acetate gave oil iodo enol **15** (1.8 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.51 (dt, *J* = 14.2, 7.6, 1H), 6.03 (dt, *J* = 14.2, 1.4, 1H), 3.48 (d, *J* = 6.1, 2H), 2.23-2.17 (m, 1H), 1.97-1.90 (m, 1H), 1.78-1.71 (m, 1H), 0.92 (d, *J* = 6.9, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 75.7, 67.3, 39.7, 35.2, 16.2.

3.7 (3R,4R,6S,7R,8S,E)-1-(benzyloxy)-3-((tert-butyldimethylsilyl)oxy)-7-hydroxy-11-iodo-4,6,8-trimethylundec-10-en-5-one (16):

The compound **4** (100 mg, 0.27 mmol) in dry DCM (5mL) was dissolved and cooled to -78 °C, to this added a solution of $TiCl_4$ 1.0 M in DCM (0.27 mL 0.27 mmol) drop wise and stirred the reaction for 15 min at -78 °C. To this reaction mixture added *N*,*N*-diisopropylethylamine (0.05 mL, 0.35 mmol) at -78 °C and the reaction was stirred at -78 °C for 1 h. The mixture was then cooled to -90 °C, added aldehyde **3** (54 mg, 0.24 mmol) in DCM (1 mL) and the solution warmed to -78 °C and stirred for 2 h. the reaction was quenched with pH = 7.0 buffer (10 mL) and allowed to RT. The product was extracted with DCM (2 x 10 mL), combined the organic extracts, washed with brine

and dried over sodium sulfate. The organic Phase was concentrated in vacuo, purified on flash column chromatography 30% ethyl acetate in hexanes afforded compound **16** (92 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 6.48 (ddd, *J* = 14.3, 6.7, 5.6, 1H), 5.99 (d, *J* = 14.3, 1H), 4.53-4.46 (m, 2H), 4.16-4.10 (m, 1H), 3.63-3.53 (m, 3H), 3.30 (d *J* = 2.0, 1H), 3.03-2.95 (m, 1H) 2.73 (dq, *J* = 7.3, 1.4, 1H), 2.47 (ddd, *J* = 9.9, 6.7, 1.5, 1H), 1.95-1.87 (m, 1H), 1.85-1.77 (m, 1H), 1.74-1.66 (m, 1H), 1.10 (d *J* = 7.3, 3H), 1.01 (d *J* = 6.9, 1H), 0.85 (s, 9H), 0.73 (d *J* = 6.9, 1H), 0.05 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.4, 144.8, 138.4, 128.3, 127.6, 127.5, 75.7, 73.0, 72.8, 71.4, 65.6, 50.1, 47.5, 39.4, 34.4, 33.2, 25,8, 17.9, 14,8, 12.4, 8.2, -4.7.

3.8 Acetonide (2)

2,2 dimethoxypropane (0.36 mL, 0.33 mmol) was added to solution of diol **17** (60 mg, 0.1 mmol), in 5 mL DCM at 0 °C, to this added *p*-TsOH hydrate (10 mg, 0.05 mmol) at 0 °C. After reaction completed, the mixture was quenched by sat. $NaHCO_3$ (5 mL). The aqueous layer and organic layer was separated and aqueous layer was extracted with DCM (2 x 5 mL). The organic extracts were combined and dried over sodium sulfate, concentrated in vacuo, purified on flash column chromatography afforded colorless oil **2** (52 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 6.49 (ddd, *J* = 14.3, 8.3, 6.0, 1H), 5.97 (d, *J* = 14.3, 1H), 4.48 (s, 2H), 4.17-4.10 (m, 1H), 3.60-3.45 (m, 2H), 3.34 (dd *J* = 10.6, 3.8, 1H), 3.07 (dd *J* = 8.3, 6.0, 1H), 2.48-2.39 (m, 1H), 1.85-1.67 (m, 4H), 1.24 (d, *J* = 7.5, 6H), 0.87 (s, 9H), 0.80 (d, *J* = 6.8, 3H), 0.04 (s, 3H), 0.01 (3, H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 138.4, 127.8, 127.0, 126.9, 99.1, 75.9, 74.9, 72.2, 72.1, 68.5, 67.6, 60.0, 44.1, 39.3, 36.2, 30.0, 25.5, 23.0, 29.6, 19.6, 17.6, 14.3, 13.7, 12.2,8.8, -4.8, --5.1

IV CONCLUSION

In conclusion, the synthesis of C32-C42 fragment of etnangien accomplished in 18 steps from propane diol and longest 13 liner steps with an overall 9.6 % yield from alcohol **5.** This work establish asymmetric alkylation and highly steroslective 1,4-*syn* aldol reaction, Sharpless epoxidation

ACKNOWLEDGEMENT

A.B.R thanks CSIR, New Delhi, India for the award of fellowship. The authors also acknowledge CSIR for funding from 12th Five Year plan project ORIGIN (CSC-108).

REFERENCES

[1] Ho¨fle. G, Reichenbach. H, Irschik. H, Schummer. D, German Patent DE 196 30 980 A1: 1-7 (5.2. **1998**). Irschik H, Schummer D, Ho¨fle, G.; Reichenbach H, Steinmetz H, Jansen, R. *J. Nat. Prod,* **2007**, *70*, 1060.

[2] Li. P, L., J, Arikan. F, Ahlbrecht. W, Dieckmann. M, Menche. D, *J. Am. Chem. Soc.* **2009**, *131*, 11678. G. Sabitha, K. Yadagiri, M. Bhikshapathi, G.Chandrashekhar, J S Yadav, *Tetrhedron: Asymetry* **2010**, *21*, 2524-2529. H. W. William, J. T. Steven, G. S. Jason, T. Pui-In, H. D. Meghan, *Tetrahedron Letters*, **2015**, *56***,** 2303-2306

[3] A. K. Ghosh, M. Shevlin, In *Modern Aldol Reactions*, R. Mahrwald, Ed, Wiley-VCH: Weinheim, 2004, 63-125.

[4] Jeremy D. Pettigrew, Peter D. Wilson, **2006,** *8*, 1427-1429.

[5] J. S. Yadav, C. D. Vani, N. Bhasker and B. Reddy, *ARKIVOC*, **2014**, 291- 300.

[6] S. K. Chattopadhyay, G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2429–2454.

[7] B. Zhu, James S. Panek, *Org. Lett.,* **2000,** 17, 2575-2578.

[8] M. Sasaki,Y. Kondo, M. Kawahata, K. Yamaguchi, k. Takeda, *Angew. Chem. Int. Ed*. **2011**, *50*, 6375 –6378