SSRG International Journal of Applied Chemistry
ISSN: 2393 – 9133 /doi:10.14445/23939133/IJAC-V7I3P104

Volume 7 Issue 3, 21-24, Sep-Dec 2020

The Asymmetric Synthesis of *tert*-Butyl (4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate: An Important Intermediate of HMG-CoA Reductase Inhibitor

Yoshifumi Yuasa

Kasai Chemical Laboratory, 7-7-402 Akashicho, Hiratsuka, Kanagawa, 254-0042, Japan

Abstract
*tert-Butyl (4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate **1**, which is the important intermediate for atorvastatin [Statin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)], could be prepared from N-carbobenzyloxy-β–alanine **3** through the asymmetric hydrogenation using the Ru-BINAP complex catalyst as the key step in 8 steps.*

Keywords — *(4R,6R)-t-Butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, N-Carbobenzyloxy-alanine, HMG-CoA reductase inhibitor, Atorvastatin, Asymmetric hydrogenation, Ru-BINAP catalyst.*

I. INTRODUCTION

tert-Butyl (4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate **1** is useful as a synthetic inter-mediate for preparing the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor known as the antilipemic agent, atorvastatin, (3*R*,6*R*)-7-[2-(4-flurophenyl)-3-phenyl-4-(phenyl-carbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxy-heptanoic acid.[1] (Fig.1)

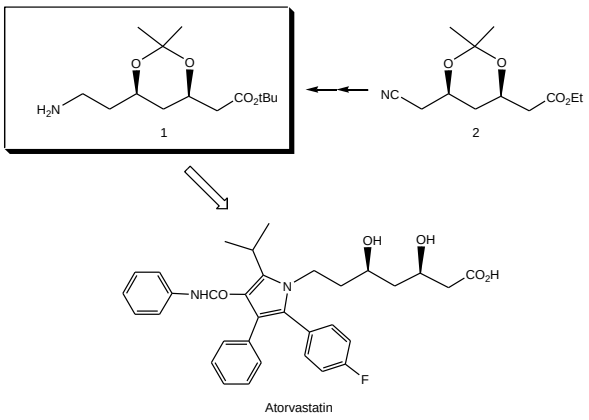


Fig. 1: The structure of *t*-butyl (4*R*,6*R*)-6-(2-amino-ethyl)-2,2-dimethyl-1,3-dioxane-4-acetate **1** and atorvastatin.

The synthetic methods of **1** are well known by the chemical reduction of the cyano group in ethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate 2 prepared using a biocatalyst.[2] However, these methods using cyanide compounds have raised safety concerns. Namely, toxic alkaline cyanide must be used for obtaining the cyanide compound, and alcohol-containing toxic ammonia gas must be employed to reduce the cyano group. Thus, these methods require complex equipment and are troublesome to carry out.

On the other hand, the enantioselective hydrogenation with the Ru-BINAP complex catalyst is one of the most powerful tools for synthesizing optically-active compounds.[3] Moreover, new chiral phosphorous ligands for enantioselective hydrogenation are used, and their review has been reported.[4] In particular, the asymmetric hydrogenations of di-ketones, β-ketoesters, and enamide esters are well known. Furthermore, it is known that hydrogenation of the γ-chloro-β-ketoester or benzyl-oxy ketoester catalyzed by Ru-BINAP gives the inter-mediates of carnitine and compactin, respectively.[3a,5]

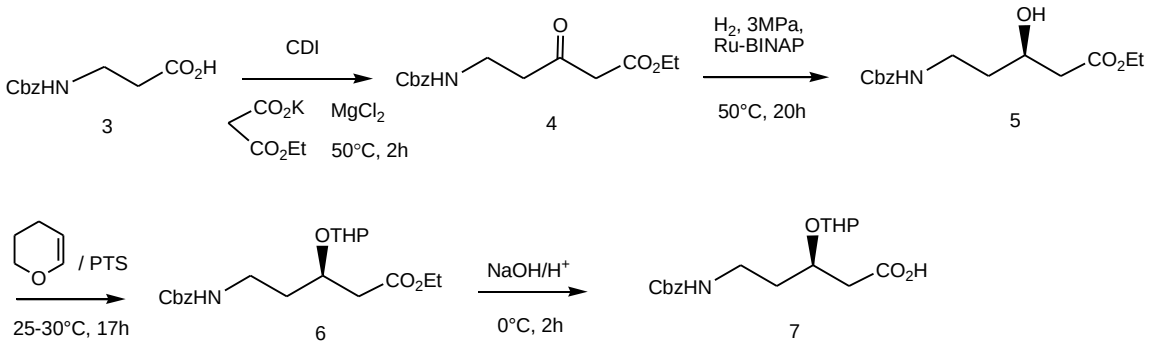
The author has studied the asymmetric hydrogen-ation to develop the synthesis of optically active compounds[6] and now reports the efficient synthesis of optically-active **1** from *N*-carbobenzyl-oxy-β-alanine **3** by asymmetric hydrogenation using the Ru-BINAP complex catalyst.[7]

II. RESULTS AND DISCUSSION

According to the method known as the Masamune reaction,[8] *N*-carbobenzyloxy-β-alanine **3**, which is commercially available, was condensed with *N*, *N*'-carbonyldiimidazole (CDI) to form the imidazoline of **3**, then reacted with the potassium malonate ethyl ester in the presence of $MgCl_2$ to give the β-ketoester **4** in 82 % yield.

The asymmetric hydrogenation of the β-ketoester **4** was next treated using $[NH_2Et_2][\{RuCl((R)\text{-}(+)\text{-BINAP})\}_2\mu\text{-}Cl)_3]$[9] as a catalyst under 30 atm at 50° C for 20 h to produce the optically-active (3*R*)-hydroxy ester **5** in 83% yield. The absolute configuration of **5** was determined by comparing the optical rotations in the literture[10] after the conversion to **1**. The enantiomeric excess of (3*R*)-**5** was 99% ee as determined by HPLC after reacting with (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenyl-acetyl chloride.

Furthermore, the hydroxy group of **5** was protected by 3,4-dihydro-2H-pyran (DHP) in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTS) to give the (3*R*)-*N*, *O*-protected aminopentanoic ester **6** in 79 % yield, then **6** was hydrolyzed by NaOH to produce the (3*R*)-*N*, *O*-protected aminopentanoic acid **7** in 82% yield. (Scheme 1)



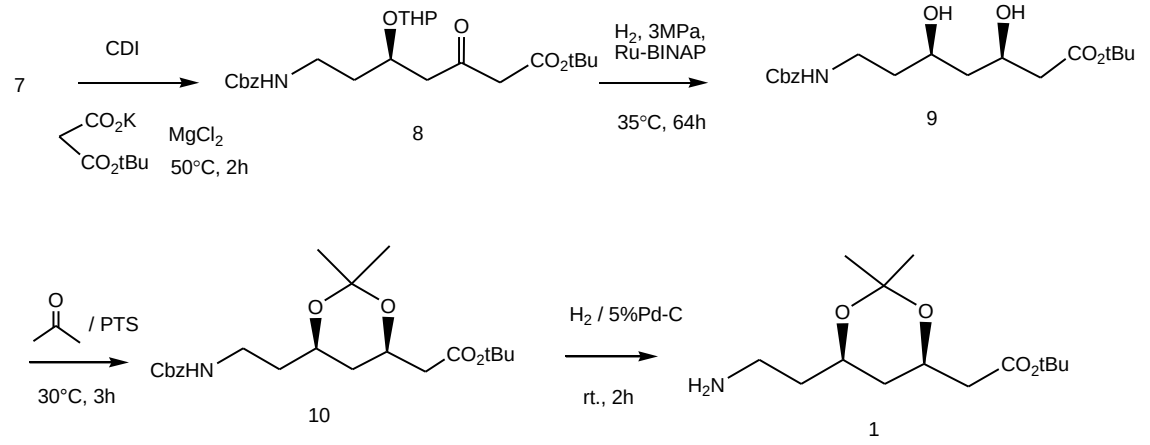
Scheme 1: Synthetic route of (3*R*)-*N*, *O*-protected aminopentanoic acid **7** from *N*-Cbz-β-alanine **3**

The acid **7** was condensed again with CDI, followed by the reaction with the potassium malonate *t*-butyl ester in the presence of $MgCl_2$ to give the (5*R*)-β-ketoester **8** in 79 % yield.

The secondary asymmetric hydrogenation of **8** was treated using $[NH_2Et_2][\{RuCl((R)\text{-}(+)\text{-BINAP})\}_2\mu\text{-}Cl)_3]$ as a catalyst under 30 atm at 35° C for 64 h. The crude product was purified and de-protected by silica gel column chromatography to give the optically-active (3*R*)-dihydroxy ester **9** as an oil in 85% yield. The diastereoselectivity of (3*R*, 5*R*)-**9** was 83%de determined by a GC analysis after reacting with acetone dimethyl acetal.

The (3*R*, 5*R*)-dihydroxy ester **9** was protected by acetone in the presence of PTS and purified by silica gel column chromatography to give the (4*R*, 6*R*)-dioxane derivative **10** in 70% yield. The diastereomeric excess of (4*R*, 6*R*)-**10** was increased by 99% de by purification using slica gel column chromatography.

Finally, according to the usual method, the benzloxycarbonyl group of the (4R, 6R)-dioxane derivative 10 was removed by hydrogenation in the presence of 5% Pd-carbon give **1** as an oil in 90 % yield. (Scheme 2)



Scheme 2: Synthetic route of *t*-butyl (4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3- dioxane-4-acetate **1** from (3*R*)-*N*,*O*-protected aminopentanoic acid **7**

Therefore, the high optical purity of *t*-butyl (4R,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate **1** was obtained from *N*-carbobenzyloxy-β-alanine **3** in 8 steps by duplicate asymmetric hydrogenation using the Ru-BINAP catalyst as the key step.

III. MATERIALS AND METHOD

All reagents and solvents were obtained from commercial sources and used without further purification. The melting points were determined using a Yanagimoto micro melting apparatus and are uncorrected. The NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard using a Bruker AM-400 (400MHz). The chemical shifts are given in ppm. The following instruments determined chemical purity, optical purity, and diastereoselectivity. GC: HP-5890 (Hewlett-Packard) with a

silicone OV-1 column (GL Science; 0.25mm x 25mm). Heating program: from 170 - 250°C. at 3°C/min. HPLC: L-6200 (Hitachi) Column-1: Inertsil ODS-2 (GL Science), 5 m, 4.6 mm x 250 mm, eluent: CH_3CN/H_2O = 70/30, flow rate: 0.6 ml/min, detection: UV (254 nm). Column-2: CHIRALCEL OD (Daicel Chemical Industries), 5 m, 4.6 mm x 250 mm, eluent: n-hexane/i-PrOH = 95/5, flow rate: 1.5ml/min, detection UV (254 nm). Optical rotation: DIP-4 (JASCO).

Synthetic procedures

Ethyl 5-*N*-carbo-benzyloxy amino-3-oxopenta-noate (4): To *N*-carbobenzyloxy-β-alanine **3** (59.4 g, 0.266 mol) in CH_3CN (500 ml), CDI (44.1 g, 0.272 mol) was added over 15 min. After the reaction mixture was cooled to 10°C, the potassium malonate ethyl ester (67.9 g, 0.399 mol) and $MgCl_2$ (25.5 g, 0.268 mol) were added and stirred for 1 h, then heated to 50°C for 2 h. After the solvent was removed under reduced pressure, EtOAc (300 ml) and a 5 % HCl solution (1L) were added. After the organic layer was separated, washed with a 5% Na_2CO_3 solution (100 ml) and saturated NaCl solution, it was then dried with anhydrous $MgSO_4$. After evaporating the solvent, the crude product was dissolved in a mixture of toluene/*n*-hexane (1/2) and cooled at -30 °C to give the crystals of **4** (64.4 g, 82.5%). mp. 25 - 27°C. ^{1}H-NMR ($CDC1_3$) 1.26 (t, *J* = 7.1 Hz, 3H), 2.79 (brs, 2H), 3.42 (s, 2H), 3.45 (brs, 2H), 4.15 (q, *J* = 7.1Hz, 14.3 Hz, 2H), 5.07 (s, 2H), 5.30 (brs, 1H), 7.27-7.37 (m, 5H).

Ethyl (3*R*)-5-*N*-carbobenzyloxyamino-3-hydroxypentanoate (5): Into a 500-ml autoclave were charged **4** (62.5 g, 0.214 mol) in EtOH (200 ml) and $[NH_2Et_2][\{RuCl((R)\text{-}(+)\text{-}BINAP)\}_2\mu\text{-}Cl)_3]$ (0.712 g, 0.854 mmol) under an atmosphere of N_2. The atmosphere was then replaced with H_2 of 3 MPa at 50° C for 20 h. The reaction solution was concentrated and the residue was recrystallized from a toluene/*n*-hexane (1/1) mixed solution to give 5 (47.5 g, 83%) as an oil. mp. 43.5 - 44°C. $[\alpha]\ ^{24}_D$ = -11.0° (c =1.0, $CHCl_3$). ^{1}H-NMR ($CDC1_3$) 1.25 (t, *J* = 7.1 Hz, 3H), 1.52 - 1.72 (m, 2H), 2.45 (brs, 2H), 3.20 - 3.24 (m, 1H), 3.38 - 3.48 (m, 1H), 3.45 (brs, 1H), 4.04 - 4.10 (m, 1H), 4.15 (q, J = 7.1 Hz, 14.3 Hz, 2H), 5.08 (s, 2H), 5.44 (brs, 1H), 7.29 - 7.34 (m, 5H). After producing the ester of **5** by reacting with (*R*)-(-)-α-methoxy-β-(trifluoromethyl)phenylacetyl chloride, the optical purity of **5** was 99% ee by HPLC using column-2.

Ethyl (3*R*)-5-*N*-carbo-benzyloxy amino-3-(2-tetrahydropyranyloxy)pentanoate (6): To **5** (40.4 g, 0.137 mole) and PTS (0.2 g) in toluene (100 ml), DHP (113.8 g, 0.164 mol) was added over 30 min at 25° C. The mixture was reacted for 18 h at the same temperature. After washing with an aqueous $NaHCO_3$ solution, the solvent was removed under the reduced pressure to give an oily product and purified by a silica gel column using *n*-hexane/EtOAc (5/7) as the eluent to give **6** (40.9 g, 79%) as an oil. ^{1}H-NMR ($CDC1_3$) 1.25 (t, *J* =7.1 Hz, 3H), 1.42 - 2.02 (m, 4H), 2.37 - 2.84 (m, 2H), 3.19 - 4.34 (m, 9H), 4.45 - 4.70 (m, 1H), 5.16 (s, 2H), 7.28 - 7.35 (m, 5H).

(3*R*)-5-*N*-Carbobenzyloxyamino-3-(2-tetra-hydropyranyloxy)pentanoic acid (7): **6** (37.1 g, 0.098 moles) in MeOH (120 ml) was cooled with ice, then a 10% NaOH solution (70ml) was added over 2h. H_2O was then added and subsequently washed with *t*-BuOAc. Toluene (120 ml) and a 5% HCl solution (100 ml) were added to the aqueous layer. The toluene layer was washed with a saturated NaCl solution and dried using anhydrous $MgSO_4$. After removing the solvent under reduced pressure, **7** was obtained as an oil (28.1 g, 82%).

***tert*-Butyl (5*R*)-7-carbobenzyloxyamino-5-(2-tetrahydropyranyloxy)-3-oxoheptanoate (8)**: To **7** (26.3 g, 0.075 mol) in CH_3CN (200 ml), CDI (11.8 g, 0.073 mol) was added over 15 min with stirring. After the reaction mixture was cooled to 10°C, potassium malonate t-butyl ester (21.1 g, 0.107 mol) and $MgCl_2$ (6.8 g, 0.071 mol) were added and stirred for 1 h, then heated at 50°C for 2 h. After the solvent was removed under reduced pressure, EtOAc (150 ml) and a 5 % HCl solution (200 ml) were added. After the organic layer was separated, washed with a 5% Na_2CO_3 solution (25 ml) and saturated NaCl solution, it was dried using anhydrous $MgSO_4$. After evaporating the solvent, the crude product was purified by a silica gel column using *n*-hexane/EtOAc (1/1) as the eluent to give 8 (34.7 g, 79%) as an oil. $[\alpha]^{24}_D$ = +3.3° (c=1.09, $CHCl_3$), ^{1}H-NMR ($CDC1_3$) 1.47 (s, 9H), 1.59 - 1.80 (m, 4H), 2.59 - 2.65 (m, 2H), 2.89 - 3.02 (m, 2H), 3.19-3.49 (m, 3H), 3.38 (brs, 1H), 3.79 - 3.82 (m, 2H), 4.17 - 4.28 (m, 2H), 4.49 - 4.60 (m, 2H), 5.08 (s, 2H), 7.27 - 7.36 (m, 5H).

***tert*-Butyl (3*R*,5*R*)-7-*N*-carbobenzyloxyamino-3,5-dihydroxyheptanoate (9)**: Into a 500-ml autoclave were charged **8** (31.8 g, 0.071 mol) in MeOH (130 ml) and $[NH_2Et_2][\{RuCl((R)\text{-}(+)\text{-}BINAP)\}_2\mu\text{-}Cl)_3]$ (0.199 g, 0.236 mmol) under an atmosphere of N_2. The atmosphere was then replaced with H_2 of 3 MPa at 35° C for 64 h. The reaction solution was concentrated and the residue was purified by a silica gel column using EtOAc/*n*-hexane (1/2) as the eluent to give **9** (22.1 g 85%) as an oil. $[\alpha]^{24}_D$ = -9.7° (c = 1.01, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) 1.45 (s, 9H), 1.47 - 1.68 (m, 2H), 2.36 - 2.40 (m, 2H), 3.16 - 3.25 (m, 1H), 3.41 - 3.50 (m, 1H), 3.94 (brs, 1H), 4.07 (s, 1H), 4.21 (brs, 1H), 4.25 (s, 1H), 5.09 (s, 1H), 5.38 (brs, 1H), 7.29 - 7.35 (m, 5H). The diastereoselectivity of **9** was 83% de by GC analysis after reacting with acetone dimethyl acetal.

***tert*-Butyl (4*R*,6*R*)-6-*N*-carbobenzyloxyamino-ethyl-2,2-dimethyl-1,3-dioxane-4-acetate (10)**: **9** (20.0 g, 0.055 mol) and PTS (0.2 g) in acetone (200 ml) was reacted at 30° C for 3 h . To the mixture, $NaHCO_3$ (2g) was added and concentrated, the residue was extracted with toluene, and washed with H_2O. After the solvent was removed under reduced pressure, the crude product was purified by a silica gel column using EtOAc/*n*-hexane (1/2) as the eluent to give **10** (15.8 g, 70%) as an oil. ^{1}H-NMR ($CDC1_3$) 1.36 (s, 3H), 1.43 (s, 3H), 1.44 (s, 9H), 1.15 - 1.27 (m, 1H), 1.51 -

1.73 (m, 3H), 2.26 - 2.44 (m, 2H), 3.20 - 3.39 (m, 2H), 3.89 - 3.97 (m, 1H), 4.18 - 4.27 (m, 1H), 5.09 (s, 2H), 5.18 (brs, 1H), 7.27 - 7.36 (m, 5H). The diastereoselectivity of **9** was 99% de by GC analysis.

***tert*-Butyl (4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (1)**: Into a 100-ml flask were charged 5% Pd-C (0.65 g) and **10** (13.0 g, 0.032 mol) dissolved in EtOAc (60mL) under atomosphere of N_2. The flask atmosphere was then replaced with H_2 at room temperature. After the H_2 absorption was completed in 2h, the catalyst was removed by filtering with Celite. The solvent was evaporated and the residue was distilled under reduced pressure to give **1** (7.9 g 90%). bp. 105 - 113° C/0.65 torr. $[\alpha]^{24}_D$ = +15.1° (c = 1.45, $CHCl_3$), Lit.[10]; $[\alpha]_D$ = +14.3° (c = 1, $CHCl_3$,). ^{1}H-NMR ($CDC1_3$) 1.18 - 1.29 (s, 1H), 1.31 (brs, 2H), 1.36 (s, 3H), 1.44 (s, 9H), 1.45 (s, 3H), 1.52 - 1.68 (m, 3H), 2.26 - 2.46 (brs, 2H), 2.79 (brs, 2H), 3.94 - 4.03 (m, 1H), 4.22 - 4.29 (m, 1H).

REFERENCES

[1] For a recent example, there are many reports. See P. Hoyos, V. Pace, and A. R. Alcantara. "*Biocatalyed Synthesis of Statins: A Sustainable Strategy for the Preparation of Valuable Drugs*" Catalysts, 2019, 9, pp. 260-292, and reference cited therein.

[2] a) P. L. Brower, D. E. Bulter, C. F. Deering, T. V. L.A. Millar, T. N. Nanninga, B. D. Rotha. "*The synthesis of (4R-cis)-1,1-dimethyl ethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, a key intermediate for the preparation of CI-981, a highly potent, tissue-selective inhibitor of HMG-CoA reductase*" Tetrahedron Lett., 1992, 33, pp. 2279-2282. b) D.E.Butler, T. V. L, A. Millar, and T. N. Nanninga. "*Process for the synthesis of (5R)-1,1-dimethyl ethyl-6-cyano-5-hydroxy-3-oxohexanoate*" US Patent 5155251, 1992. c) N. J. Turner, E. O'Reilly. "*Biocatalytic retrosynthesis*" Nat. Chem. Biol., 2013, 9, pp. 285-288.

[3] a) K. E. Koenig. In Asymmetric synthesis. Vol. 5. Edited by J. D. Morrison. Academic Press, New York. 1985. p.71. b) R. Noyori, and H. Takaya. "*BINAP: An Efficient Chiral Element for Asymmetric Catalysis*" Acc. Chem. Res., 1990, 23, pp. 345-350. c) H. Takaya and R. Noyori. In Comprehensive organic synthesis. Vol. 8. Edited by B. M. Trost and I. Fleming. Pergamon Press, Oxford. Chap. 3.2. 1991, pp.433-469. d) R. Noyori. "*Asymmetric Catalysis by Chiral Metal Complexes*" CHEMTECH, 1992, pp. 360-367. e) H. Takaya, T. Ohta, R. Noyori. "*In Asymmetric Catalytic Synthesis*," Edited by Ojima, I. VCH Publishers, New York. 1993. f) R. Noyori. In Asymmetric catalysis in organic synthesis. John Wiley & Sons, Inc., New York. 1994. Chap. 2. g) R. Noyori. "*Organometallic ways for the multiplication of chirality*" Tetrahedron 1994, 50, pp. 4259-4292.

[4] W. Tang, and X, Zhang. "*New Chiral Phosphorus Ligands for Enantioselective Hydrogenation*" Chem. Rev., 2003, 103, pp. 3029-3070, and reference cited therein.

[5] M. Kitamura, T. Ohkuma, H. Takaya, and R. Noyori. "*A practical asymmetric synthesis of carnitine*" Tetrahedron Lett., 1988, 29, pp. 1555-1556.

[6] a) Y. Yuasa. "*The practical, efficient, diastereoselective synthesis of (3R,1'S)-3- [(1'-N-methylamino)ethyl]-pyrroli-dine: A chiral side chain unit for quinolone type anti-fungus agents*" Indian J. Chem., 2018, 58B, pp. 1189-1193. b) Y. Yuasa. "*The Synthesis of Optically-Active erythro-Methylphenidate by Diastereoselective Hydrogenation Using Ru-BINAP Complex Catalyst*" SSGR Int. J. Appl. Chem., 2020, 7, pp. 70-74.

[7] T. Ikariya, Y. Ishii, H. Kawano, T. Arai, S. Yoshikawa, and S. Akutagawa. "*Synthesis of novel chiral ruthenium complexes of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and their use as asymmetric catalysts*" J. Chem. Soc., Chem. Commun., 1985, pp. 922-924.

[8] a) D. W. Brooks, L. D.-L. Lu and S. Masamune. "*C-Acylation under virtually neutral conditions*" Angew. Chem. Int. Ed. Engl., 1970, 18, pp. 72-74. b) T. Nishi, K. Higashi, T. Soga, M. Takemura, and M. Sato. "*Synthesis and Antibacterial Activity of New 2-Substituted Penems. II*" The Journal of Antibiotics, 1994, 47, pp. 357-369.

[9] T. Ohta, Y. Tonomura, K. Nozaki, H. Takaya, and K. Mashita. "*An Anionic Dinuclear BINAP-Ruthenium (II) Complex: Crystal Structure of $[NH_2Et_2][\{RuCl((R)$-p-MeO- BINAP)$\}_2(\mu$-Cl$)_3]$ and Its Use in Asymmetric Hydrogenation*" Organiometallics, 1996, 15, pp. 1521-1523.

[10] L. B. Kelvin, D. E. Bulter, C. F. Deering, K. E. Mennen, A. Millar, T. N. Nanninga, C. W. Palmer, and B. D. Rotha. "*The Convergent Synthesis of CI-981, an Optically Active, Highly Potent, Tissue Selective Inhibitor of HMG-CoA Reductase*" Tetrahedron Lett., 1992, 33, pp. 2283-2284.