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A NOVEL AND INDUSTRIAL APPROACH FOR THE SYNTHESIS OF VALSARTAN

Rajarshi N. Patel[1]*, Dinesh S. Patel[1],Ravi B. Patel[1] and Ketan S. Patel[1]

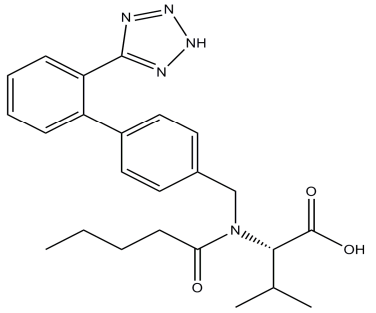
1. *Department of Chemistry , Shree P.M.Patel institute of PG studies and Research in Science .*
**Corresponding author: Phone: +91-9033231942, E-mail: Dadaji.raja@gmail.com*

Abstract
An economical synthesis of the angiotensin-II substance valsartan (Diovan®) is bestowed. Directed ortho-metalation of 5-phenyl-1-trityl-1H-tetrazole (6) and its Negishi coupling with aryl bromide five square measure the key steps of the synthesis. This methodology overcomes several of the drawbacks related to antecedently rumored syntheses.

Keywords:
Antihypertensive therapy; aryl bromide; Negishi coupling; tetrazole; valsartan, Diovan

Introduction

Valsartan (Figure 1) may be a member of a category of compounds known as (angiotensin II) Hypertensin antagonists receptor. This class combines effective anti-hypertensive activity with a superb profile of safety and tolerability. Activation of angiotensin II receptors in the outer membrane of tube sleek muscle cells of the heart and arteries causes the tissues to constrict. angiotensin II receptors are activated by the octapeptide angiotensin II. angiotensin II helps to keep up constant pressure level [1] despite fluctuations during a person's state of association, metal intake and alternative physiological variables. Angiotensin II conjointly performs the regulative tasks of inhibiting the excretion of metal by the kidneys, inhibiting norephedrine re-uptake and stimulating mineralocorticoid biogenesis.



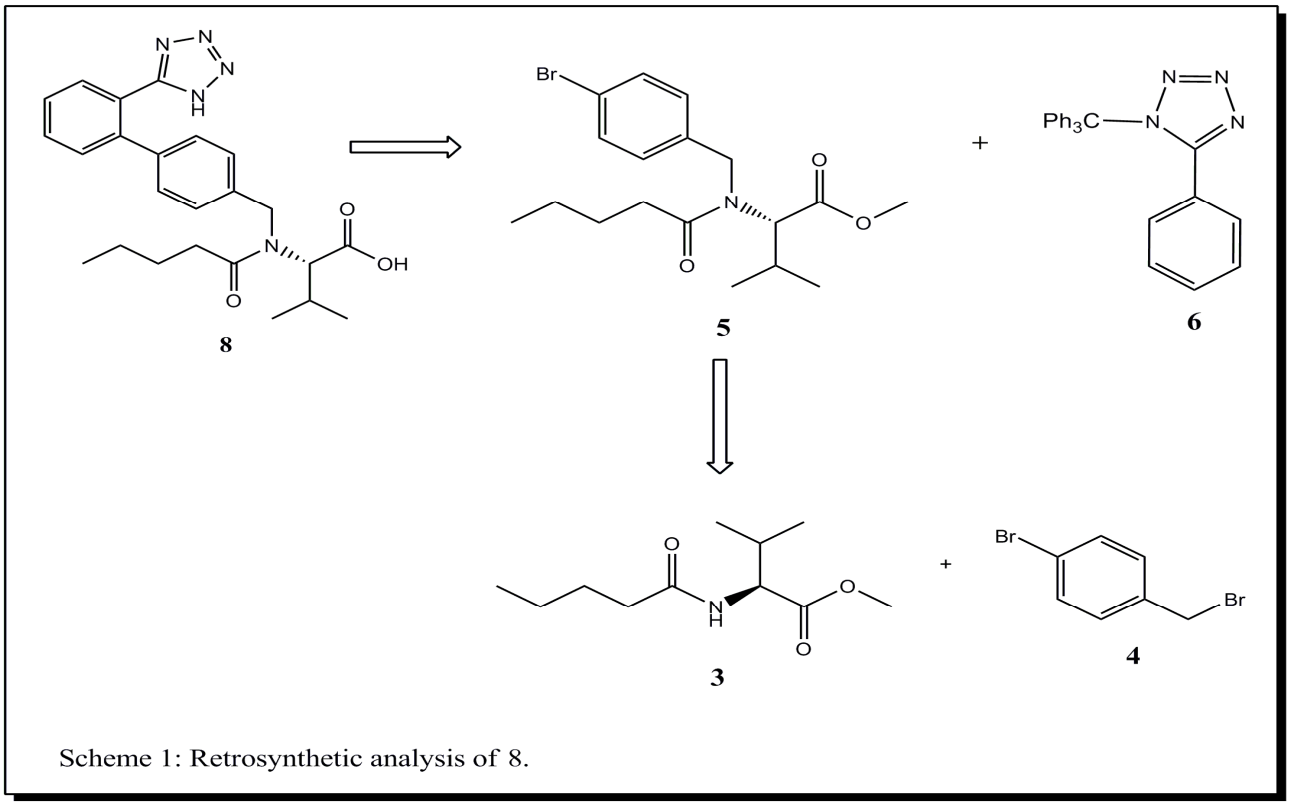
(S)-3-methyl-2-(N-{[2'-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido)butanoic acid
Figure:1 Valsrtan

Valsartan [2] is thus a non-peptide antagonist say angiotensin II. Blocking the actions of angiotensin II on its receptors, valsartan prevents the rise of force per unit area created by the hormone–receptor interactions. Hence, it's employed in the treatment of vessel complaints like cardiovascular disease and failure. Comparative trial studies have shown that valsartan is as effective as angiotensin-converting protein inhibitors (ACE) [3], calcium channel blocker (CCB) and α-adrenergic-antagonists and is mostly higher tolerated. Valsartan is marketed because the free acid underneath the brand name Diovan®. additionally, together with diuretics like thiazide, valsartan offers specific blessings as an anti-hypertensive agent.

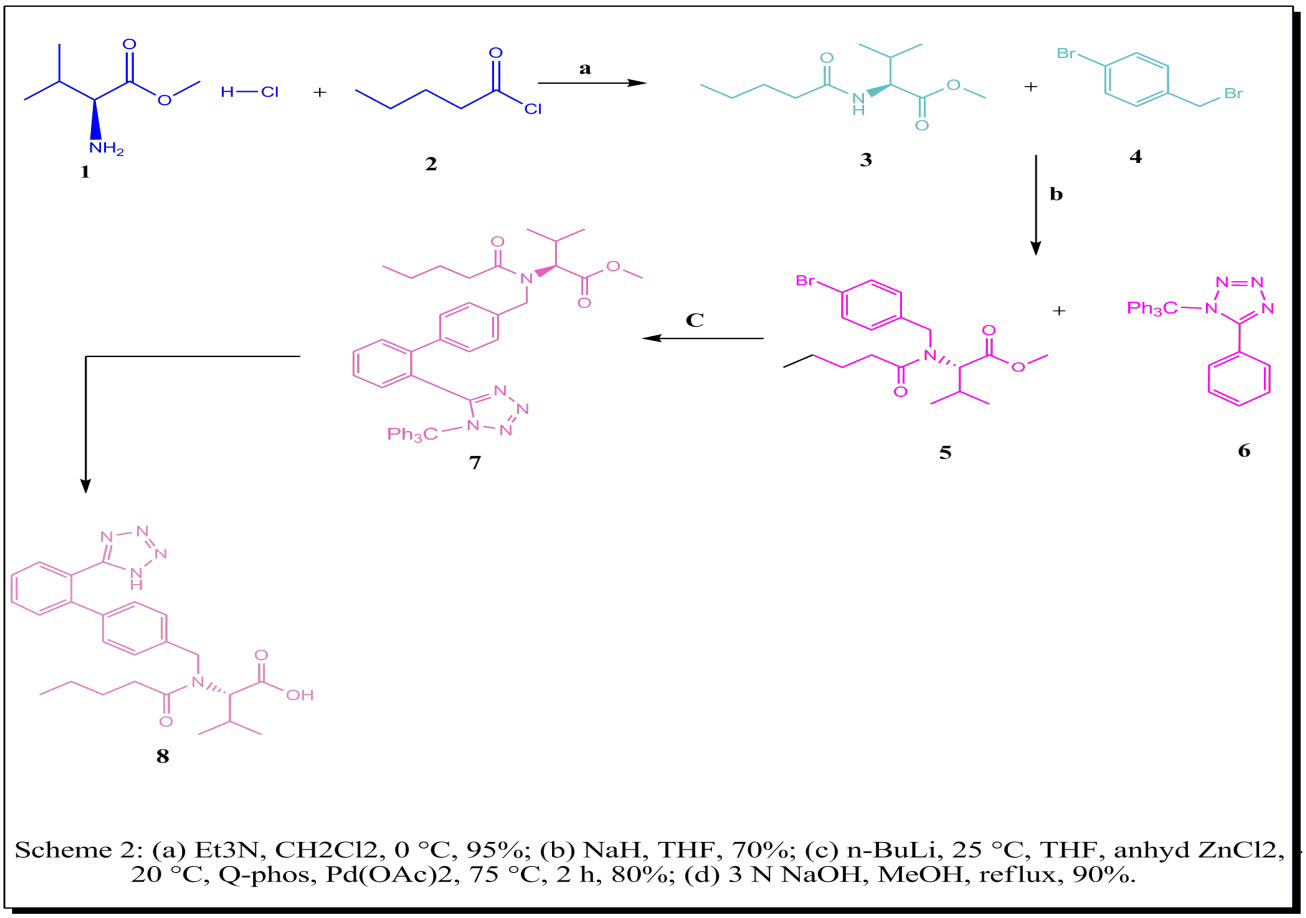
The formation of the aryl–aryl bond represents the key step within the synthesis of sartans: while the synthesis of losartan [4] as represented within the literature makes use of Negishi [5,6] and Ullmann [7] couplings, the revealed strategies for the preparation of valsartan utilize Suzuki–Miyaura couplings [8]. Of these, Negishi reactions have proven to be terribly economical.

However, the utilization of organozinc compounds provides higher transmetalation activity than that obtained by the utilization of organoboron reagents further pretty much as good chemoselectivity since most typical useful teams don't seem to be attacked by organozinc species. though preparations of many biphenyl ring systems associated with valsartan are according, variety of challenges and a few disadvantages - like tedious reaction conditions, low yields and multistep sequences - still exist. Therefore, developing an economical artificial strategy with fewer steps that provides numerous access to those bioactive compounds is a crucial goal. during this paper, we tend to report a replacement, elliptic and economical synthesis of valsartan via Negishi coupling.

Reaction Schemes



Scheme 1: Retrosynthetic analysis of 8.



Scheme 2: (a) Et3N, CH2Cl2, 0 °C, 95%; (b) NaH, THF, 70%; (c) n-BuLi, 25 °C, THF, anhyd ZnCl2, 20 °C, Q-phos, Pd(OAc)2, 75 °C, 2 h, 80%; (d) 3 N NaOH, MeOH, reflux, 90%.

Experimental

Materials and instruments

All solvents and reagents were purchased from the suppliers and used while not any purification. All reactions that are non-aqueous were performed in dry tableware below a dry atomic number 7 atmosphere. Organic solutions were focused below reduced pressure. skinny layer action was performed on Merck recoated Silica-gel sixty F_{254} plates. 1H and 13C magnetic resonance spectra were recorded on a Varian Gemini four hundred megacycle foot magnetic resonance prism spectroscope victimisation $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts square measure reportable in δ ppm relative to TMS. Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS were used to record mass spectra.

(S)-Methyl 3-methyl-2-pentanamidobutanoate (3). Triethylamine (8.33 mL, 59.88 mmol) was value-added to a suspension of L-valine alkyl group organic compound complex a pair of (5.0 g, 29.94 mmol) in methylene chloride (50 mL). Valeryl chloride one (3.95, 32.93 mmol) was then value-added at zero °C and also the mixture stirred at twenty five °C for one h. Water (50 mL) was value-added to the reaction mixture and also the organic layer separated and focused. The solid compound was triturated with heptanes (50 mL) to present associate off white solid three (6.11 g, 95% yield). Rf = 0.6 (7:3; heptanes/EtOAc), 1H proton magnetic resonance (400 rate, DMSO-d6): δ eight.01 (s, 1H), 4.12 (m, 1H), 3.60 (s, 3H), 2.44 (m,2H), 2.12 (m, 2H), 1.90 (m, 1H), 1.46 (m, 3H), 1.25 (m, 5H), 0.86 (d, J = 4.4 Hz, 3H); 13C proton magnetic resonance (100 rate, CDCl3): δ 173.2, 76.3, 55.7, 51.2, 34.3, 33.8, 32.3, 28.6, 23.1, 17.7; ESIMS: m/z calcd [M]+: 215; found: 216 [M+H]+.

(S)-Methyl-2-(N-(4-bromobenzyl)pentanamido)-3-methylbutanoate (5). Hydride dispersion (60%) in oil (1.83 g,46.51 mmol) was further to an answer of compound three (5.0 g,23.25 mmol) and 1-bromo-4-(bromomethyl)benzene (4) (6.39 g, 25.58 mmol) in tetrahydrofuran (80 mL). The reaction mixture was refluxed for one h. when cooling, the mixture was diluted with ether (100 mL) and washed in turn with saturated aq NH4Cl (50 mL) and water (100 mL). The organic layer was dried over Na2SO4 and targeted in vacuum. The residue was chromatographed on colloid. extraction with a mix of heptanes and ester (70:30) yielded the title compound five (6.25 g, 70%) as a colorless oil. Rf = 0.5 (7:3; heptanes/EtOAc), 1H nuclear magnetic resonance (400 rate, DMSO-d6): δ seven.54 (d, J = 6.8 Hz,2H), 7.29 (d, J = 8.8 Hz, 2H), 5.01 (s, 2H), 4.13 (m, 1H) 3.31(s, 5H), 2.32 (t, J = 14.8 Hz, 2H) 1.50 (m, 2H), 1.93 (m, 1H),1.24 (m, 3H), 1.22 (m, 3H), 0.83 (d, J = 7.6 Hz, 3H); 13C nuclear magnetic resonance (100 MHz, DMSO-d6): δ 174.9, 135.5, 134.1, 130.3, 120.1,67.3, 53.5, 50.1, 33.2, 24.5, 26.2, 23.1, 24.2, 20.1, 18.2; ESIMS: m/z calcd [M]+: 384; found: 385 [M+H]+. HRMS (ESI): m/z calcd [M]+: 384.3079; found: 384.3085 [M]+.

(S)-Methyl3-methyl-2-(N-((2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl) pentanamido)butanoate (7). To a mixture of 5-phenyl-1-trityl-1H-tetrazole (6) (2.0 g, 5.15 mmol) in THF (20 mL), n-BuLi (2.5 M in hexane) (2.5 mL, 6.18 mmol) was added at twenty five °C beneath a N_2 atmosphere. The reaction mixture was stirred at twenty five °C for one h and so cooled to − 20 °C. anhydrous ZnCl2 (1.25 g, 9.27 mmol) was other to the reaction mixture and so stirred at − 20 °C for thirty min. The reaction mixture was allowed to consider twenty five °C. Aryl bromide five (2.37 g, 6.18 mmol) followed by Q-phos (0.182 g, 0.25 mmol) and Pd(II)OAc (0.06 g, 0.25 mmol) was other to the reaction blend. The blend was heated at seventy five °C for two h to reflux.The reaction was monitored by tender loving care till the beginning material was consumed. Water (30 mL) was other to the reaction mixture and extracted with ester (3 × fifty mL). The ester layer was separated and focused beneath vacuum. The residue was chromatographed on colloid. extraction with a combination of heptanes and ester (70:30) gave the title compound seven (2.84 g, 80%) as a white solid, mp 45–47 °C, Rf = 0.6 (7:3; heptanes/EtOAc), 1H magnetic resonance (400 megahertz, DMSO-d6) δ seven.72 (d, J = 7.2 Hz, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.44 (m, 1H), 7.35 (m, 11H), 6.99 (m, 1H), 6.78 (m, 7H), 4.60 (m, 2H), 3.25 (s, 3H), 3.15 (s, 1H), 2.20 (m, 2H), 2.02 (m, 1H), 1.33 (m, 2H), 1.20 (m, 3H), 1.01(m, 2H), 0.86 (d, 3H), 0.74 (d, 3H); 13C magnetic resonance (100 megahertz, DMSO-d6) δ 173.8, 171.9, 170.5, 163.0, 142.6, 143.3, 140.1, 136.6, 131.9, 131.0, 128.3, 127.7, 127.3, 127.0, 126.9, 126.4, 125.2, 81.7, 63.3, 50.7, 49.6, 34.6, 35.6, 28.6, 27.5, 21.3, 20.7, 15.4; ESIMS: m/z calcd [M]+: 691; found: 692 [M+H]+;

(S)-2-(N-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)pentanamido)-3-methylbutanoicacid (8). To a mixture of compound seven (2 g, 2.89 mmol) in wood alcohol (20 mL), three N NaOH (2.85 mL) was more and also the mixture heated below reflux for six h. The progress of the reaction was monitored by tending till the beginning material was absent. The reaction mixture was focused below reduced ressure and also the residue was diluted with EtOAc (100 mL) and distilled water (20 mL). acid (2 N HCl) was more dropwise to the mixture till the pH reached four.0. Then the organic part was separated and also the binary compound part extracted with EtOAc (3 × fifty mL). The combined organic extracts were dried over anhydrous Na_2SO4. Evaporation of the solvent gave the crude product (1.12 g, 90%). Recrystallization from EtOAc afforded the anticipated product valsartan 8; mp 114–118 °C; 1H proton magnetic resonance (400 megahertz, DMSO-d6): δ twelve.6 (brs, 1H), 7.72 (m, 4H),7.24 (m, 1H), 7.15 (m, 2H), 6.93 (m, 1H), 4.57 (m, 1H), 4.41 (m, 1H), 3.32 (m, 1H), 2.25 (m, 1H), 1.52 (m, 6H), 0.9 (m, 3H), 0.84

(m, 3H), 0.74 (m, 3H); 13C proton magnetic resonance (100 megahertz, DMSO-d6): δ 173.0, 171.4, 172.8, 140.7, 139.2, 132.54, 132.1, 132.0, 130.3,129.8, 129.2, 128.4, 127.7, 71.3, 64.4, 50.9, 31.9, 29.05, 26.3, 21.2, 21.6, 15.2; ESIMS: m/z calcd [M]+: 435; found: 436 [M+H]+; HRMS (ESI): m/z calcd [M]+: 435.5187; found: 435.5125 [M]+

Results and Discussion

From a retro-synthetic analysis (Scheme 1), compound eight can be created via Negishi coupling from aryl bromide five and 5-phenyl-1-trityl-1H-tetrazole (6), that successively can be obtained from commercially offered benzonitrile. Aryl bromide five can be accessed by many separate reactions of compound three and compound four via a nucleophilic substitution reaction. As shown in theme two, cheap and commercially pronto offered valeryl chloride one was plus L-valine alkyl radical organic compound coordination compound (2) within the presence of triethylamine in chloride at zero °C to afford alkyl radical N-pentanoyl-Lvalinate in ninety fifth yield. Compound three was N-protected with 1-bromo-4-(bromomethyl)benzene in presence of hydride in tetrahydrofuran to present alkyl radical N-(4-bromobenzyl)-N-pentanoyl-L-valinate (5) [9] in seventieth yield. Ortho-metalation of 5-phenyl-1-trityl-1H-tetrazole (6) [10] with n-butyllithium at twenty five °C followed by treatment with atomic number 30 chloride at − 20 °C gave the specified organozinc chloride compound. These will couple finally with aryl bromide five in presence of a chemical process quantity of Q-phos and atomic number 46 acetate in tetrahydrofuran at 75 °C made (S)-methyl3-methyl-2-(N-((2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl) -pentanamido)butanoate (7) in eightieth yield. Hydolysis of seven with three N NaOH in wood alcohol gave valsartan eight [11].

Conclusion

In summary, a extremely economical approach to the biphenyltetrazole structure of the angiotensin-II antagonists has been developed which involves Negishi coupling of metalated 5-phenyl-1-trityl-1H-tetrazole. The strategy is commercially viable and applicable to plant scale . This synthesis route provides an industrial viable procedure for the synthesis of valsartan.

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