Paper

Efficient Synthesis of a 5α -Reductase Inhibitor, 3-(Tetrazol-5-yl)-3,5-pregnadien-20-one through Allylic Rearrangement of Cyanophosphates

1791

Hiroki Yoneyama Yoshihide Usami Shinya Harusawa^{*}



Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan harusawa@gly.oups.ac.jp





Received: 28.11.2018 Accepted after revision: 06.12.2018 Published online: 28.01.2019 DOI: 10.1055/s-0037-1612060; Art ID: ss-2018-m0800-op

Abstract We describe the use of allylic rearrangements of cyanophosphates for the efficient and practical synthesis of 3-(tetrazol-5-yl)-3,5-pregnadien-20-one, which is a potent 5α -reductase inhibitor (IC₅₀: 15.6 nM), from pregnene-3,20-dione in 92% overall yield in four steps.

Key words synthesis, DEPC, cyanophosphates, allylic rearrangement, 3-(tetrazol-5-yl)-3,5-pregnadien-20-one, 5AR inhibitor

Androgens play a vital role in benign prostatic hyperplasia (BPH) and cancer growth in the prostate.¹ 5 α -Reductase (5AR) catalyzes the conversion of testosterone into more potent dihydrotestosterone (DHT). DHT stimulates several growth factors that drive cellular proliferation in the human prostate. Therefore, the inhibition of 5AR has been considered as a valid therapeutic target. There are two main isozymes, 5AR-1 and 5AR-2, with different tissue distribution patterns and distinct biochemical and pharmacological properties.² The most commonly used 5AR inhibitor in BPH treatment is finasteride (1), which was the first 5AR inhibitor approved in the U.S. for the treatment of BPH (Figure 1).^{3,4} However, its limited activity and side effects, which are related to sexual function, have prompted the development of new 5AR inhibitors.⁵





Kumar and co-workers recently reported a series of steroidal tetrazole derivatives; 3-(tetrazol-5-yl)-3,5-pregnadien-20-one (TzPD, **2**) showed the most potent 5AR-2 inhibition with an IC₅₀ of 15.6 nM, while that of clinically used drug finasteride is 40 nM (Figure 1).⁶ Compound **2** also showed significant 5AR-1 inhibition with an IC₅₀ 547 nM, whereas that of finasteride is IC₅₀ 453 nM.

Kumar et al. prepared TzPD **2** in 67% yield through treatment of diene nitrile **4** with sodium azide and triethylamine hydrochloride (Scheme 1).⁶ However, the yields of the two steps (bromination and cyanation)⁷ for the preparation of **4** from pregn-4-ene-3,20-dione (progesterone, **3**) were not reported.



Scheme 1 Synthesis of 2 using Kumar's method

α-Cyanophosphates (CPs)⁸ have been widely utilized as synthetic intermediates in organic synthesis.⁹ In 1985, we reported that CPs derived from α,β-unsaturated ketones were transformed into diene nitriles through a BF₃·OEt₂catalyzed allylic rearrangement, as shown in Scheme 2.¹⁰ In the case of 6-methylbicyclo[4,4,0]dec-1-en-3-one (**5**),^{10a} treatment with diethyl phosphorocyanidate (DEPC)⁹ in the

1792

Syn<mark>thesis</mark>

H. Yoneyama et al.

presence of lithium cyanide afforded CP **6**, bearing a 3 α -cyano-3 β -diethylphosphooxy group.⁸ Subsequent treatment of **6** with BF₃·OEt₂ afforded diene nitrile **8** (94%) through allylic rearrangement to give phosphate **7** and subsequent elimination of (EtO)₂P(O)OH.¹⁰ It has been considered that the rearrangement is a suprafacial [3,3]-sigmatropic rearrangement.¹¹



 $\mbox{Scheme 2}\xspace$ Formation of diene nitrile $\mbox{8}\xspace$ through allylic rearrangement of CP $\mbox{6}\xspace$

In a continuation of our recent program on the utilization of CPs,¹² we were encouraged to look once again for a practical synthetic method to access key intermediate **4** for TzPD **2**. Herein, we report the efficient and practical synthesis of potent 5AR-2 inhibitor **2** by using the allylic rearrangement of CPs.

Starting from progesterone **3**,¹³ the synthesis of precursor **4** towards target tetrazole **2**¹⁴ was carried out through the allylic rearrangement of CPs followed by dephosphorylation, as illustrated in Scheme 3. Reaction of **3** with DEPC (4.0 equiv) in the presence of LiCN (2.0 equiv) easily afforded $C_{3,20}$ -bis-CP **9**.⁸ Compound **9** was subsequently treated with BF₃·OEt₂ (3.0 equiv) in benzene at room temperature (rt) for 1 hour (h) to give diene nitrile **10**; C₂₀-CP was left unchanged.¹⁰ Subsequent hydrolysis of **10** with a solution of 20% NaOH produced diene nitrile **4** in 94% overall yield in three steps from starting compound **3**. Furthermore, it should be noted that the CP group also plays a significant role as a protecting group for the C₂₀-ketone.^{9,15}

We next investigated the transformation of diene nitrile **4** into TzPD **2** by using two reagent systems: sodium azide (NaN₃) in the presence of triethylamine hydrochloride (Et₃N·HCl) (Table 1, entries 1–3) and the system described in Wittenberger's method,¹⁶ namely trimethylsilyl azide (TMSN₃) in the presence of a catalytic amount of Bu₂SnO (entries 4–6).^{12a} Although the reaction of **4** with NaN₃/Et₃N·HCl gave diene tetrazole **2** in low yields in tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) (entries 1 and 2), compound **4** was converted into **2** in 93%



Scheme 3 Synthesis of diene nitrile **4** using BF₃·OEt₂-catalyzed allylic rearrangement of bis-CP **9**

yield under microwave (MW) irradiation conditions in DMF at 130 °C (entry 3).¹⁷ Alternatively, it was found that **4** was transformed favorably into the corresponding tetrazole **2** in 98% yield when heated at reflux with 2 equivalents of TMSN₃ in the presence of Bu₂SnO (0.1 equiv) in toluene for 24 h (entry 6). Therefore, the synthesis of target molecule **2** from progesterone **3** was completed successfully in 92% overall yield in four steps, as summarized in Scheme 4.





Entry	RN₃ (equiv)		Solv.	Time (h)	Temp (°C)	Yield (%)
1	NaN ₃ (3)	Et ₃ N·HCl (3)	THF	24	reflux	12
2	$NaN_3(3)$	Et ₃ N·HCl (3)	DMF	24	130	11
3	$NaN_3(3)$	Et ₃ N·HCl (3)	DMF	2	MW, 130	93
4	$TMSN_3(1)$	Bu ₂ SnO (0.1)	toluene	1	reflux	3
5	$TMSN_3(1)$	Bu ₂ SnO (0.1)	toluene	24	reflux	84
6	$TMSN_3$ (2)	Bu ₂ SnO (0.1)	toluene	24	reflux	98

Paper

Syn thesis

H. Yoneyama et al.



Scheme 4 Synthesis of TzPD **2** from pregnene-3,20-dione (**3**)

In conclusion, we have described the efficient and practical synthesis of TzPD **2** from progesterone (**3**) by using an allylic rearrangement in CP **9**. The present method for the synthesis of **2** is experimentally straightforward and it is suitable for the synthesis of some steroidal 5AR inhibitors.⁷ The present study also helps increase the diversity of available CPs.⁹ In addition, application of this method involving CPs to the synthesis of many biologically important substrates is under investigation in our laboratory.

Reactions were carried out under an Ar atmosphere. Anhydrous solvents (THF, benzene, and toluene) were purchased from Wako Chemical Company. Solvents were dried over Na₂SO₄, and removed on a rotary evaporator under reduced pressure. Fuji Silysia FL-60D silica gel was used for flash column chromatography. Thin-layer chromatography (TLC) was performed on pre-coated TLC plates (Wako silica gel 70 F254). ¹H and ¹³C NMR spectra were recorded with Agilent 400-MR-DD2 spectrometers in CDCl₃ with tetramethylsilane (TMS) as an internal standard or deuterated dimethyl sulfoxide (DMSO- d_6) with chemical shifts given relative to DMSO (δ = 2.5 ppm). Coupling constants (J) are reported in hertz (Hz). For multiplicities, the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. High-resolution mass spectra were obtained with a JEOL JMS-700 mass spectrometer in positive-ion mode, with 3-nitrobenzyl alcohol (NBA). The melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Specific rotations were measured with a JASCO model P-2300 digital polarimeter.

Synthesis of TzPD 2 from Pregnene-3,20-dione (3)

3-Cyano-3,5-pregnadien-20-one (4)

To a solution of progesterone (**3**; 1727 mg, 5.5 mmol) in anhydrous THF (20 mL) were added DEPC (3.3 mL, 22 mmol) and LiCN (363 mg, 11 mmol). After stirring for 0.5 h at r.t., the reaction mixture was diluted with EtOAc, washed with H₂O and brine, and dried over Na₂SO₄. After filtration, the solvent was evaporated to give crude $C_{3,20}$ -bis-CP **9**, which was dissolved in anhydrous benzene (50 mL). To the resulting crude product solution was added BF₃·OEt₂ (2.0 mL, 16.5 mmol). After it was stirred for 1 h at r.t., the reaction mixture was diluted with EtOAc, washed with H₂O and brine, and dried over Na₂SO₄. After filtration, the solvent was evaporated to give crude C₃-cyano-C₂₀-CP **10**, which was dissolved in MeOH (60 mL). To the solution of crude **10** was added NaOH (2.0 g, 50 mmol). After being stirred for 1 h at r.t.,

the reaction mixture was evaporated to give a residue, which was diluted with EtOAc/hexane (1:1), washed with H_2O and brine, and dried over Na_2SO_4 . After filtration, the solvent was evaporated to give a residue, which was purified using column chromatography (EtOAc/hexane, 3:17) to give **4**.

Yield: 1678 mg (94%); white powder.

¹H NMR (CDCl₃, 400 MHz): δ = 6.66 (d, J = 2.4 Hz, 1 H), 5.78 (t, J = 3.6 Hz, 1 H), 2.55 (t, J = 8.8 Hz, 1 H), 2.06–2.44 (m, 4 H), 2.14 (s, 3 H), 1.63–1.72 (m, 6 H), 1.16–1.52 (m, 6 H), 1.02–1.10 (m, 1 H), 0.93 (s, 3 H), 0.66 (s, 3 H).

 ^{13}C NMR (CDCl₃, 100 MHz): δ = 209.3, 143.2, 139.8, 132.4, 120.3, 106.6, 63.5, 56.7, 47.6, 44.0, 38.6, 34.4, 32.7, 32.0, 31.5 (31.51), 31.5 (31.45), 24.3 (24.29), 24.3 (24.28), 22.8, 20.9, 18.9, 13.3.

HRMS (EI): m/z [M]⁺ calcd for C₂₂H₂₉NO: 323.2249; found: 323.2250.

TzPD 2

To a solution of 3-cyano-3,5-pregnadien-20-one (**4**; 162 mg, 0.50 mmol) in anhydrous toluene (5 mL) were added TMSN₃ (0.13 mL, 1.00 mmol) and Bu₂SnO (13 mg, 0.05 mmol). The mixture was heated under reflux for 24 h and then evaporated to give a crude mixture, which was purified by column chromatography (EtOAc) to give **2**.

Yield: 180 mg (98%); white powder; mp 241–244 °C (Lit.⁶ 240–242 °C); $[\alpha]_D$ –151.2 (*c* 1.00, DMF).

 ^1H NMR (DMSO- $d_6,$ 400 MHz): δ = 6.94 (br s, 1 H), 5.75 (br s, 1 H), 2.60–2.70 (m, 1 H), 2.40–2.56 (m, 2 H), 2.18–2.32 (m, 1 H), 2.05 (s, 3 H), 1.88–2.10 (m, 2 H), 1.48–1.84 (m, 5 H), 1.30–1.48 (m, 2 H), 1.10–1.28 (m, 3 H), 1.00–1.08 (m, 1 H), 0.91 (s, 3 H), 0.55 (s, 3 H).

¹³C NMR (DMSO- d_6 , 100 MHz): δ = 208.4, 155.5, 140.3, 132.0, 129.5, 118.7, 62.5, 56.1, 47.2, 43.3, 37.8, 34.2, 32.6, 32.5, 31.5, 31.1, 23.8, 22.6, 22.2, 20.6, 18.8, 13.0.

HRMS (EI): *m*/*z* [M]⁺ calcd for C₂₂H₃₀N₄O: 366.2420; found: 366.2418.

Funding Information

This work was supported financially by research funds from Osaka University of Pharmaceutical Sciences.

Acknowledgment

We would like to thank Professor Emeritus Takayuki Shioiri at Nagoya City University for encouraging us.

Supporting Information

Supporting Information for this article is available online at https://doi.org/10.1055/s-0037-1612060. Included are investigations of the reaction mechanism for the transformation of enone CPs into dienes, and ¹H and ¹³C NMR spectra for compounds **2** and **4**.

References

- (1) Schmidt, L. J.; Tindall, D. J. J. Steroid Biochem. Mol. Biol. 2011, 32.
- (2) Andersson, S.; Russell, D. W. Proc. Natl. Acad. Sci. U.S.A. 1990, 87, 36402.
- (3) Vaughan, D.; Imperato-McGinley, J.; McConnell, J.; Matsumoto, A. M.; Bracken, B.; Roy, J.; Sullivan, M.; Pappas, F.; Cook, T.; Daurio, C.; Meehan, A.; Stoner, E.; Waldstreicher, J. Urology 2002, 60, 1040.

H. Yoneyama et al.

- (4) Bull, H. G.; Garcia-Calvo, M.; Andersson, S.; Baginsky, W. F.; Chan, H. K.; Ellsworth, D. E.; Miller, R. R.; Stearns, R. A.; Bakshi, R. K.; Rasmusson, G. H.; Tolman, R. L.; Myers, R. W.; Kozarich, J. W.; Harris, G. S. J. Am. Chem. Soc. **1996**, *118*, 2359.
- (5) Uygur, M. C.; Gur, E.; Arik, A. I.; Altud, U.; Erol, D. Andrology 1998, 30, 5.
- (6) Aggarwal, S.; Mahapatra, M. K.; Kumar, R.; Bhardwaj, T. R.; Hartmann, R. W.; Haupenthal, J.; Kumar, M. *Bioorg. Med. Chem.* 2016, 24, 779.
- (7) (a) Baine, N. H.; Owings, F. F.; Kline, D. N.; Resnick, T.; Pig, L.-J.; Fox, M.; Mewshaw, R. E.; Tickner, A. M.; Kowalski, C. J. *J. Org. Chem.* **1994**, *59*, 5987. (b) Aggarwal, S.; Thareja, S.; Bhardwaj, T. R.; Haupenthal, J.; Hartmann, R. W.; Kumar, M. *Eur. J. Med. Chem.* **2012**, *54*, 728. (c) Lao, K.; Sun, J.; Wang, C.; Lyu, W.; Zhou, B.; Zhao, R.; Xu, Q.; You, Q.; Xiang, H. Steroids **2017**, *124*, 29.
- (8) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. Tetrahedron Lett. 1984, 25, 427.
- (9) For the recent reviews on DEPC and CPs, see: (a) Harusawa, S.; Shioiri, T. *Tetrahedron* **2016**, 72, 8125. (b) Patel, H. H.; Shioiri, T. *Encyclopedia of Reagents for Organic Synthesis, 2nd ed., Vol.* 5; Paquette, L. A.; Crich, D.; Fuchs, P. L.; Molander, G. A., Ed.; John Wiley & Sons: New York, **2009**, 3737–3743.
- (10) (a) Harusawa, S.; Miki, M.; Yoneda, R.; Kurihara, T. *Chem. Pharm. Bull.* **1985**, 33, 2164. (b) Kurihara, T.; Miki, M.; Yoneda, R.; Harusawa, S. *Chem. Pharm. Bull.* **1986**, 34, 2747. (c) Kurihara, T.; Miki, M.; Santo, K.; Harusawa, S.; Yoneda, R. *Chem. Pharm. Bull.* **1986**, 34, 4620.

- (11) In connection with this study, the reaction mechanism for the transformation of enone CPs into diene nitriles was reinvestigated (see Supporting Information)
- (12) (a) Yoneyama, H.; Numata, M.; Uemura, K.; Usami, Y.; Harusawa, S. J. Org. Chem. 2017, 82, 5538. (b) Yoneyama, H.; Uemura, K.; Usami, Y.; Harusawa, S. Tetrahedron 2017, 73, 6109.
 (c) Yoneyama, H.; Hisaka, F.; Fujisue, D.; Usami, Y.; Zhao, Z.; Harusawa, S. Heterocycles 2018, 96, 106. (d) Yoneyama, H.; Uemura, K.; Usami, Y.; Harusawa, S. Tetrahedron 2018, 74, 2143.
 (e) Yoneyama, H.; Harusawa, S. Heterocycles 2018, 96, 2037.
- (13) Progesterone (3) was purchased from TCI Co., Ltd
- (14) For recent reviews on tetrazoles, see: (a) Bhatt, U. Five-Membered Heterocycles with Four Heteroatoms: Tetrazoles, In Modern Heterocyclic Chemistry, Vol. 3; Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J., Ed.; Wiley-VCH: Weinheim, 2011, 1401–1430. (b) Ostrovski, V. A.; Popova, E. A.; Trifonov, R. E. Developments in Tetrazole Chemistry (2009-16), In Advances in Heterocyclic Chemistry, Vol. 123; Scriven, E.; Ramsden, C. A., Ed.; Academic Press: New York, 2017, 1–62.
- (15) Harusawa, S.; Nakamura, S.; Yagi, S.; Kurihara, T.; Hamada, Y.; Shioiri, T. Synth. Commun. **1984**, *14*, 1365.
- (16) Wittenberger, S. J.; Donner, B. G. J. Org. Chem. 1993, 58, 4139.
- (17) Yoneyama, H.; Usami, Y.; Komeda, S.; Harusawa, S. *Synthesis* **2013**, *45*, 1051.

Paper