Organic Process Research & Development

TECHNICAL NOTE

pubs.acs.org/OPRD

Diastereoselective Reduction of the Enone Intermediate of Travoprost

C. Aswathanarayanappa,[†,‡,*] E. Bheemappa,[§] and Yadav D. Bodke[‡]

[†]Biocon Ltd., 20th KM, Hosur Road, Electronics City, Bangalore-560100, Karnataka, India

[‡]Kuvempu University, Department of Industrial Chemistry, Shimoga-577451, Karnataka, India

[§]Sir M.V. Govt. Science College, Bhadravathi-577301, Karnataka, India

ABSTRACT: A scalable process for the diastereoselective reduction of the prochiral enone intermediate **1** has been developed with DEANB/(*R*)-methyl CBS as reducing agent, to obtain the key intermediate alcohol 15*R*-isomer **2**, used in a process for the manufacture of Travoprost (**3**). Various advantages of this process against the DMSB reduction assisted by (*R*)-methyl CBS have been studied. Specific comparison has been made to highlight the salient features of the chosen process on yield and optical purity with those of the DMSB reduction.

INTRODUCTION

Industrial and commercial applications of amine borane complexes have been known for decades in various fields[1] on account of their mild reducing ability, broad range of stability, and reactivity.

N,*N*-Dialkyl amine borane complexes are found to have significant reactivity compared with most amine boranes, and their corresponding borane complexes have been demonstrated to be apt as good reducing agents. *N*,*N*-Diethylamine is an inexpensive amine and can be converted to *N*,*N*-diethylanilene borane (DEANB) in large scale for industrial applications. A wealth of literature is available on its versatility in reducing a variety of functional groups.[2−6]

In this present work, we report the diastereoselective reduction of the prochiral enone **1** in the synthetic process for Travoprost (**3**, a synthetic prostaglandin-Fα2) (as shown in Scheme 1) to yield the key intermediate alcohol 15*R*-isomer **2** in good yield and optical purity. The importance of chiral purity of pharmaceutical drugs is well established.[7,8] In the course of the reduction of the ketone to a pair of diastereomeric alcohols, one isomer could be utilized as an active drug. Inversion of the stereochemistry at the C-15 position of ocular hypertensive prostaglandins generally lowers the activity.[9,10] Careful considerations have to be made to achieve the required optical purity while not compromising on the yield, in order to obtain a commercially viable process. Glaucoma is a state of hyperpressure in the eye leading to permanent, irreparable damage to optic nerves leading to loss of vision,[11] and Travoprost is a highly efficient pharmaceutical for the treatment of glaucoma and ocular hypertension.[12] The global demand for Travoprost warrants efficient scale-up methods that would facilitate viable commercial production. In the previous synthesis of Travoprost, various reducing agents utilized for the reduction of the enone were associated with shortcomings such as lower selectivity,[13,14] and reduction using DMSB/(*R*)-Me CBS[15] was associated with very many shortcomings such tedious disposal of by products, as well as the stench of dimethyl sulfide. An alternative synthesis of Travoprost was designed by Chirotech to overcome the need for diastereoselective reduction of ketone.[16] DEANB/(*R*)-Me CBS provides high selectivity and optical purity without any trade-off on the yield, and the process proved to be easier to operate.

RESULTS AND DISCUSSION

Lab Synthesis. Initial efforts were focused on synthesis of 15*R*-isomer **2** using DMSB as reducing agent (as shown in Scheme 2). During the development of the process, the stench associated with dimethyl sulfide (DMS) byproduct disposal, the requirement for efficient scrubbing of vented gases during the process, and additional time and costs needed for proper disposal of distillates, mother liquors, and washes laced with DMS discouraged the use of DMSB for large scale synthesis. Another important factor considered when working with DMSB was deactivation of small samples. DMSB should always be added to material (e.g., methanol) being used to deactivate the product. Addition of methanol to a flask containing DMSB could cause a runaway reaction.[17] The logical alternative reagent DEANB was chosen. In the lab, DEANB reproduced results better than those with DMSB. DEANB had several advantages over DMSB: (a) no necessity for refrigeration, (b) no odor and therefore no need to scrub the gas stream, (c) consistent selectivity, (d) better yields, and (e) reduced pyrophoric nature. In addition, the byproduct diethyl aniline formed can be easily removed by washing the reaction mixture with dilute aqueous HCl. Enone **1** was prepared according to known methods.[13−15] In the lab, the diastereoselective reduction of enone **1** was efficiently conducted using DEANB catalyzed by methyl oxazaborolidine [(*R*)-Me CBS] (as shown in Scheme 3).

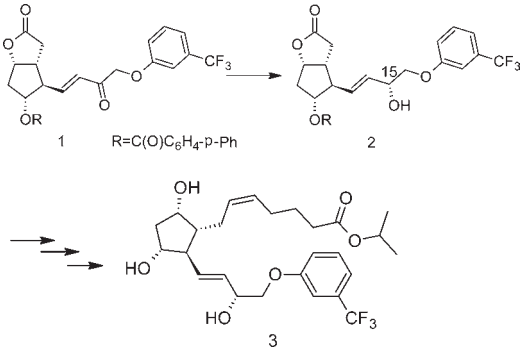
The comparative study showed that DEANB/(*R*)-Me CBS provided 15*R*-isomer **2** in higher purity than with DMSB/(*R*)-Me CBS and other selective reducing agents (Table 1). With the other selective reducing agents, the best selectivity obtained was dr 81:19 using DMSB/(*R*)-Me CBS, whereas DEANB/(*R*)-Me CBS gave dr 90.5:9.5. Though the aim was to circumvent the stench associated with DMSB, the diastereoselectivity was better using DEANB/(*R*)-Me CBS proving it to be environmentally friendly.

The reactions were studied in depth by varying the amounts of DEANB and (*R*)-Me CBS (Tables 2 and 3), and the effect of temperature on diastereoselectivity was also studied.

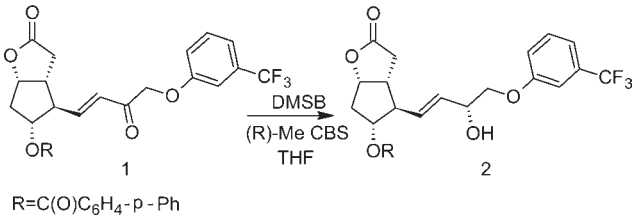
Received: June 8, 2011
Published: August 15, 2011

dx.doi.org/10.1021/op200154p | *Org. Process Res. Dev.* 2011, 15, 1085−1087

Scheme 1. Synthesis of Travoprost 3



Scheme 2. Synthesis of 15*R*-Isomer 2 Using DMSB/(*R*)-Me CBS as Reducing Agent



Scheme 3. Synthesis of 15*R*-Isomer 2 Using DEANB/(*R*)-Me CBS as Reducing Agent

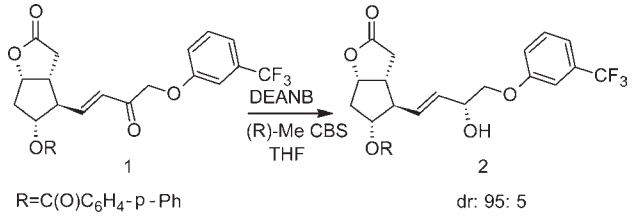


Table 1. Comparison of the Diastereomeric Ratio of 15*R*-Isomer 2 Using DEANB/(*R*)-Me CBS against DMSB/(*R*)-Me CBS and Reducing Agents

entry	borane reagent	reaction conditions	dr
1	DMSB/(*R*)-Me CBS	THF, 0−5 °C, 1 h.	81:19
2	DEANB/(R)-Me CBS	THF, 0−5 °C, 1 h.	90.5:9.5
3	$NaBH_4/CeCl_3.7H_2O$	methanol, −78 °C, 1 h.	58:42
4	(−)-DIP chloride	THF, 20−25 °C, 14 h.	67:33

Effect of Temperature on the Selectivity of 15*R*-Isomer 2. When enone **1** was added to (*R*)-Me CBS and DEANB at 0−5 °C and maintained at that temperature, it was not consumed completely (observed by TLC). Enone **1** needed to be added at low temperature; −15 to −20 °C proved to be the optimal temperature for addition. After the addition of enone **1** the reaction mass temperature was slowly increased to 0−5 °C to take the reaction to completion.

Table 2. Effect of (*R*)-Me CBS on the Diastereomeric Ratio of 15*R*-Isomer 2[a]

entry	(*R*)-Me CBS equiv	dr
1	0.1	89:11
2	0.15	94:6
3	0.2	95:5
4	0.25	95:5

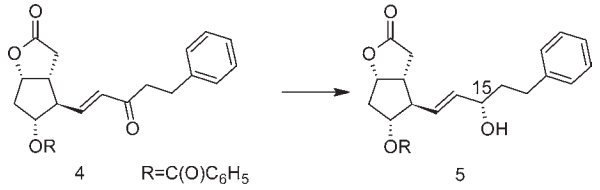
[a] Reagents and conditions: 2.5 equiv of DEANB was kept constant for all reactions.

Table 3. Effect of DEANB on the Diastereomeric Ratio of 15*R*-Isomer 2[a]

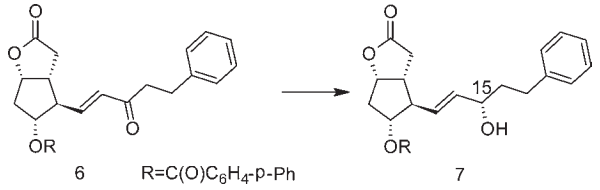
entry	DEANB equiv	dr
1	2.5	95:5
2	3.0	95:5

[a] Reagents and conditions: 0.2 equiv of (R)-Me CBS was kept constant for all the reactions.

Scheme 4. Synthesis of Compound 5



Scheme 5. Synthesis of Compound 7



As shown in Table 2, the diastereomeric ratio of 15*R*-isomer **2** decreased as the equivalents of (*R*)-Me CBS was decreased. Employing 0.2 equiv of (*R*)-Me CBS provided 15*R*-isomer **2** in dr 95:5. The diastereoselectivity was determined on crude product prior to the purification. A minimum of 2.5 molar equiv of DEANB was required to consume enone **1**. Increase in equivalents of DEANB had no effect on diastereomeric purity of 15*R*-isomer **2** (Table 3). Using 2.5 equiv or greater of DEANB and 0.2 equiv of (*R*)-Me CBS resulted in high diastereomeric purity of 15*R*-isomer **2**.

To investigate the advantages and limitations of reduction of enones with DEANB/(*R*)-Me CBS as reducing agent, the optimized conditions were applied to similar substrates (as shown in Schemes 4 and 5), and compound **5** was obtained with dr 85:15 and compound **7** with dr 82:18. These results shows that the selectivity of reduction with DEANB/(*R*)-Me CBS is substrate-dependent and provides high selectivity and good yield in case of 15*R*-isomer **2**.

Multigram Scale Development. On a scale from 100 to 500 g, the diastereomeric ratio remained consistent and the chemical yields were >60%. DEANB was purchased as a neat solution from

dx.doi.org/10.1021/op200154p |*Org. Process Res. Dev.* 2011, 15, 1085–1087

Table 4. Comparison of Diastereomeric Ratio of 15*R*-Isomer 2 with DEANB from Different Vendors

scale (g)	vendor	dr
100	S-A	95:5
200	BASF	95:5
500	BASF	96:4

Sigma-Aldrich and BASF and used for scale-up studies that showed no much difference in the selectivity using that reagent from either source.

The diastereomeric ratio and chemical purities of scale-up batches are shown in Table 4.

CONCLUSION

We have demonstrated that the use of DEANB/(*R*)-Me CBS as reducing agent in a process for the manufacture of Travoprost intermediate 15*R*-isomer **2** provides high selectivity with good yields. The results from numerous multigram batches have proved that DEANB is a superior source of boron in the reduction reactions than DMSB.

EXPERIMENTAL SECTION

General. All the reagents, raw materials, and solvents were purchased from commercial suppliers and used without further purification. All of the reactions were conducted under atmosphere of nitrogen unless noted otherwise. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing by TLC or HPLC. TLC was performed using one of the following systems: 2:1 or 1:1 ethyl acetate/hexane visualized under UV or with Dragendrorff reagent. HPLC analysis was performed at an ambient temperature on a reversed phase stable bond Zorbax SB C8 5 μm column using a mobile phase consisting of 20 mM ammonium acetate and acetonitrile with 70% of ammonium acetate for the first 5 min, changing to 30% ammonium acetate in 17 min and 10% ammonium acetate in 22−25 min at a flow rate of 1.2 mL. The detector was set at 220 nm. The normal phase chromatogrphic separation was performed at ambient temperature on a silica 5 μm column using a mobile phase consisting of 900 mL of *n*-hexane and 100 mL aof bsolute alcohol at a flow rate of 1.0 mL. The detector was set at 220 nm.

Synthesis of 15*R*-Isomer (3a*R*,4*R*,5*R*,6a*S*)-4-((*R*,*E*)-3-Hydroxy-4-(3-(trifluoromethyl)phenoxy)but-1-enyl)-2-oxohexahydro-2*H*-cylopenta[*b*]furan-5-yl Biphenyl-4-carboxylate 2. Detailed description of the process on 500 g scale is as follows. (*R*)-Me CBS (181 mL, 1 M solution in toluene) was charged along with tetrahydrofuran (5 L) under nitrogen atmosphere, and the mixture was stirred at 25 ± 5 °C. *N*,*N*-Diethylaniline-boarane (370 g) was added in a slow stream and stirred for 30 min at 25 ± 5 °C. The contents were cooled to −15 ± 5 °C, and to this mixture was added enone **1** solution (500 g dissolved in 1 L of THF) in about 30 min. The temperature of the reaction mass was increased to 0 ± 5 °C, and the mixture was stirred at that temperature for 1 h. The reaction completion was monitored by TLC. The reaction was quenched with methanol (2 L) at 0 ± 5 °C and stirred at 25 ± 5 °C for 10 min. To the above mass was added 1.5 N hydrochloric acid (2 L), the mixture was stirred at 25 ± 5 °C for 10 min, diluted with ethyl acetate (5 L) and water (5 L), and stirred, and the layers were separated. The organic layer was washed with 1.5 N hydrochloric acid (2 × 1 L), water (2 × 1 L) and saturated sodium chloride solution (1 L), dried using anhydrous sodium sulphate, filtered, and evaporated under vacuum. The crude product obtained gave a 95:5 epimeric mixture of 15*S*-isomer and 15*R*-isomer **2**. The epimers were separated by flash column chromatography on silica gel of 230−400 mesh using ethyl acetate and petroleum ether solvents. This purification step provided 15*R*-isomer **2** as a solid (315 g) in 63% yield with mp 130−133 °C and $[\alpha]^{25}_{D}$ −93.8° (*c* 1.0 in acetonitrile). ^{1}NMR (400 MHz, $CDCl_3$) δ 2.30 (m, 1H), 2.44 (s, 1H), 2.59 (m, 2H), 2.84 (m, 3H), 3.88 (m, 2H), 4.57 (m, 1H), 5.10 (m, 1H), 5.32 (m, 1H), 5.76 (m, 2 H); 7.03 (dd, *J* = 8 Hz, 2 Hz, 1H), 7.13 (s, 1H), 7.23 (d, *J* = 8 Hz, 1H), 7.36 (m, 4H), 7.61 (m, 4H), 8.06 (d, *J* = 8 Hz, 2H).

AUTHOR INFORMATION

Corresponding Author

*Tel: +91 2808 2438. Fax: +91 2808 2303. E-mail: chandrashekar.ashwath@gmail.com.

ACKNOWLEDGMENT

We thank Dr. P. V. Srinivas for his continued advice and M/s. Biocon Ltd. for technical and analytical support.

REFERENCES

(1) Tazi Hemida, A.; Pailler, R.; Birot, M.; Pillot, J. P.; Dunogues, J. *J. Mater. Sci.* **1997**, *32*, 3237–3242.
(2) Brown, H. C.; Murray, L. T. *Inorg. Chem.* **1984**, *23*, 2746–2753.
(3) Periasamy, M.; Bhaskar Kanth, J. V.; Kishan Reddy, Ch. *J. Chem. Soc., Perkin Trans. 1* **1995**, 427–430.
(4) Periasamy, M.; Bhaskar Kanth, J. V.; Bhanu Prasad, A. S. *Tetrahedron* **1994**, *50*, 6411–6416.
(5) Bhaskar Kanth, J. V.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1990**, *17*, 1145–1147.
(6) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1519–1522.
(7) Nguyen, L. A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci.* **2006**, *2*, 85–100.
(8) De Camp, W. H. *Chirality* **1989**, *1*, 2–6.
(9) Resul, B.; Stjernschantz, J.; No, K.; Liljebris, C.; Selen, G.; Astin, M.; Karlsson, M.; Bito, L. Z. *J. Med. Chem.* **1993**, *36*, 243–248.
(10) Hellberg, M. R.; Conrow, R. E.; Sharif, N. A.; McLaughlin, M. A.; Bishop, J. E.; Crider, J. Y.; Dean, W. D.; DeWolf, K. A.; Pierce, D. R.; Sallee, V. L.; Selliah, R. D.; Severns, B. S.; Sproull, S. J.; Williams, G. W.; Zinke, P. W.; Klimko, P. G. *Bioorg. Med. Chem.* **2002**, *10*, 2031–2049.
(11) Resnikoff, S.; Pascolini, D.; Etya'ale, D.; Kocur, I.; Pararajasegaram, R.; Pokharel, G. P.; Mariotti, S. P. *Bull. World Health Org.* **2004**, *82*, 844–851.
(12) Klimko, P. G.; Bisho, J.; Desantis Jr., L.; Sallee, V. L. EP 0639563, 1995; *Chem. Abstr.* **1995**, *122*, 290579
(13) Bowler, J.; Crossley, N. S. U.S. Patent 4,321,275, 1982; *Chem. Abstr.* **1977**, *86* 43256.
(14) Gutman, A.; Nisnevich, G.; Etinger, M.; Zaltzman, I.; Yudovich, L.; Pertsikov, B.; Tishin, B. U.S. Patent 2005029337, 2005; *Chem. Abstr.* **2005**, *143*, 326127.
(15) Greenwood, A. K.; McHattie, D.; Thompson, D. G.; Clissold, D. Patent WO 2002096898, 2002; *Chem. Abstr.* **2002**, *138*, 24587.
(16) Boulton, L. T.; Brick, D.; Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parkin, N.; Rhodes, D.; Ruecroft, G. *Org. Process Res. Dev.* **2002**, *6*, 138–145.
(17) Atkins, W. J.; Burkhardt, E. R.; Matos, K. *Org. Process Res. Dev.* **2006**, *10*, 1292–1295.