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An efficient synthesis of dexlansoprazole employing asymmetric oxidation strategy ☆

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ABSTRACT

An alternative and scalable synthesis of dexlansoprazole ((*R*)-(+)-**1**); the (*R*)-enantiomer of Lansoprazole with an enantiomeric excess of >99.8% is presented.

Introduction

Enantiopure sulfoxide derivatives belong to the family of several biologically active compounds and there are many candidates of this class which got approved by various regulatory authorities.[1] Likewise, dexlansoprazole ((*R*)-(+)-**1**), (*R*)-enantiomer of lansoprazole, is a new proton pump inhibitor (PPI) specifically developed for anti ulcer activity by TAP pharmaceuticals Ltd employing new modified-release technology (Fig. 1).[2]

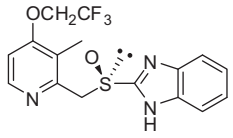
Dexlansoprazole ((*R*)-(+)-**1**) was first approved by United States of Food and Drug Administration (USFDA) in the form of 30 and 60 mg capsules for the management of patients with erosive oesophagitis and non-erosive reflux disease (GERD or GORD), under the brand name of DEXILANT.[3] Extensive research work has been directed/published by various groups on asymmetric sulfoxidation with excellent results, in particular, the oxaziridine mediated asymmetric oxidation[4l] is the recent advancement that has been documented in this area.[4]

Nevertheless, an asymmetric sulfoxidation of prochiral sulfides is one of the most straight forward and convenient approaches to obtain corresponding chiral sulfoxides. In this class, Astra's approach that allows the synthesis of Esomeprazole via modification of Kagan's asymmetric oxidation method is assumed to be one of the best strategies to our knowledge.[5] The detailed mechanistic studies towards present asymmetric sulfoxidation were also reported by the same group in collaboration with Stockholm University research group.[6] Thereafter, the same methodology has been utilized by TAP's group to synthesize the compound of present interest (Scheme 1).[7]

In order to develop an alternative, robust and scalable process, we embarked our studies towards asymmetric sulfoxidation of the related prochiral nitrosulfide analogue **3** that has been utilized later for dexlansoprazole ((*R*)-(+)-**1**) synthesis.[8] Herein, we wish to disclose our approach based on the understanding of the physical properties of the prochiral nitrosulfide **3** hydrates specifically solubility profile under asymmetric oxidation reaction conditions and influence of water on enantioselectivity of *R*-(+)-**4** to establish a robust and highly reproducible large-scale synthetic process for dexlansoprazole with >99.8% ee and ICH quality of final API.

Results and discussion

Our approach began with enantioselective oxidation of the prochiral nitrosulfide intermediate **3** under modified Kagan's selective oxidation conditions to obtain either enantiopure or enantiomerically enriched nitrosulfoxide intermediate (*R*)-(+)-**4** that can easily be converted to Dexlansoprazole ((*R*)-(+)-**1**) in the subsequent step as shown in Scheme 2. The optimized route consists of two steps involving asymmetric oxidation of **3** with cumene hydroperoxide[9] (CHP) in presence of titanium derived chiral complex prepared in situ from L-(+)-Diethyl tartarate (L-(+)-DET), Ti-(O^iPr)$_4$ and water applied in the molar ratio of 2.2:1.1:0.6 to obtain (*R*)-(+)-**4** with



(*R*)-(+)-**1**

Figure 1. Structure of dexlansoprazole.

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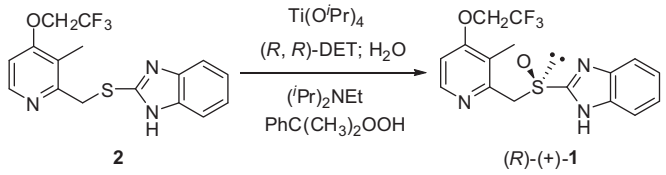


Scheme 1. TAP's approach on dexlansoprazole synthesis.

>90% ee. The enantiomerically enriched (*R*)-(+)-**4** was subjected to acetone mediated preferential crystallization to yield enantiopure (*R*)-(+)-**4** (>97% ee) which on treatment with potassium salt of 2,2,2-triflouroethanol in dimethylformamide (DMF) yielded Dexlansoprazole (after necessary aqueous work up) with ICH quality having >99.8% ee. The detailed experimental study carried out to arrive at the above two step process is discussed in length here in this account.

Enantioselective oxidation of prochiral nitrosulfide intermediate 3 under modified Kagan's conditions

Despite the lack of consistency in the initial laboratory asymmetric oxidation experiments that vary from one lot to another lot of **3**, we decided to continue our efforts to make the process highly consistent and robust. As the project progresses, it was understood that nitrosulfide **3** exists in two different hydrate forms viz., hemihydrates and monohydrate (Fig. 2). Moreover, the solubility profile of each was found to play dramatic role in the presence of a chiral moiety in the initial chiral complex formation step.

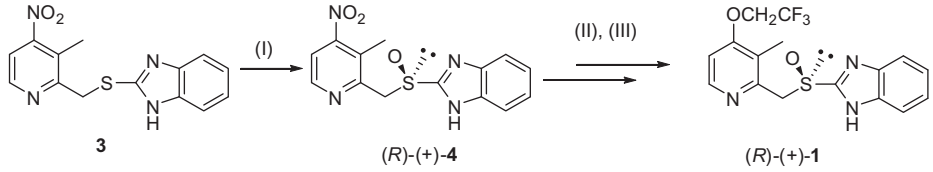
Reaction profile was excellent only with hemihydrate compared to other hydrate and anhydrous forms mainly due to its high solubility during reaction. Reaction profile with anhydrous **3** was found to be heterogeneous that did not go to completion even after introducing equivalent amount of water into the reaction system. Since we did not have good control over consistency of nitrosulfide **3** hydrates, an azeotropic distillation (~110 °C under atmospheric condition) was incorporated at the beginning of the process (reaction components: nitrosulfide **3** + Toluene) before introducing the chiral moiety into the reaction system. At this particular stage, after ensuring total water removal, reaction temperature was brought down to 70 °C and added desired amount of water (i.e., slightly excess to hemihydrate equivalent—0.6 equiv or ~3.6% with respect to input **3**) before introducing the chiral moiety into the reaction system. With this change, reaction profile was found to be consistent ending up with 90–95% ee (95–98% chiral purity). The quantity of water has been thoroughly studied and validated afterwards by monitoring enantiomeric excess of (*R*)-(+)-**4** (chiral HPLC) along with the mole equivalents optimization of L-(+)-DET, and Ti-(O^iPr)$_4$ used for in situ chiral complex generation (Table 1, see Supplementary data).

The other reaction parameters such as mole equivalents of base, oxidizing agent, addition time & temperature, reaction maintenance time, temperature and other work-up conditions (including isolation) were thoroughly optimized and the resulting process has been successfully implemented on the large-scale (85 kg batch size) with predetermined yield and quality. The screening and optimization results are summarized in Table 2 (see Supplementary data). The systematic approach to the optimization led us to arrive at optimal reaction conditions. Our efforts are detailed in the experimental section (see Supplementary data).

Crystallization to wash the (*S*)-(−)-4, undesired enantiomer followed by nucleophilic substitution reaction to introduce 2,2,2-triflouroethoxy group on enantiomerically purified (*R*)-(+)-4

Crystallization method has been developed to remove undesired (*S*)-(−)-**4** from enantiomerically enriched (*R*)-(+)-**4**. The undesired (*S*)-(−)-**4** precipitates out as racemic compound (*RS*)-(±)-**4** under reaction conditions leaving pure (*R*)-(+)-**4** into the filtrate. Solubility profile of the individual isomers ((*R*)-(+)-**4** and (*S*)-(−)-**4**) versus Racemic (*RS*)-(±)-**4** and solvent screening studies led us to the conclusion that acetone is the best solvent system for effective removal of *S*-(−)-**4** by attaining maximum yield and >97% ee as shown in Table 3 (see Supplementary data). Acetone quantity, crystallization/isolation time and temperature also played a dramatic role to attain desired chiral purity with substantial yield as mentioned in the Table 4 (see Supplementary data). The optimum solvent quantity was found to be 22 times with respect to input (*R*)-(+)-**4** as per the brief process described here: Enantiomerically enriched (*R*)-(+)-**4** was suspended in a desired amount of acetone and heated to 45–50 °C for 15–20 min to get the clear solution. Changes in reaction mass description were observed if the solution is kept at 45–50 °C for more than 25 min. The resulting clear solution was cooled to 25–35 °C and then −5 to 0 °C thereby stirred at same temperature for 60–90 min. During the course of operation, (*RS*)-(±)-**4** was thrown out as a solid in the reaction mass leaving pure (*R*)-(+)-**4** into the filtrate. The precipitated (*RS*)-(±)-**4** has been separated by filtration and then filtrate has been subjected to evaporation under vacuum to obtain enantiopure (*R*)-(+)-**4** in ~80% yield [purity: 98.6% (HPLC); chiral purity: 95.2% (HPLC) (>90% ee)]. The resulting enantiopure (*R*)-(+)-**4** has directly been used in the next step of $-NO_2$ substitution reaction. The structure of (*R*)-(+)-**4** has been unambiguously confirmed by single crystal analysis (Fig. 3, see Supplementary data).

Finally, the resulting enantiopure (*R*)-(+)-**4** has been subjected to nucleophilic substitution reaction conditions using potassium salt of 2,2,2-triflouroethanol generated in situ to afford the compound of present interest with ICH (International Conference on Harmonization) quality in ~59% yield [purity: 99.64% (HPLC); chiral purity: 99.98% (HPLC)]. DMF is found to be an excellent choice of solvent and reaction temperature (85–90 °C) is somewhat critical in controlling impurity formation. Furthermore, extensive optimization of work-up conditions (viz., solvent screening, quantity, pH range, isolation time and temperature etc) helped us to washout carryover impurities specifically sulfone and undesired (*S*)-(−)-**1** to the desired limit (<0.15% by HPLC). Other variables of



Scheme 2. Dexlansoprazole synthesis via nitrosulfide **3** asymmetric oxidation. Reagents and conditions: (i) Ti(O-^{i}Pr)4/(*R*,*R*)-DET/H_2O, $PhCH_3$, (^{i}Pr)2NET, $PhC(CH_3)_2OOH$; 0–5 °C, 4–5 h, aq NH_3 and piperidine, acetonitrile, acetic acid; (ii) acetone, 45–50 °C; (iii) K_2CO_3, DMF, CF_3CH_2OH, acetonitrile, acetic acid, water.

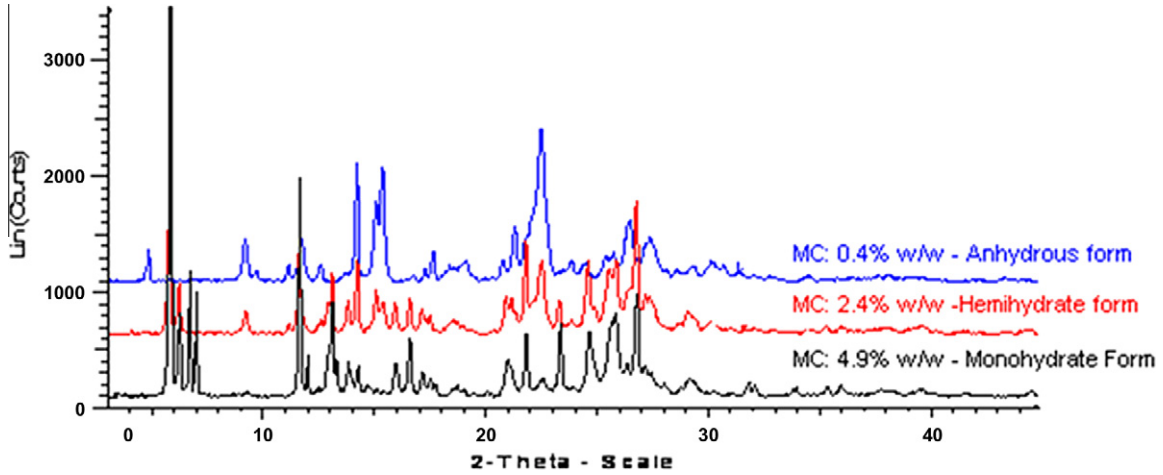


Figure 2. pXRD data for various hydrate forms of the prochiral nitrosulfide derivative **3**.

the reaction conditions involved in overall process were thoroughly optimized and implemented as a single step process in the commercial scale.

Conclusion

An efficient and alternative synthetic protocol for Dexlansoprazole ((*R*)-(+)-**1**) was developed with thorough understanding over solubility profile of the prochiral sulfide hydrates and influence of water on Ti-derived chiral complex preparation that has been used in the asymmetric oxidation step. This optimized process has successfully been implemented in the commercial scale with zero failure obtaining predetermined yield and quality. Apparently, the present method has potential to serve as an alternative synthetic protocol for other enantiopure prazole compounds viz., Omeprazole, Pantoprazole, Rabeprazole etc.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.033.

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