Impurity Synthesis, one of the challenging tasks!

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Introduction

Impurity is a substance, which exists with the active chemical entity. These could originate from the starting materials, or intermediates, typically formed due to some side reactions. The impurities may also appear in the formulated products, as a result of interaction with the co-formulants, immediately or on ageing. Such impurities, even in small quantities, could potentially reduce efficacy, and moreover raise genotoxic/toxic alarms! Development of a process with least harmful impurities/process for removing the impurities, thus are a prime focus during the commercial manufacture. Impurity profiling includes identification, structure elucidation, and quantitative determination of impurities and/or degradation products in the products. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products, and residual solvents (e.g., Q3A(R) Impurities in New Drug Substances, Q3C Impurities: Residual Solvents, and Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances). According to ICH guidelines, an impurity should not exceed 0.1 %, and total impurity should not exceed 1.0 % in manufacturing each batch of the drug. Impurities present in excess of 0.1 % should be identified and quantified by sufficiently selective methods. Moreover, each impurity must be assessed for genotoxic/toxic effects as per the relevant guidelines.

Our synthesis experts at Jai Research Foundation (JRF) offers services for the drug, impurity/degradant route design as well as synthesis. The team is proficient in identification, isolation, route design, synthesis, concentration/purification and characterization. Dedicated in house analytical capabilities, e.g. preparatory and analytical chromatography, facilitate isolation and characterization of the impurities. These capabilities are well augmented by the characterization of the reaction products using LC-MS/MS and multi-nuclear NMR.

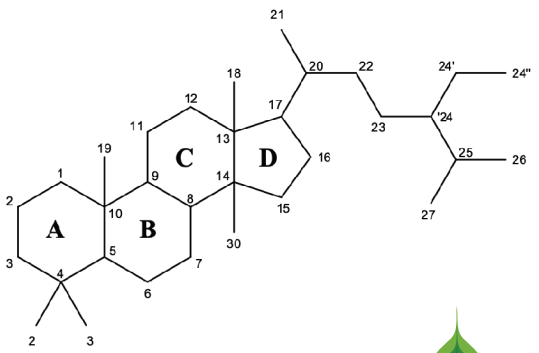
We share herewith, one of our exciting challenges, the synthesis of a dimeric Impurity of Corticosteroid!

Corticosteroids

Corticosteroids are a class of drug that is used for suppressing inflammation, as well as immunity, under critical treatment conditions. They help treating the ailments like asthma, arthritis & allergies. The Dimeric impurity we describe belongs glucocorticoid drug family. It is typically administered as oral, injectable, or topical. It is generally used for treating inflamed joints.

Typical Structure of Corticosteroids

Our challenge was to construct a bond between two molecules of corticosteroids which led to formation of a dimeric impurity. It sounded as simple as forming a bond between C22 and C23, in the above structure!



Challenges in front of us were:

1. **There were no reports of previous publication about synthetic route for this impurity**
2. **The normal manufacturing process tends to find this impurity in trace quantities (0.15%), while synthesizing parent corticosteroid**

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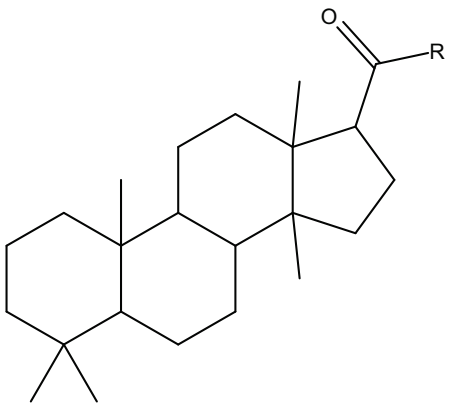
Ideally, the simplest procedure would be to isolate from the mother liquor, after repeated multi-step purification. This option wasn't available to us!

Our team was excited to wet their hands. Their passion to develop a novel synthetic route based on their proven expertise of synthesizing various novel molecules, was infectious!

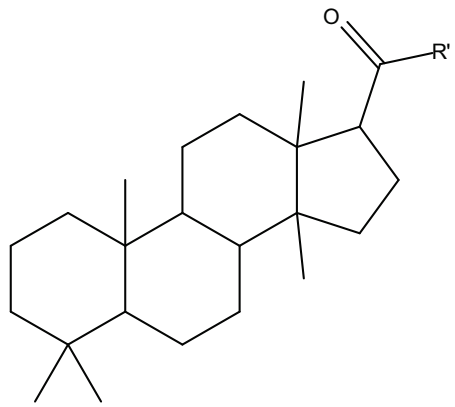
We started with a retro, breaking bonds wherever possible to find a clue which will lead to the target molecule. After some tossing and twisting, we came to a point where we realized that we must connect two different molecules with a desired core structure facilitating bond between C 22 and 23 or bring the two molecules close enough so that the desired bond is formed in between the two!

To achieve this, we formed teams A, B. **Team-A** developed a route for synthesis of **Intermediate-A**, while the **Team-B** focused on **Intermediate-B**.



Int-A

R= -CHO, -CH_2OH, -COOH



Int-B

R'= -CH_2OH, -CHO, -COOH

In due course of time, another **Team-C** is formed which will couple parent corticosteroid with one of the intermediates developed by **Team-A & B**.

Finally, on one fine morning, both the intermediate A & B are ready in our hands. Initially, we attempted Lewis acid catalyzed and base catalyzed reactions. However, nothing seemed to work, with the starting materials remaining intact, in few cases SMs degraded too. Despite these failures, our spirits are high. It was disappointing to know that our designed schemes were not working as predicted. We were optimistic, this wasn't the first time for us to face such a situation. We continued attempting whatever reagent/scheme could work.

Our team believes strongly in the use of Microwave reaction. They believe, that if nothing works in conventional method, it will surely work in Microwave. For our team it's akin to Bramhastra; an ancient Indian assured-win weapon. We used Microwave (ANTON PARR, 200 MonoWave). So, with all the hopes in hand we attempted similar reaction conditions with Int-A & B in the Microwave, however, our perceived **BRAHMASTRA** failed!

Team-C was waiting for directive to go forward to use and react parent corticosteroid with either **Int-A** or **Int-B**. Started with similar plan of coupling using Lewis acid catalyst and attempted based catalyzed reactions. In most of cases, starting materials remains intact. We continued our toil. One fine morning, one of our chemist as usual trying different conditions of coupling and in one reaction serendipitously observed the formation of desired dimeric impurity in trace amounts! This was like appearance of our shiny North Star in the dark nights in the galaxy's.

This was an invigorating development. The team got energized and started driving the process of optimizing the reaction conditions. We started screening using different parameters of temperature, solvent, additives etc. Lo and behold, we got the ideal reaction conditions. We found conversion rate at such levels, that was good enough for concentration using chromatographic conditions. Reaction conditions (set of reagents, solvents, temperature) were finally optimized. The resultant process yielded ~16% of the desired impurity, as a mixture of two diastereomers.

To conclude, the corticosteroid Impurity synthesis, we used Prep-HPLC, to isolate, and polished to achieve the desired purity and quantity.

About the Author:

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Dr. Abdul received his Doctorate from Kyoto Pharmaceutical University, Kyoto, Japan. He is working as a Head of Synthetic Chemistry division at JRF, engaged in customer management, building productive relationships and expanding business opportunities. He has 16+ years of experience of working with critical steps like designing routes for challenging new chemicals, transforming them into robust and efficient processes, for intermediates and final products. As an experienced team leader, having the ability to plan and execute the project to meet the deliverables along with close monitoring of the utilization of all the resources to achieve best possible results. A team player maintaining working relationships with wider spectrum of teams, to achieve the project needs. A highly motivated scientist constantly strives to meet challenging business targets.

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