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## SCALE-UP DEVELOPMENT OF AGGARWAL ENAL BICYCLIC INTERMEDIATE – TOWARDS MODERN MANUFACTURING OF PROSTAGLANDIN DRUGS

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Prostanoids are important class of potent lipid mediators that are involved in the regulation of many biological processes such as inflammation, pain response and fever. This class of compounds has found wide-spread use as pharmaceuticals for the treatment of several diseases including pulmonary arterial hypertension and glaucoma (4.5 billion EUR global market). Recently a multitude of modern and short syntheses of various prostanoids were reported, rejuvenating this historically rich synthesis field. Remarkably short seven step synthesis of PGF2 $\alpha$  reported by Aggarwal group in 2012 has good potential for industrialization [1].

Herein, we report the results of scale-up investigation of enantioselective two step route to Aggarwal enal bicyclic intermediate using extensively reoptimized reaction conditions [2]. Kilogram scale synthesis of succinaldehyde starting material was developed. Safety assessment of this volatile, unstable and polymerization prone compound was performed revealing recommended handling guidelines. Challenging organocatalytic dimerization of succinaldehyde was achieved on hectogram scale. The transfer from magnetically stirred small scale reactions to mechanically stirred large scale reactions in reactor required the finding of appropriate proline catalytic crystalline form [3].

### References:

- [1] Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature*, 2012, 489, 278–281.
- [2] Pelšs, A.; Gandhamsetty, N.; Smith, J. R.; Mailhol, D.; Silvi, M.; Watson, A.; Perez-Powell, I.; Prévost, S.; Schützenmeister, N.; Moore, P.; Aggarwal, V. K. *Chem. Eur. J.* 2018, 24, 9542–9545.
- [3] Pelšs, A.; Shubin, K. *Org. Process Res. Dev.* 2022, accepted, in revision.

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