Organocatalytic Dimerization of Succinaldehyde

Steven H. Bennett and Varinder K. Aggarwal*1,2

School of Chemistry, University of Bristol, Cantock’s Close, Bristol, BS8 1TS

Checked by Tufan K. Mukhopadhyay and Dirk Trauner

Procedure (Note 1)

A. Succinaldehyde (1). A 500 mL round-bottomed flask equipped with a 4.0 cm magnetic stirrer bar and a 30 cm reflux condenser is charged 2,5-dimethoxytetrahydrofuran (100 mL, 0.772 mol, 1.00 equiv) (Note 2) and deionized H₂O (200 mL, 11.1 mol, 14.4 equiv). The biphasic reaction mixture is then placed into a pre-heated IKA heating block at 90 °C and stirred at 500 rpm. The reaction mixture is stirred while heating for 2 h, producing a clear homogenous light-yellow solution (Figure 1).
Figure 1. Reaction set-up for step A after 2 h at 90 °C  
(photo provided by checkers)

The condenser is replaced by a distillation apparatus equipped with a thermometer port and a vacuum adaptor. A 250 mL round-bottomed flask is attached at the receiving end (Note 3) (Figure 2).
Figure 2. Distillation set-up following insulation with aluminum foil and cotton wool using a water-jacketed distillation apparatus and 250 mL round-bottomed receiving flask (photo provided by checkers)

The reaction temperature is increased to 120 °C and the distillate is collected for 2.5 h at atmospheric pressure (Note 4). The remaining solvent is removed by rotary evaporation (Note 5) over 40–45 min at 75 mmHg with the water bath temperature set at 65 °C (Note 6). Toluene (100 mL) is added to the yellow oil and the solvent removal process is continued (75 mmHg, 65 °C) to facilitate azeotropic removal of any residual water. This process is repeated twice more with toluene (2 x 100 mL) to leave behind crude succinaldehyde (ca. 60 g) as a yellow oil (Note 7). The crude product is then transferred to a 100 mL round-bottomed flask (Note 8) equipped with a 2.5 cm magnetic stirrer bar for purification by short-path single-bulb distillation. To this flask is attached a distillation apparatus equipped with a thermometer and vacuum adapter. A 100 mL round-bottomed receiving flask is attached at the end. The receiving flask is subsequently cooled to −78 °C (dry ice/acetone) (Note 9) and the system is placed under high-vacuum (0.08 mmHg) (Figure 3).
The round-bottomed flask containing the crude product is subsequently heated to 80 °C (IKA heating block) and succinaldehyde (48.5 g, 73% yield) is obtained at 38–40 °C (vapor temperature) as a colorless oil (Notes 10–13).

B. (3aR,6aS)-2-Hydroxy-3a,6a,6-tetrahydro-2H-cyclopenta[b]furan-5-carbaldehyde (2). To a 2 L round-bottomed flask equipped with a 4.0 cm magnetic stirrer bar is added freshly distilled succinaldehyde (25.0 g, 0.290 mol, 1.00 equiv) and EtOAc (390 mL, 0.75 M) (Note 14). The solution is briefly stirred (800 rpm, 30 sec) to ensure full dissolution of succinaldehyde and formation of a homogenous solution (Note 15). To the rapidly stirring solution is added 1,3,5-trimethoxybenzene (1.22 g, 7.25 mmol, 2.50 mol%) as an internal standard, followed by L-proline (669 mg, 5.81 mmol, 2.00 mol%). The reaction mixture is stirred (800 rpm) at room temperature for 40 h (Figure 4) (Note 16).
Figure 4. Visual appearance of the reaction following stirring at room temperature for 40 h (photo provided by checkers)

The reaction mixture is subsequently diluted to 0.35 M by the addition of EtOAc (440 mL) and an aliquot (0.1 mL) is taken to check for conversion of succinaldehyde (Note 17). Thiomorpholine trifluoroacetate (1.26 g, 5.81 mmol, 2.00 mol%) (Note 18) is then added before the reaction mixture is placed into a pre-heated IKA heating block (70 °C) and stirred for 2 h (Notes 19 and 20) (Figure 5).
Following this, an aliquot (0.1 mL) is taken to check for conversion of succinaldehyde and the NMR yield of bicyclic enal 2 (Note 21). Pre-treated wet silica gel (Note 22) is then added, and the reaction mixture is removed from the heating block and allowed to cool to room temperature (Note 16) while stirring vigorously for 30 min (Note 23). The crude reaction mixture is filtered through a Büchner funnel into a 2 L filter flask equipped with a 4.0 cm oval magnetic stir bar. The reaction flask and filter cake are then washed thoroughly with EtOAc (2 × 250 mL) (Note 24). Aqueous Na₂SO₄ (500 mL, 12% w/w) (Note 25) is added to the mother liquor and the biphasic mixture is stirred vigorously for 10 min before transferring to a 2 L separating funnel and allowing the phases to separate (Note 26). The aqueous phase is separated, and the organic phase is collected. Extraction of the aqueous phase is repeated two more times with EtOAc (2 × 500 mL) and the organic phases are combined, dried with MgSO₄, filtered, and concentrated under reduced pressure (7.5 mmHg, 25 °C) to afford a crude brown oil (Figure 6).
Figure 6. TLC of the crude reaction mixture (50% EtOAc in n-pentane) stained with p-anisaldehyde showing bicyclic enal 2 alongside succinaldehyde (photo provided by checkers)

The crude product is placed under high vacuum (0.01 mmHg) for 1 h to facilitate further removal of succinaldehyde prior to flash column chromatography (Note 27). Crude bicyclic enal 2 is charged directly onto a column (5 × 45 cm) containing pre-treated wet silica gel (150 g) (Note 22) using dichloromethane (25 mL) to facilitate transfer. The desired product is eluted with 50% EtOAc in n-pentane (45 mL fractions) and obtained in fractions 30–72 (Note 28). The fractions containing product are combined and concentrated under reduced pressure (7.5 mmHg, 25 °C) to afford bicyclic enal 2 (5.76 g, 26% yield, >99:1 e.r., 1.94:1 d.r.) as a light brown solid (Notes 29, 30, and 31) (Figure 7).
Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated...
website “Hazard Assessment in Research Laboratories” at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with 2,5-dimethoxytetrahydrofuran, deionized H₂O, toluene, succinaldehyde, dry ice, acetone, ethyl acetate, 1,3,5-trimethoxybenzene, l-proline, thiomorpholine, thiomorpholine trifluoroacetate, silica gel, sodium sulfate, magnesium acetate, dichloromethane, n-pentane, methanol, chloroform-d, potassium carbonate, acenaphthene, diethyl ether, and trifluoroacetic acid.

2. 2,5-Dimethoxytetrahydrofuran (mixture of cis- and trans-isomers, 99%) was purchased from Acros Organics and used as received.

3. All exposed hot surfaces were insulated with cotton wool and aluminum foil to ensure constant distillation.

4. A distillate (mixture of H₂O and MeOH) of 110 mL was collected during this period.

5. Attempts to remove the remaining solvent by distillation required lower pressures and higher temperatures, which facilitated polymerization and more polymer content in succinaldehyde. Therefore, rotary evaporation was used for further removal of solvent, which did not interfere with the yield and purity.

6. The reaction mixture was allowed to cool to 65 °C over the course of 45 minutes. The distillation apparatus was disassembled, and the flask was connected to a rotary evaporator with the water bath set to 65 °C. The pressure was reduced in a slow and controlled manner to ensure the reaction mixture did not bump.

7. Caution: Succinaldehyde has a particularly distinct and unpleasant odor. At this stage, crude succinaldehyde can be diluted with dichloromethane (ca. 4 mL/g) and stored in a freezer (−20 °C) prior to distillation the following day. The crude succinaldehyde can be stored in dichloromethane at −20 °C for up to a month, but it must be distilled, and purity assessed by NMR prior to use in the next reaction. Distillation temperature and vacuum must be carefully maintained to prevent any polymerization.

8. Crude succinaldehyde was transferred to the 100 mL round-bottomed flask using dichloromethane to facilitate transfer. The dichloromethane was then carefully removed under reduced pressure (22 mmHg, 25 °C) and the crude product was stirred under high vacuum (0.1 mmHg) for
30 min to ensure thorough removal of dichloromethane and residual toluene prior to distillation. Care should be taken during distillation to avoid bumping of the crude product over to the receiving flask. If this is a problem, it can be mitigated by gradual heating or use of a larger distilling flask (e.g. a 250 mL round-bottomed flask).

9. The dry ice/acetone bath is necessary to prevent potential polymerization of neat succinaldehyde during the distillation process.

10. All exposed hot surfaces were insulated with cotton wool and aluminum foil to ensure constant distillation. Towards the end of the distillation process, the oil bath can be increased to 90 °C to assist with the complete distillation of succinaldehyde.

11. Following completion of distillation, the dry ice/acetone bath was removed and the receiving flask containing the colorless solid succinaldehyde was allowed to warm under high vacuum to provide succinaldehyde as a colorless oil. This slow-warming process also prevents the rapid polymerization of neat succinaldehyde.

12. Succinaldehyde can be stored as a solution in dichloromethane (ca. 4 mL/g) and kept in a freezer (−20 °C) for 4 weeks. However, to ensure reliable and reproducible results, succinaldehyde must always be freshly distilled prior to use and its quality checked by 1H NMR analysis. The quality of distilled succinaldehyde can be determined by 1H NMR analysis using 13C–1H satellites in a manner similar to that described by Davies and co-workers.3 13C–1H satellites are 1.108% abundant and provide a ratio of 1:178.5 vs. the parent 12C–1H resonance. Integration of one of the 13C–1H satellites of succinaldehyde’s aldehydic hydrogen resonance (d = 9.82 ppm, chloroform-d) to provide a value of 1.00 allows for comparison against the integration of the oligomeric hemi-acetal region (d = 5.80 – 5.30 ppm, chloroform-d). Where the integration of oligomeric material is ≤15.00, the subsequent L-proline-catalyzed dimerization will provide yields between 25–29% as described. Freshly distilled succinaldehyde always shows the oligomeric proton integration ≤6.00. But storage period of >45 min causes the integration to increase >15.00. For this and subsequent analysis, the chloroform-d used was treated with K2CO3 to remove any DCl, which can promote succinaldehyde oligomerization as well as decomposition of bicyclic enal 2, which is prepared in the next step.
If excess oligomers are observed in the \textsuperscript{1}H NMR, succinaldehyde is distilled again. In our experience, the re-distillation of succinaldehyde can lead to bumping and as such, a short solvent still head placed between the distilling flask and condenser can mitigate this.

13. Succinaldehyde has the following physical and spectroscopic properties: \( R_f = 0.34 \) (50\% EtOAc in \( n \)-pentane); \textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \( d\): 9.80 (s, 2H), 2.79 (s, 4H); \textsuperscript{13}C NMR (101 MHz, Chloroform-\textit{d}) \( d\): 199.8, 36.2; IR (neat) \( \nu_{\text{max}} \): 2910, 2839, 2734, 1711, 1387, 1355, 1261, 1195, 1052, 979, 925, 870 and 764 cm\(^{-1}\). Quantitative \textsuperscript{1}H NMR analysis using 14.0 mg of succinaldehyde and 26.0 mg of acenaphthene (99\%, Sigma Aldrich) as an internal standard provided a purity assessment of 93.3\% by weight. Two other reactions performed by the checkers on full scale provided 48.8 g (73\%) and 55.9 g (84\%) of succinaldehyde.

14. Succinaldehyde (25.0 g, 0.290 mol, 1.00 equiv) was transferred to the 2 L round-bottomed flask using a glass Pasteur pipette as previous transfers using a syringe and needle had resulted in the rapid polymerization of neat succinaldehyde. The quality of succinaldehyde must be checked by \textsuperscript{1}H NMR analysis prior to setting up the \( L \)-proline catalyzed dimerization as the presence of oligomers will result in the observable formation of
numerous purple oligomers that stick to the walls of the round-bottomed flask and result in a poor yield of bicyclic enal 2.

15. It is essential to ensure full dissolution of succinaldehyde in ethyl acetate prior to the addition of L-proline (free-flowing solid) (ReagentPlus®, ≥99%; purchased from Sigma–Aldrich). This can be confirmed by briefly stirring the solution (800 rpm, 30 seconds to 2 min) and observing the dissolution of succinaldehyde to form a homogenous solution. If this is not performed, rapid formation of pink/purple oligomers is observed.

16. Room temperature was typically (20–24 °C).

17. An aliquot (0.1 mL) of the reaction mixture was taken and concentrated under high vacuum (0.01 mmHg) to remove ethyl acetate. Chloroform-\(d\) was added (0.5 mL) and the solution transferred to an NMR tube. \(^1\)H NMR analysis using a Bruker 400 MHz NMR spectrometer (16 scans, 30° pulse angle, 30 s relaxation delay, 25 °C) followed by integration of the aromatic signal of 1,3,5-trimethoxybenzene (\(d = 6.08, s, 3H\)), then the aldehyde of succinaldehyde (\(d = 9.82, s, 2H\)) quantified the amount of succinaldehyde remaining by the following method: The integration of the succinaldehyde peak was divided by 80 to account for both the 2.50 mol% of internal standard used and the two aldehyde protons of succinaldehyde. The value obtained was then multiplied by 100 to convert into a percentage. At this point in the reaction, 10% of succinaldehyde remained.

18. Thiomorpholinium trifluoroacetate was prepared according to a procedure outlined by List and co-workers: To a rapidly stirring solution of freshly distilled thiomorpholine (1.00 mL, 10.0 mmol, 1.00 equiv) in anhydrous diethyl ether (20 mL) was added a solution of trifluoroacetic acid (0.84 mL, 11 mmol, 1.10 equiv) in anhydrous diethyl ether (10 mL) at 0 °C slowly dropwise (syringe pump: 1 mL/min). The reaction was allowed to stir at 0 °C for 1 h before warming to room temperature and stirring overnight. The white precipitate obtained was filtered and washed thoroughly with diethyl ether before leaving to dry under high vacuum (0.1 mmHg) overnight to afford thiomorpholinium trifluoroacetate (2.12 g, 98%) as a white solid.

19. The reaction temperature reaches ~65 °C after 30 min of being immersed in the oil bath and is stirred for 2 h from this point.

20. The reaction mixture color turns from a luminous red (5 min) to a deep purple (15 min), and finally, to a brown heterogeneous mixture (30 min).

21. An aliquot of the reaction mixture (0.1 mL) was taken at this point to quantify the amount of succinaldehyde remaining using the method
described in Note 12 (5% of succinaldehyde remained). The NMR yield of bicyclic enal 2 was also obtained using the same method: following integration of the aromatic signal of 1,3,5-trimethoxybenzene (δ = 6.08, s, 3H), the diastereomeric alkene protons of bicyclic enal 2 (δ = 6.78, app. q, 1H; δ = 6.65, app. q, 1H; 1:9:1 d.r.) were integrated and the values obtained added together. This number was divided by 20 to account for the 2.50 mol% of internal standard used and the 0.5 equivalents of bicyclic enal 2 formed (dimerization). The value obtained was then multiplied by 100 to convert into a percentage. At this point in the reaction, a 30% NMR yield of bicyclic enal 2 was obtained.

22. Pre-treated wet silica gel was prepared by adding H₂O (25 mL) to silica gel (50 g; Sigma–Aldrich technical grade, 40–63 µm) (33% w/w) inside a sealable container. The container lid was closed, and the mixture was shaken vigorously until a uniform consistency was obtained (this process is exothermic, and care should be taken when venting the container). The wet silica gel was then allowed to stand for 1 h prior to use.

23. The pre-treated wet silica gel helps by binding the polymers produced during the dimerization process as well as assisting with the decomposition of succinaldehyde.

24. An aliquot (0.1 mL) of the mother liquor can be taken at this point and analyzed according to Notes 17 and 21 to quantify the level of succinaldehyde remaining and the NMR yield of bicyclic enal 2 to ensure thorough removal of the desired product from the wet silica gel.

25. The 12% w/w aqueous Na₂SO₄ solution was prepared by slowly adding Na₂SO₄ (120 g) portion wise to vigorously stirred H₂O (880 mL). Gentle heating was used to assist with the dissolution of Na₂SO₄. Previously, 17% w/w aqueous Na₂SO₄ solutions were used for this “salting-out” extraction process. However, this increased saturation often led to Na₂SO₄ crashing out of the aqueous phase during extraction.

26. An aliquot (the tip of a glass Pasteur pipette) of the crude product can be taken at this point and analyzed according to Notes 17 and 21 to quantify the level of succinaldehyde remaining and the NMR yield of bicyclic enal 2.

27. Residual succinaldehyde co-elutes with the product during flash column chromatography and also causes streaking.

28. Following elution of fraction 30 (~1.5 L of eluent) the gradient can be increased to 75% EtOAc in n-pentane to facilitate quicker removal of product. However, this results in bicyclic enal 2 being obtained in slightly lower purity as a dark brown solid.
29. Bicyclic enal 2 has the following physical and spectroscopic properties: mp 88–90 °C; \( R_e = 0.20 \) (50% EtOAc in \( n \)-pentane); \(^1\)H NMR (400 MHz, Chloroform-\( d \)) \( \delta \): 9.77 (s, 0.3 × 1H),* 9.76 (s, 0.7 × 1H), 6.78 (app. q, \( J = 2.1 \) Hz, 0.3 × 1H),* 6.65 (app. q, \( J = 2.1 \) Hz, 0.7 × 1H), 5.56 (d, \( J = 5.0 \) Hz, 0.7 × 1H), 5.52 (dd, \( J = 4.8, 0.3 \) × 1H),* 4.96 (broad t, \( J = 6.1, 0.7 \) × 1H), 4.89 (dt, \( J = 6.9, 4.1 \) Hz, 0.3 × 1H),* 3.66 (dt, \( J = 11.0, 6.0 \) Hz, 0.7 × 1H), 3.59-3.52 (broad m, 0.3 × 1H),* 3.08 – 2.66 (m, 3H),* 2.33 – 2.17 (m, 1H),* 2.10 (d, \( J = 13.3 \) Hz, 0.3 × 1H),* 1.94 (dt, \( J = 13.3, 5.1 \) Hz, 0.7 × 1H) ppm (peaks which contain minor diastereomer have been marked with an asterisk (*)); \(^{13}\)C NMR (101 MHz, Chloroform-\( d \)): \( \delta \): 190.2,* 190.1, 153.3,* 152.4, 144.7,* 144.7, 99.0,* 98.6, 82.9,* 80.9, 50.0,* 49.4, 38.2,* 38.0, 35.5 ppm (peaks which contain minor diastereomer have been marked with an asterisk (*)); HRMS (ESI) \( m/z \) calculated for \( \text{C}_{14}\text{H}_{26}\text{O}_2\text{Na}_2\text{[M+Na]}^+ \): 177.0522, found: 177.0526; IR, \( \nu_{\text{max}} \): 3468, 2993, 2928, 2855, 1659, 1617, 1444, 1367, 1261, 1162, 1086, 1036, 995, 979, 870, 797, 764 cm\(^{-1}\). Quantitative \(^1\)H NMR analysis using 25.0 mg of bicyclic enal 2 and 25.0 mg of acenaphthene (99%, Sigma Aldrich) as an internal standard provided a purity assessment of 92.0–94.0% by weight. This can be improved to 98.5 wt.% purity following recrystallization from toluene.

30. The enantiomeric ratio of the enal was determined following chiral GC analysis as described by Aggarwal and co-workers.\(^5\) Chiral GC analysis showed the enantiomeric ratio to be >99:1: Supelco Beta Dex™ 325, Fused silica capillary column (30 m × 0.25 mm x 0.25 µm film thickness); Gas - \( N_2 \), constant pressure 20 psi, Inlet temperature: 250 °C, Split ratio 10:1, Detector: FID 250 °C, Temperature regime: Start 70 °C (3 min hold), heating to 200 °C with speed 3 °C/min (10 min hold). Sample concentration ~ 0.25mg/mL, \( t_r = 36.749 \) (major), \( t_r = 36.420 \) (minor). The other isomer was prepared using D-proline as the catalyst following the identical procedure.

31. A second reaction by the checkers on the same scale provided 5.61 g (25%) of the light brown solid.

**Working with Hazardous Chemicals**

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with
chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in Organic Syntheses, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in Organic Syntheses are provided as published and are conducted at one’s own risk. Organic Syntheses, Inc., its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Prostaglandins (PGs) are a unique family of fatty acid derived local hormones that are responsible for a diverse range of physiological processes, from pain-signaling to inflammation and even bone remodeling. Owing to their biological significance, PGs and their analogues have been attractive targets in total synthesis for over 50 years. In that time, several strategies have emerged for their total synthesis, such as Corey’s bicyclic lactone 3 that contains all the stereochemistry required to access a host of PGs (Scheme 1).
Scheme 1. The original enantioenriched Corey lactone synthesis from cyclopentadiene and its application towards the total synthesis of PGF$_{2\alpha}^{9a,10,11}$

More recently, we have reported the use of bicyclic enal 2, synthesized through the L-proline catalyzed dimerization of succinaldehyde, as a key intermediate in the synthesis of several medicinally-relevant prostaglandins and thromboxanes (Scheme 2)$^{2,5,7,12-15}$

Scheme 2. Aggarwal’s universal approach to prostanoid total synthesis from key bicyclic enal 2.$^{2,5,7,12-15}$

Bicyclic enal 2 is prepared in only two steps from commercially available 2,5-dimethoxytetrahydrofuran. Following initial hydrolysis of the
2,5-dimethoxytetrahydrofuran to produce succinaldehyde, L-proline is used to facilitate the organocatalyzed dimerization before thiomorpholinium trifluoroacetate is added to enable a final aldol condensation to take place (Scheme 3).\textsuperscript{2,3,12}

Mechanistically, this dimerization process proceeds through the formation of an anti-enamine with succinaldehyde and L-proline, followed by pseudo-equatorial approach of a second succinaldehyde to give trialdehyde 5 via transition state 4. Trialdehyde 5 is in equilibrium with its hemi-acetal form 6. Finally, thiomorpholinium trifluoroacetate is added and the final aldol condensation takes place to give bicyclic enal 2 (scheme 4).\textsuperscript{2,5,12}

The highly-defined nature of transition state 4 ensures an excellent level of enantiocontrol within the process (99:1 e.r.); however, the yields are often low (25–29%, 25 g scale) due to the high reactivity of trialdehyde 5, which can undergo further aldol reactions in combination with L-proline, leading to the formation of oligomers. However, through optimization of this procedure,
bicyclic enal 2 can now be reliably and reproducibly synthesized on upwards of 50 g scale with no detriment to the yield or enantioselectivity.\textsuperscript{2,5}

In summary, bicyclic enal 2 is a useful building block in the total syntheses of numerous medicinally-relevant prostaglandins.\textsuperscript{2,5,12,13} This crystalline intermediate can be produced on multigram scale with excellent enantioselectivity (99:1 e.r.) through the L-proline-catalyzed dimerization of succinaldehyde. Recent work from our group has also shown that this key intermediate can be applied to the total synthesis of stable prostacyclin and thromboxane analogues, further highlighting its utility\textsuperscript{14,15}.

References

1. School of Chemistry, University of Bristol, Cantock’s Close, Bristol, BS8 1TS, United Kingdom; orcid.org/0000-0003-0344-6430; Email: v.aggarwal@bristol.ac.uk. The authors thank EPSRC (EP/M012530/1) for financial support and Dr. Andrejs Pelšs (Latvian Institute of Organic Synthesis) for helpful discussions.


9. For a selection of reviews covering the total synthesis of prostaglandins, see:


11. For a selection of other strategies to synthesise Corey lactones, see:


Appendix

**Chemical Abstracts Nomenclature (Registry Number)**

2,5-Dimethoxytetrahydrofuran; (696-59-3)
Succinaldehyde: butanedial; (638-37-9)
Thiomorpholine; (123-90-0)
Trifluoroacetic acid (76-05-1)
L-Proline; (147-85-3)
Steven H. Bennett studied Chemistry with Drug Discovery at the University of Strathclyde, receiving his Master’s degree with First-Class Honours in 2016. Following this, he moved to the University of Bristol to commence his Ph.D. studies under the supervision of Prof. Varinder K. Aggarwal on the total synthesis of prostanoids and the difunctionalization of C–C s-bonds enabled by strained boronate complexes (2016–2020). After completion of his doctoral studies, he continued in the Aggarwal group as a postdoctoral research associate before joining the group of Prof. Andrew L. Lawrence at the University of Edinburgh in October 2021 to focus on the development of new approaches towards enantioconvergent catalysis.

Varinder K. Aggarwal studied chemistry at Cambridge University and received his PhD in 1986 under the guidance of Dr. Stuart Warren. After postdoctoral studies (1986–1988) under Prof. Gilbert Stork, Columbia University, he returned to the UK as a Lecturer at Bath University. In 1991 he moved to Sheffield University, where he was promoted to Professor in 1997. In 2000 he moved to Bristol University where he currently holds the Alfred Capper Pass Chair in Synthetic Chemistry. He was elected Fellow of the Royal Society in 2012.

Tufan K. Mukhopadhyay was born in India and studied organometallic catalysis during his Ph.D. at Arizona State University under the supervision of Prof. Ryan J. Trovitch. After two years of postdoctoral experience, he joined the research group of Prof. Dirk Trauner at NYU as a postdoc to pursue synthesis of bioactive small molecules, natural products, and lipids. His research interests include organic synthesis, catalysis, and medicinal chemistry.
\(^1\text{H NMR of purified succinaldehyde 1}\)
$^{13}$C NMR of purified succinaldehyde 1

\[ \text{f1 (ppm)} \]

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
TKM-succinaldehyde – qNMR:

14 mg freshly distilled succinaldehyde + 26 mg Acenaphthene (99% Sigma Aldrich) in 0.5 mL CDCl₃ (neutralized with K₂CO₃ prior to use) – 400 MHz
$^1$H NMR of purified bicyclic enal 2
$^{13}$C NMR of purified bicyclic enal 2
TKM-OS-II-Bicyclic Enal – qNMR

25.0 mg bicyclic enal (recrystallized from toluene) + 25.0 mg Acenaphthene (99%, Sigma-Aldrich) + 0.5 mL CDCl₃ (neutralized with K₂CO₃ prior to use) – 400 MHz