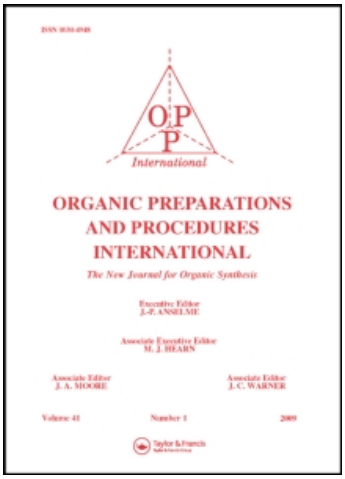


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF AN AZAPROSTAGLANDIN ANALOG

P. A. Zoretic[a]; N. D. Sinha[a]
[a] Department of Chemistry, Southeastern Massachusetts University, North Dartmouth, Massachusetts

To cite this Article Zoretic, P. A. and Sinha, N. D.(1978) 'SYNTHESIS OF AN AZAPROSTAGLANDIN ANALOG', Organic Preparations and Procedures International, 10: 1, 33 — 38
To link to this Article: DOI: 10.1080/00304947809355002
URL: http://dx.doi.org/10.1080/00304947809355002

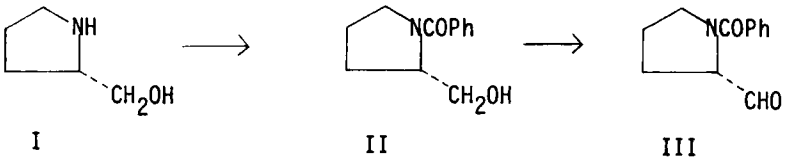
ORGANIC PREPARATIONS AND PROCEDURES INT. 10(1), 33-38 (1978)

SYNTHESIS OF AN AZAPROSTAGLANDIN ANALOG

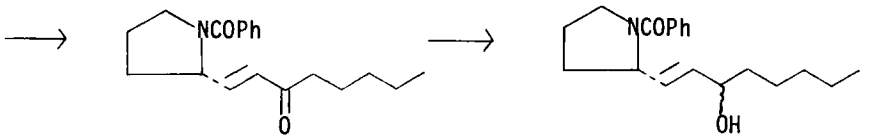
P. A. Zoretic* and N. D. Sinha

Department of Chemistry
Southeastern Massachusetts University
North Dartmouth, Massachusetts 02747

In our continuing efforts toward the synthesis of 8-aza-PGE type analogs, we were interested in synthesizing the pyrrolidines V. Reaction of L-2-hydroxymethylpyrrolidine I with benzoyl chloride in chloroform afforded a 97% yield of the optically active alcohol II, [α] D -142.19°. Oxidation of the alcohol II with Collins reagent[2] in methylene chloride at -23° for 2.75 hrs. and subsequent treatment with powdered sodium bisulfate monohydrate at -23° followed by chromatography on silica gel G and elution with ether-hexane solutions gave the aldehyde III in 61% yield. Treatment of the aldehyde III with the lithium salt of dimethyl (2-oxoheptyl)-phosphonate in tetrahydrofuran at 0° for 3 hrs.



I II III



IV V

followed by chromatography on silica gel G and elution with ether-hexane solutions afforded a 68% yield of the enone IV, [α] D -103.68°. Reduction of the enone IV with powdered sodium borohydride in methanol at 0° for 1.25 hrs. and subsequent chromatography afforded an 86% yield of a 1:1 mixture of the C-15 epimeric amide alcohols V, [α] D -80.82°. Several attempts to separate the amide alcohols V by preparative thin layer chromatography failed. The alcohols appeared as one elongated spot in several different solvent systems.

The amide alcohols V displayed mild activity[3] with respect to inhibiting platelet aggregation.

EXPERIMENTAL

1-Benzoyl-2-hydroxymethylpyrrolidine (II). - A solution of 1-2-hydroxymethylpyrrolidine I[4] (7.0 g, 0.0693 mole) dissolved in 25 ml of chloroform was cooled to 0°. A solution of benzoyl chloride (4.9 g, 0.0349 mole) dissolved in 10 ml of chloroform was added dropwise over a 0.5 hr. period. The reaction mixture was stirred at 0° for 1 hr. and then allowed to warm to room temperature and stirred for an additional hr. The reaction was poured into 50 ml of chloroform and extracted with 30 ml of a 10% HCl solution, 50 ml of H_2O, 50 ml of a 10% $NaHCO_3$ solution and 50 ml of a saturated NaCl solution. The chloroform solution was dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator and additional pumping at 0.1 mm with heat yielded 6.9 g (97%) of the amide alcohol II, bp.[5] 170° (0.08 mm), [α] D -142.19°, nmr (CCl_4) δ 6.85-7.75 (m 5H), 4.52 (s, OH) and 2.95-5.05 (m) [6H] and 1.35-2.40 (m, 4H), ir (neat): 3390 (broad) and 1625 (broad) cm^{-1}. A small amount of (II) was chromatographed on silica gel G and elution with ether afforded an analytical sample.

Anal. Calcd for $C_{12}N_{15}NO_2$: C, 70.22; H, 7.37, N, 6.82. Found: C, 70.24; H, 7.40; N, 6.88.

1-Benzoyl-2-formylpyrrolidine (III). - A 1ℓ three-neck flask fitted with a mechanical stirrer, addition funnel and serum cap was flamed and deaerated with nitrogen. Purified celite 545 (75 g) was placed in the reaction vessel and a solution of Collins reagent (37.8 g, 0.0147 mole) dissolved in 380 ml of dry CH_2Cl_2 was added under nitrogen and the resulting mixture was cooled to -23° (dry ice - CCl_4). A solution of the amide alcohol II (2.5 g, 0.0122 mole) dissolved in 100 ml of dry CH_2Cl_2 was added all at once under nitrogen. The resulting reaction mixture was stirred at -23° for 2.75 hr. Powdered $NaHSO_4 \cdot H_2O$ (75 g) was added all at once at -23° and the reaction was stirred for an additional 0.75 hr. at -23°. The reaction mixture was filtered through a tightly packed cake of anhydrous $MgSO_4$ in a fritted funnel under suction. The reaction vessel was washed with four 500 ml portions of dry CH_2Cl_2 and filtered through the $MgSO_4$ cake. The methylene chloride solution was concentrated on a rotary evaporator to afford 2.0 g of crude (III). The crude aldehyde III was immediately chromatographed on silica gel G and elution with ether-hexane solutions yielded 1.5 g (61%) of the pure aldehyde III, NMR (CCl_4) δ 9.56 (s, 1H), 6.90-7.75 (m, 5H), 4.10-4.85 (m, 1H), 3.58 (t, 2H) and 1.50-2.35 (m, 4H), ir (neat): 1635 (broad) and 1740 cm^{-1}.

The aldehyde III was not characterized further, but committed directly to the Wadsworth-Emmons reaction.

1-Benzoyl-2-(trans-oct-1-en-3-one)-pyrrolidine (IV). - A three neck flask fitted with an addition funnel, nitrogen inlet tube, serum cap and magnetic stirring bar was flamed and deaerated with nitrogen. Dimethyl-(2-oxo-heptyl)-phosphonate (1.42 g, 0.0064 mole) dissolved in 30 ml of dry THF

was placed in the reaction vessel and cooled to 0°. A 2.5 M n-Butyl lithium solution (2.56 ml. 0.0064 mole) was added with a syringe and the reaction mixture was stirred for 30 min at 0°. The aldehyde III (1.37 g, 0.00675 mole) was dissolved in 25 ml of dry THF and added all at once at 0°. The reaction mixture was stirred at 0° for 3 hrs.and then poured into 150 ml of cold H_2O. The resulting mixture was extracted with three 150 ml portions of $CHCl_3$. The combined chloroform extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentration with a rotary evaporator afforded 2.5 g of an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions yielded 1.3 g (68%) of the pure enone IV, [α] D -103.68°, nmr (CCl_4) δ 7.15-8.0 (m, 5H), 5.65-6.95 (m, 2H), 4.35-5.15 (m, 1H), 3.25-3.85 (m, 2H), and 1.08-2.80 (m) and 0.91 (t) [15H], ir (neat): 1625 (broad) and 1660 (shoulder) cm^{-1}. Mass spectrum m/e 299 (M); 270 ($M-C_2H_5$); 256 ($M-C_3H_7$); 243 ($M-CH_2=CH-CH_3$); 200 ($M-C_5H_{11}C=O$); 194 ($M-C_6H_5C=O$); 174 [$M-C_5H_{11}-(C=O)-CH=CH_2$]; 138 ($M-CH_2=CH-C_2H_5$ and $C_6H_5C=O$); 105 [$M-C_4H_7N-CH=CH(C=O)C_5H_{11}$].

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.23; H, 8.35; N, 4.78.

1-Benzoyl-2-(trans-oct-1-en-3-ol)-pyrrolidines V. - The enone IV (0.68 g, 0.00227 mole) was dissolved in 5 ml of methanol and cooled to 0°. Sodium borohydride (50 mg, 0.00132 mole) was added in small portions over a 10 min period at 0° with stirring and the reaction mixture was allowed to stir for an additional 1.25 hr.at 0°. The reaction mixture was poured into a cold aqueous NaOH solution [H_2O(50 ml) and a 10% NaOH solution (10 ml)] and extracted with three 75 ml portions of $CHCl_3$. The chloroform extracts were combined, washed with two 50 ml portions of H_2O, dried

over anhydrous $MgSO_4$, filtered, and concentration with a rotary evaporator yielded 0.65 g of an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions afforded 0.590 mg (86%) of a C-15 epimeric mixture of the pure amide alcohols V, [α] D -80.82°, nmr (CCl_4) δ 7.17-8.10 (m, 5H), 5.15-6.18 (m, 2H) 3.09-4.90 (m, 5H), and 1.09-2.50 (m) and 0.92 (t, distorted) [15H], ir (neat): 3410 (broad) and 1615 cm^{-1}. Mass spectrum m/e 301 (M); 284 (M-OH), 283 (M-H_2O); 272 (M-C_2H_5); 230 (M-C_5H_{11}); 226 (M-C_4H_9 and H_2O); 200 (M-$C_5H_{11}CHOH$); 174 (M-$C_5H_{11}CHOH$); 105 (M-C_4H_7N-CH=CHCHOH-C_5H_{11}).

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.24; H, 9.03; N, 4.57.

REFERENCES

1. P. A. Zoretic, N. D. Sinha and B. Branchaud, Syn. Commun., 7, 299 (1977); P. A. Zoretic, N. D. Sinha and B. Branchaud, J. Org. Chem., 42, 3201 (1977); P. A. Zoretic and J. Chiang, J. Org. Chem., 42, 2103 (1977); P. A. Zoretic, B. Branchaud and N. D. Sinha, Org. Prep. and Proced. Int., 9, 159 (1977) and P. A. Zoretic and P. Soja, J. Heterocyclic Chem. (in press, 1977).
2. J. C. Collins, W. W. Hess and F. J. Frank, Tetrahedron Lett., 3363 (1968).
3. We would like to thank Dr. W. J. Welstead, Jr. and Dr. C. Lunsford of the A. H. Robins Pharmaceutical Co., Richmond, Virginia for making these results known to us; Mr. M. Stone for the microanalyses, Mr. J. Forehand for the mass spectral data and Mr. A. F. Johnson for coordinating the data obtained from the Robins Co.

4. Obtained from the Aldrich Chemical Company.
5. Distillation of the amide alcohol produced a less polar top spot via tlc analysis. The amide alcohol obtained from column chromatography was therefore used directly in the Collins oxidation reaction.

(Received July 8, 1977; in revised form December 7, 1977)