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TOTAL SYNTHESIS OF PROSTAGLANDINS. V. A SYNTHESIS OF (-)-PROSTAGLANDIN E_2 VIA A TOTALLY ASYMMETRIC PROCESS.[1]

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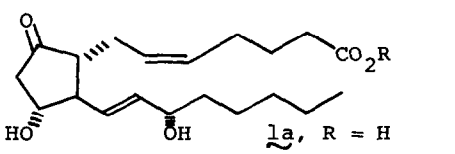
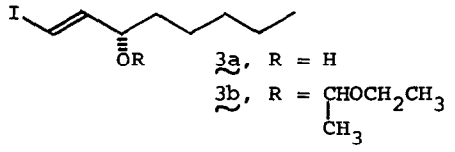
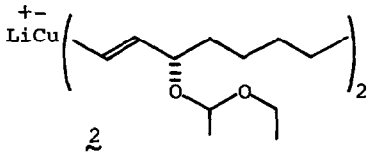
We wish to report the synthesis of prostaglandin E_2 (PGE_2, 1a) via conjugate addition of the vinyl cuprate 2, derived from trans-3(S)-(1-ethoxyethoxy)-1-iodo-1-octene (3b), to 2-(6-carbomethoxy-cis-2-hexenyl)-4(R)-(2-tetrahydropyranyloxy)-2-cyclopenten-1-one (4b). We also describe herein a novel synthesis of the key intermediates 3a and 4a in their optically active forms without chemical resolution. This totally asymmetric process constitutes an additional refinement of our approach to the synthesis of the prostaglandins.



1a, R = H
1b, R = CH_3



3a, R = H
3b, R = $CHOCH_2CH_3$ (CH_3)



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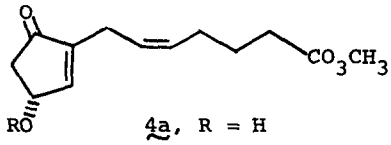
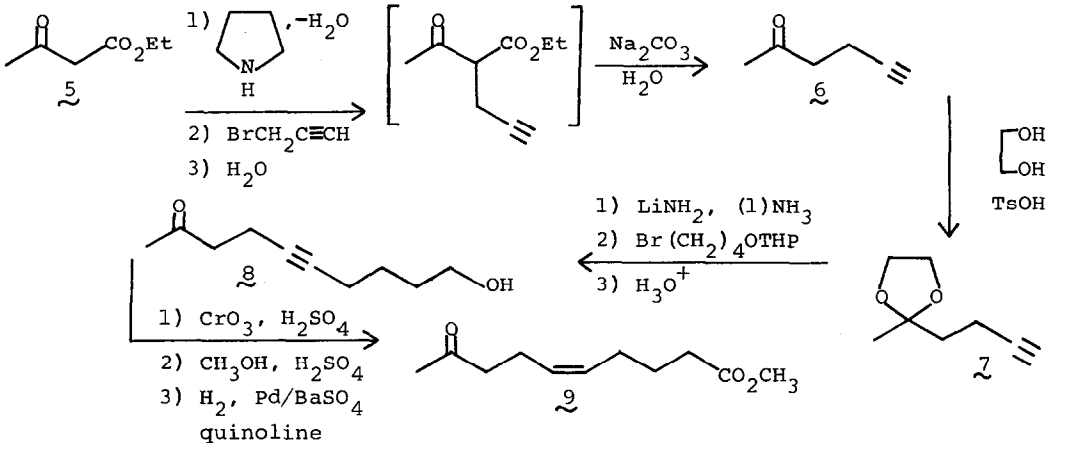


4a, R = H
4b, R = THP

Reaction of the pyrrolidine enamine of acetoacetic ester (5) with propargyl bromide[2], followed by alkaline hydrolysis and decarboxylation afforded 1-hexyn-5-one[3a,b] (6) in 70% yield[4]. After conversion of 6 into the cycloethylene ketal[3b,c] (7, 90% yield) in the usual manner, 7 was treated with lithium amide in liquid NH_3 and condensed with 1-bromo-4-tetrahydropyranyloxybutane[5] using tetrahydrofuran as co-solvent. Acidic hydrolysis of the resultant ethylene ketal-THP ether gave 9-oxo-5-decyn-1-ol (8) in greater than 85% yields from 7. Jones oxidation of 8, followed by acid-catalyzed esterification and hydrogenation over Lindlar's catalyst, afforded methyl cis-9-oxo-5-decenoate (9) in 60%

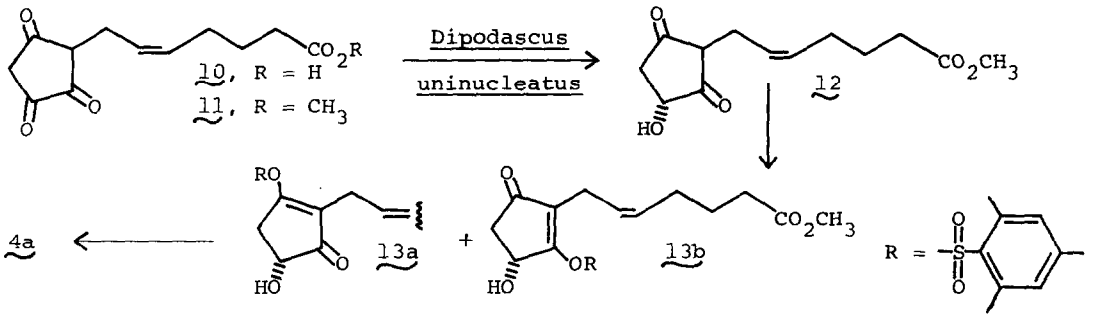
yield overall. Condensation of 9 with diethyl oxalate (sodium ethoxide, ethanol)[6], followed by acid hydrolysis, gave 2-(6-carboxy-cis-5-hexenyl)-cyclopentane-1,3,4-trione (10) in 50% yield. After re-esterification, 11 was



incubated with Dipodascus uninucleatus following the conditions previously described[1] to yield the 4(R) alcohol 12 (60%), mp 61.5-62.5°; uv max (CH_3OH) 272 nm (ε 21,000); $[\alpha]_D^{24}$ +24.7° (c 1.47, $CHCl_3$).

Reaction of 12 with 1.2 equiv of 2-mesitylenesulfonyl chloride and triethylamine at -10° afforded two isomeric enol sulfonates (13a and b) in a ratio of 9:1[7]. This mixture was directly reduced with an excess of sodium bis(2-methoxyethoxy)aluminum hydride in toluene at -70°, followed by acid-catalyzed rearrangement and elimination (oxalic acid, sodium oxalate, $CHCl_3$, r.t., 2 hr), to afford 4a as an oil in 50% yield from 12; uv max (CH_3OH) 220 nm (ε 8,000); $[\alpha]_D^{24}$ +10.85° (c 2.62, CH_3OH).[8]

By analogy to the PGE_1 series[1], the attack of the vinyl cuprate 2 should also proceed from the least hindered side of 4b and the protonation of the resulting enolate should produce PGE_2 possessing the correct all-trans stereochemistry at the 8, 11, and 12 positions. Thus, three of the four asymmetric centers in PGE_2 are controlled by the configuration of the alkoxy function at C-4 in 4b. The problem of chirality at C-15, which was surmounted earlier in the PGE_1 series by chemical resolution of 3a[9] or (±)-1-octyn-3-ol[1,9], a precursor of 3a, can now be introduced asymmetrically via microbial reduction of 1-iodo-1-octen-3-one[10] (14).



It is known that α,β-unsaturated ketones do not yield allylic alcohols by enzymic reduction owing to resonance stabilization of the carbon-oxygen double bond.[11] However, introduction of an electronegative substituent onto the unsaturated ketone system promotes enzymic reduction to substituted allylic alcohols. By this rationale it seemed possible that iodo ketone 14 might yield hydroxy iodide 3a on microbial reduction. Indeed, it was found that washed cells[12] of Penicillium decumbens in 0.025 M borate buffer (pH 8.5) catalyzed this reduction of 14 to the desired 3(S) alcohol 3a (10% yield), $[\alpha]_D^{24}$ +7.51°[13] (c 3.7, CH_3OH). Under similar conditions, Aspergillus ustus gave the 3(R) enantiomer of 3a (12% yield), $[\alpha]_D^{24}$ -8.0° (c 5.97, CH_3OH).

The iodo alcohol 3a was protected as the ethoxyethyl ether 3b. Treatment with two molar equivalents of tert-butyllithium[10] to generate the vinyllithium reagent (ca. 87% yield as assayed by the benzophenone method[10]) followed by addition of 0.44 molar equivalents of tri-n-butylphosphine-copper iodide complex[14] gave the cuprate 2. Protection of 4a as the tetrahydropyranyl ether 4b and reaction with 1.2 equiv of cuprate 2 (-20°, 1 hr) gave, after acidic hydrolysis of the protecting groups[15] and chromatography, (-)-PGE_2 methyl ester (1b) in 50-60% yield based on 4a. Exposure of 1b to Rhizopus oryzae afforded (-)-PGE_2 (1a), $[\alpha]_D^{24}$ -52° (c 1.15, THF), identical (infrared, nuclear magnetic resonance and mass spectra) to an authentic specimen.[16]

Acknowledgment

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Footnotes and References

1. Paper IV of this series: C. J. Sih, J. B. Heather, G. P. Peruzzotti, P. Price, R. Sood, and L. F. H. Lee, J. Amer. Chem. Soc., 95, 1676(1973).

2. Propargylation of ethyl acetoacetate enamines have been previously reported: cf. J. F. Tinker and T. E. Whatmough, ibid., 74, 5235(1952) and G. Eglington and M. C. Whiting, J. Chem. Soc., 3053(1953).

3. a) J. Colonge and R. Gelin, Bull. soc. chim. France, 208(1954);
b) C. Feugeas, ibid., 2579(1963);
c) G. Stork and R. Borch, J. Amer. Chem. Soc., 86, 935(1964).

4. The yields reported are minimal and no efforts were expended in optimization of the reactions. Spectral data were in complete agreement with assigned structures.

5. 1-Bromo-4-tetrahydropyranyloxybutane was prepared from 1,4-butanediol (ca. 60%) by monotetrahydropyranylation, mesylation and treatment of the mesylate with LiBr in acetone.

6. For the related reaction with methyl 9-ketodecanoate see J. Katsube and M. Matsui, Agri. Biol. Chem., 33, 1078(1969).

7. The ratio of the two isomeric enol tosylates can be readily estimated by the nmr signal of the carbinolic protons at C-4 (δ 4.25 for 13a and δ 5.10 for 13b in $CDCl_3$). For analogous example (13a and b with R = Me) see R. Pappo, P. Collins, and C. Jung, Ann. N. Y. Acad. Sci., 180, 64(1971).

8. These conditions for the conversion of 12 to 4a constitute an improvement over those previously reported (ref. 1). Application to the 5,6-dihydro derivative of 12 led to the dihydro analog of 3a in 60% overall yield in the PGE_1 series.

9. A. F. Kluge, K. G. Untch, and J. H. Fried, J. Amer. Chem. Soc., 94, 7827 (1972).

10. E. J. Corey and D. J. Beams, ibid., 94, 7210(1972).

11. H. J. Ringold, in Hormonal Steroids, Proceedings of the 1st Intern. Cong. on Hormonal Steroids, 1, (1964), Academic Press, N. Y., p. 305.

12. Using growing cultures, the yield of 3a was only ca. 3% since the majority of substrate 14 was consumed by the microorganism.

13. This value represents an optical purity of ca. 80% since optically pure 3a possesses $[\alpha]_D^{24}$ +9.52° (c 1.56, CH_3OH).

14. G. B. Kaufman and L. A. Teter, Inorg. Syn., 7, 9(1963).

15. E. J. Corey, T. K. Schaff, W. Huber, U. Koelliker, and N. Weinshenker, J. Amer. Chem. Soc., 92, 397(1970).

16. C. Takeguchi, E. Kohno, and C. J. Sih, Biochemistry, 10, 2372(1971).