

TOTAL SYNTHESIS OF 11(R,S)-HETE (13)

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**ABSTRACT:** An expedient preparation of 11(R,S)-HETE which may be adapted to the synthesis of 11(S)-HETE is described.

Corey and Kang<sup>1</sup> recently described the synthesis of 11(R)-HETE (13), which could serve as a precursor to the corresponding hydroperoxide 14 or peroxy-radical 15, substances implicated in prostaglandin biosynthesis<sup>2</sup>.

We wish to report an alternate synthesis of 11(R,S)-HETE, which, since glycidol is available as the R isomer<sup>3</sup>, constitutes a formal synthesis of S-13, the enantiomer of opposite configuration to that described by Corey, and probably a better precursor for the preparation of 11(R)-HPETE.

To suitably protected propargyl alcohol 1<sup>4</sup> (60 mmol) in THF (60 ml) at 5° was added first n-butyllithium (55 mmol) and then glycidol derivative 2<sup>5</sup> (50 mmol) and HMPA (3 ml). After heating at 65° for 2.5 h and the usual work-up, reaction with t-butyldimethylsilyl chloride<sup>6</sup> gave fully protected triol 3. Crude 3 was hydrolyzed<sup>7</sup>, and the resulting alcohol 4 mesylated (2 eq MsCl, 4 eq NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 5°, 5 min). Treatment of 5 with NaI (4 eq) in acetone at 20° (1 h) gave iodide 6. Although all steps appeared to proceed in quantitative yield, and no purifications were necessary, the isolated yield for 1 → 6 was only 50-60%. Acetylenic ortho-ester 7<sup>8,9</sup> (1.15 eq) and CuI (0.5 eq) in THF (4 ml) were treated at -78°, under argon, with n-butyllithium (1.15 eq). After 15 min, crude iodide 6 (4 mmol, 1 eq) in 3 ml THF was added, and the mixture was stirred at 20° for 3 h. The crude product was hydrolyzed<sup>10</sup>, and the resulting hydroxy ester 8 reduced with hydrogen, using nickel boride<sup>11</sup> as "catalyst" in stoichiometric amount. Flash

chromatography<sup>12</sup>, using petroleum ether:ethyl acetate (20:3) as eluant, afforded pure *Z,Z*-diolefinic alcohol 9 in 38% yield, based on iodide 6. Its isomeric purity and structure were ascertained by g.c.-mass spectrometry and <sup>13</sup>C and H n.m.r. spectroscopy at 200 MHz.

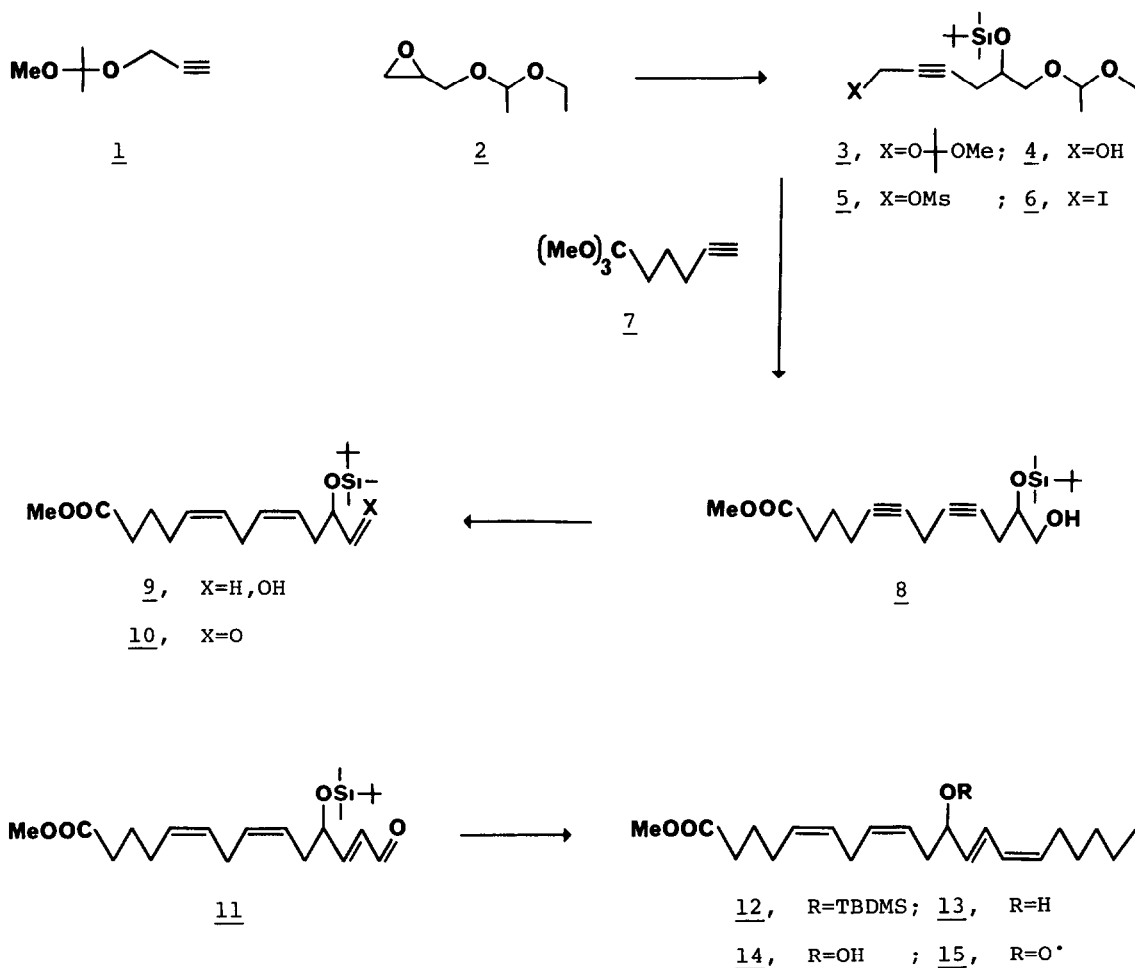
Oxidation with pyridinium chlorochromate<sup>13,14</sup> (40°, 4 h) gave aldehyde 10 in only 45% yield, despite the fact that t.l.c. indicated a fairly pure product. Treatment of crude 10 with formylmethylenetriphenylphosphorane<sup>15</sup> (1 eq) in DMF at 60° for 6 h<sup>16</sup> afforded the *E*- $\alpha,\beta$ -unsaturated adduct 11 in 85% yield; it was contaminated with less than 5% of the *Z*-isomer, as established by proton and <sup>13</sup>C n.m.r. Reaction of aldehyde 11 with a Wittig reagent prepared from triphenylhexylphosphonium bromide<sup>16</sup> gave 12, contaminated by ~10% of the corresponding 14*E* isomer. Upon desilylation with tetra-*n*-butylammonium fluoride, the *E* and *Z* isomers of alcohol 13 could be separated by repeated flash chromatography (petroleum ether:ethyl acetate, 5:1).

The proton n.m.r. (200 MHz) spectrum of 13 was identical within experimental error to that reported by Corey and Kang<sup>1</sup>. The structure and purity of 13 were further confirmed by g.c.-mass spectrometry of the trimethylsilyl ether of 13<sup>17</sup>, and by the <sup>13</sup>C n.m.r. data of 12.

Although Corey reports that alcohol 13 is relatively unstable, we have found that silyl ether 12 could be stored at -15° for several weeks without taking any further precaution.

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#### REFERENCES AND NOTES

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2. M. Hamberg, J. Svensson, T. Wakabayashi, and B. Samuelsson, *Proc. Natl. Acad. Sci. USA*, **71**, 345 (1974), and references cited therein.
3. J.J. Baldwin, A.W. Raab, K. Mensler, B.H. Arison, and D.E. McLure, *J. Org. Chem.*, **43**, 4876 (1978).
4. Propargyl alcohol (8.4 g, 1 eq), 2-methoxypropene (1.1 eq), pyridinium tosylate (PPTS, 0.1 eq), CH<sub>2</sub>Cl<sub>2</sub> (400 ml), 4 h at 5°, wash with aqueous NaHCO<sub>3</sub>; b.p. 55°/30 mm Hg.

5. Glycidol (8.8 g, 1 eq), ethyl vinyl ether (2 eq), PPTS (0.1 eq),  $\text{CH}_2\text{Cl}_2$  (400 ml),  $5^\circ \rightarrow 22^\circ$ , 4 h, wash with aqueous  $\text{NaHCO}_3$ ; b.p.  $75^\circ/20$  mm Hg.
6. E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94, 6190 (1972).
7. Approximately 2 ml MeOH/mmol of 3, 0.1 eq PPTS,  $0^\circ$ , 1 h; for larger scale, the amount of MeOH was reduced, since product recovery could be best effected by ether extraction without prior removal of MeOH.
8. We thank Dr. A. Wissner, Lederle Laboratories, Pearl River, N.Y., for a generous gift of 7.
9. Prepared by adding 1.1 eq MeOH to an anhydrous  $\text{Et}_2\text{O}$  solution (750 ml) of the appropriate nitrile (2 mol), saturating at  $0^\circ$  with HCl for 0.5 h, and repeating the procedure with 2.2 eq MeOH. Addition of petroleum ether (750 ml) and stirring at  $0^\circ$  gave crystalline iminoether·HCl (68% yield) after drying in vacuo over KOH. Its suspension in petroleum ether (700 ml) containing 3 eq MeOH was stirred at  $20\text{--}25^\circ$  for 3 days. Filtration ( $\text{NH}_4\text{Cl}$ ) and distillation provided 7, b.p.  $71\text{--}2^\circ/0.75$  mm Hg (89% yield). We thank Dr. Wissner for making the procedure available.
10. 0.05 eq PPTS, 15 ml MeOH,  $40^\circ$ , 40 min.
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12. W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 43, 2923 (1978).
13. E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
14. Very recently, the oxidation yield was substantially improved on a similar compound by using DMSO-oxalyl chloride- $\text{NEt}_3$  as described by A.J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 43, 2480 (1978), procedure A.
15. S. Trippett and D.M. Walker, *J. Chem. Soc.*, 1266 (1961).
16. For general procedures, see G. Just and C. Luthe, *Can. J. Chem.*, 58, 2286 (1980).
17. Trimethylsilyl-13 and the corresponding 14E-isomer could be separated on a 2% silar 10C on Chromosorb WHP column. Their mass spectra were virtually identical and showed  $\text{M}^+$  (40%) and  $-\overset{\cdot}{\text{Si}}-\overset{+}{\text{O}}\text{CH}-\text{CH}=\text{CH}-\text{CH}=\text{CHC}_5\text{H}_{11}$  (225, 66%).  
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