$SO_2$ according to ref 26 was carefully added to a well-stirred, ice-cooled 40% aqueous solution of $NHMe_2$. The *N,N*-dimethylsulfonamide, which precipitated immediately, was recrystallized twice from water: mp 103 °C (lit.[27] 102–103 °C).

**Acknowledgment.** The authors wish to thank Professor W. P. Purcell, University of Tennessee Medical Units, for his helpful discussions and his critical review of the manuscript prior to publication.

## References and Notes

(1) (a) E.R.A. No. 393; (b) E.R.A. No. 142.
(2) (a) A. F. Crowther work cited in J. H. Biel and B. K. B. Lum, *Prog. Drug Res.*, **10**, 71 (1966); (b) R. F. Meyer, C. D. Stratton, S. G. Hastings, and R. M. Corey, *J. Med. Chem.*, **16**, 1113 (1973).
(3) J. R. Kilborn and P. Turner, *Br. J. Clin. Pharmacol.*, 1, 143 (1974).
(4) R. Howe, B. S. Rao, and M. S. Chodnekar, *J. Med. Chem.*, **13**, 169 (1970).
(5) B. Basil, E. C. J. Coffee, D. L. Gell, D. R. Maxwell, D. J. Sheffield, and K. R. H. Wooldridge, *J. Med. Chem.*, **13**, 403 (1970).
(6) C. Bernhart and C. G. Wermuth, *Eur. J. Med. Chem.*, 11, 378 (1976).
(7) J. L. Imbs, F. Miesch, J. Schwartz, J. Velly, G. Leclerc, A. Mann, and C. G. Wermuth, *Br. J. Pharmacol.*, **60**, 357 (1977).
(8) A. Martani, M. Magli, G. Orzalesi, and R. Selleri, *Farmaco, Ed. Sci.*, **30** (5), 370 (1975).
(9) H. L. Pan and T. L. Fletcher, *Chem. Ind. (London)*, 240 (1968).
(10) M. L. Hoefle, S. G. Hastings, R. F. Meyer, R. M. Corey, A. Holmes, and C. D. Stratton, *J. Med. Chem.*, **18**, 148 (1975).
(11) C. F. Schwender, R. E. Pike, J. Shavel, Jr., and H. R. Kaplan, *J. Med. Chem.*, **18**, 211 (1975).
(12) B. Rouot, G. Leclerc, C. G. Wermuth, F. Miesch, and J. Schwartz, *J. Med. Chem.*, **19**, 1049 (1976).
(13) M. S. Tute, *Adv. Drug Res.*, **6**, 1 (1971).
(14) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 7, 525 (1971).
(15) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4326 (1968).
(16) C. Hansch, A. Leo, S. H. Hunger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
(17) R. W. Taft in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 556.
(18) O. R. Quayle, *Chem. Rev.*, **53**, 439 (1953).
(19) B. Basil, J. R. Clark, E. C. J. Coffee, R. Jordan, A. H. Loveless, D. L. Pain, and K. R. H. Wooldridge, *J. Med. Chem.*, **19**, 399 (1976).
(20) H. A. Germer, *J. Pharm. Pharmacol.*, **26**, 799 (1974).
(21) J. P. Hieble and S. Ellis, *Clin. Res.*, **23** (4), 551A (1975).
(22) D. Horii, T. Kanada, K. Takeda, and S. Imai, *Arzneim.-Forsch.*, **24**, 1275 (1974).
(23) B. Levy and B. E. Wilkenfeld, *Eur. J. Pharmacol.*, 11, 67 (1970).
(24) F. Miesch, J. C. Turlot, J. D. Ehrhardt, and J. Schwartz, *J. Pharmacol.*, **8** (1), 27 (1977).
(25) A. T. Fuller, I. M. Tonkin, and J. Walker, *J. Chem. Soc.*, 633 (1945).
(26) C. Tröltzsch, *J. Prakt. Chem.*, **4** (22), 192 (1963).
(27) W. A. Gregory, U.S. Patent 2 680 135 (1954); *Chem. Abstr.*, **49**, 7596c (1955).

# *Notes*

## Prostaglandins and Congeners. 16.[1] Synthesis and Bronchodilator Activity of *dl*-11-Deoxy-3-thiaprostaglandins

Jerauld S. Skotnicki,* Robert E. Schaub, Martin J. Weiss,

*Metabolic Disease Research Section, Lederle Laboratories, American Cyanamid Company, Pearl River, New York 10965*

and Franz Dessy

*UCB S.A. Division Pharmaceutique, rue Berkendael 68, 1060 Brussels, Belgium.* *Received April 28, 1977*

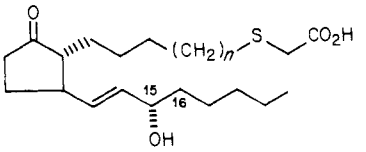
The interesting bronchodilator activity of certain *dl*-11-deoxy-3-thiaprostaglandins and their preparation by the conjugate addition of appropriately substituted (*E*)-1-alkenyllithio cuprate reagents to requisite cyclopentenones are described.

A recent report[2] from these laboratories described the preparation of several *dl*-11-deoxyprostaglandins which could be presumed to be resistant to fatty acid oxidation, a major route of prostaglandin metabolic inactivation.[3] One of the compounds reported, *dl*-11-deoxy-3-thiaprostaglandin $E_1$ (**10**), was found to be a potent bronchodilator in the guinea pig bronchodilator assays[4] (Table I) showing an extended duration of effect.

In order to further develop this interesting observation, we have prepared a series of *dl*-11-deoxy-3-thiaprostaglandins wherein the $\alpha$ chain ($C_1$–$C_7$) has been abbreviated or homologated by one carbon. Also prepared were several congeners in which the $\beta$ chain was altered by the introduction of alkyl substituents[1,5] at $C_{15}$ or $C_{16}$, features that would make these compounds ineffective substrates for 15-hydroxyprostaglandin dehydrogenase,[6] the primary agent of prostaglandin metabolism.[3]

**Chemistry.** Our approach to the synthesis of the *dl*-11-deoxy-3-thiaprostaglandins[7] relies on the facile lithio cuprate conjugate addition of fully elaborated alkenyl $\beta$-chain precursors to requisite cyclopentenones by the procedure of Sih and co-workers.[8] Sequential treatment of vinyl iodides **1**,[2] **2**,[1] and **3**[1] with *tert*-butyllithium and copper(I) pentyne ($CuC{:}CC_3H_7$)[9] in hexamethylphosphorous triamide[9b] afforded the lithium cuprate reagents **4**–**6**. The conjugate addition of cuprates **5** and **6** to cyclopentenone **8**,[10] followed by acidic removal of the trimethylsilyl ($Me_3Si$) protecting group of the conjugate adducts, dry column chromatography, and alkaline hydrolysis, furnished *dl*-11-deoxy-15ξ-methyl-3-thiaprostaglandin $E_1$ (**12**)[11] and *dl*-11-deoxy-16,16-dimethyl-3-thiaprostaglandin $E_1$ (**13**) and its $C_{15}$ epimer **14**.[7] The

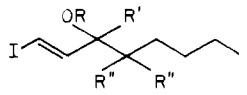
Table I. Bronchodilator Activity of *dl*-11-Deoxy-3-thiaprostaglandins



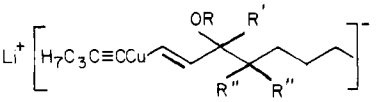
| Compd[a] | $n$ | β-Chain variant[b] | Formula | Analyses[c] | Yield,[d] % | Guinea pig bronchodilator assays,[e] $ED_{50}$, g/kg | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Serotonin | Histamine | Acetylcholine |
| **10**[f] | 1 | None | | | | $1.29 \times 10^{-6}$ | $5.07 \times 10^{-6}$ | $5.14 \times 10^{-6}$ |
| **11**[f] | 1 | 15-Epi | | | | $23.3 \times 10^{-6}$ | $11.3 \times 10^{-6}$ | $(200 \times 10^{-6})$[g] |
| **12** | 1 | 15ξ-Methyl | $C_{20}H_{34}O_4S$ | C, H, S | 33 (80)[h] | $5.40 \times 10^{-6}$ | $1.85 \times 10^{-6}$ | $19.3 \times 10^{-6}$ |
| **13** | 1 | 16,16-Dimethyl | $C_{21}H_{36}O_4S$ | C, H, S | 40 (87) | $52.3 \times 10^{-6}$ | $24.2 \times 10^{-6}$ | $604 \times 10^{-6}$ |
| **14** | 1 | 16,16-Dimethyl, 15-epi | $C_{21}H_{36}O_4S$ | C, H, S | (87) | $32 \times 10^{-6}$ | $324 \times 10^{-6}$ | *i* |
| **15** | 0 | None | $C_{18}H_{30}O_4S$ | *j* | 17 (59)[k] | *i* | *i* | *i* |
| **16** | 0 | 15ξ-Methyl | $C_{19}H_{32}O_4S$ | C, H, S | 24 (76)[h] | *i* | $2.99 \times 10^{-3}$ | *i* |
| **17** | 2 | None | $C_{20}H_{34}O_4S$ | C, H, S | 7 (71) | *i* | *i* | *i* |
| **18** | 2 | 15-Epi | $C_{20}H_{34}O_4S$ | C, H, S | (79) | *i* | *i* | *i* |
| **19** | 2 | 16,16-Dimethyl | $C_{22}H_{38}O_4S$ | *l* | 10 (84)[k] | *i* | *i* | *i* |
| *dl*-11-Deoxyprostaglandin $E_1$ (**20**)[m] | | | | | | $0.397 \times 10^{-6}$ | $3.4 \times 10^{-6}$ | $32 \times 10^{-6}$ |
| *dl*-11-Deoxy-15-methylprostaglandin $E_1$ (**21**)[n] | | | | | | $6.99 \times 10^{-6}$ | $4.24 \times 10^{-6}$ | $(3.2 \times 10^{-6})$[g] |
| *dl*-11-Deoxy-16,16-dimethylprostaglandin $E_1$ (**22**)[n] | | | | | | $25.9 \times 10^{-6}$ | $4.17 \times 10^{-6}$ | $42.9 \times 10^{-6}$ |

[a] Spectral data for all compounds are consistent with the assigned structures. [b] Reference 7. [c] Analyses indicated by letter only are within ±0.4% of the calculated value. [d] Yields without parentheses denote total yield of purified conjugate addition products. Yields in parentheses refer to saponification yields of 15-epimeric racemates separated at the ester stage by dry column chromatography (see Experimental Section). [e] The broncholytic activity of each compound was measured in at least four guinea pigs for each of the spasmogenic substances at each dose level. Average standard errors (log units) for $ED_{50}$ values of the test compounds were 0.2, 0.30, and 0.30 for serotonin, histamine, and acetylcholine, respectively. [f] Reference 2. [g] The lowest dose providing >50% inhibition of constriction; a flat dose–response effect was obtained. [h] Reference 11. [i] At 3.2 mg/kg the inhibition of bronchoconstriction was less than 50%. [j] Calculated for $C_{18}H_{28}O_3S$ (M − $H_2O$): 324.1758. Found: 324.1764. [k] Reference 12. [l] Calculated for $C_{22}H_{36}O_3S$ (M − $H_2O$): 380.2385. Found: 380.2413. [m] Reference 15. [n] Reference 1.

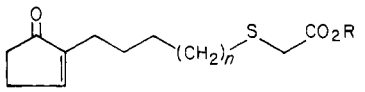
corresponding 4-nor (**15**[12] and **16**[11]) and 4-homo (**17**–**19**[12]) congeners of this series were analogously prepared using cuprates **4**–**6** and cyclopentenones **7**[13] and **9**,[10] respectively.



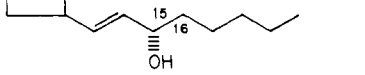
**1**, R = Tr; R′ = R″ = H
**2**, R = $Me_3Si$; R′ = $CH_3$; R″ = H
**3**, R = $Me_3Si$; R′ = H; R″ = $CH_3$



**4**, R = Tr; R′ = R″ = H
**5**, R = $Me_3Si$; R′ = $CH_3$; R″ = H
**6**, R = $Me_3Si$; R′ = H; R″ = $CH_3$



**7**, $n$ = 0; R = $n$-$C_4H_9$
**8**, $n$ = 1; R = $C_2H_5$
**9**, $n$ = 2; R = $C_2H_5$



**10**, $n$ = 1
**11**, $n$ = 1; 15-epi
**12**, $n$ = 1; 15ξ-methyl
**13**, $n$ = 1; 16,16-dimethyl
**14**, $n$ = 1; 16,16-dimethyl, 15-epi
**15**, $n$ = 0
**16**, $n$ = 0; 15ξ-methyl
**17**, $n$ = 2
**18**, $n$ = 2; 15-epi
**19**, $n$ = 2; 16,16-dimethyl

**Biology.** The *dl*-11-deoxy-3-thiaprostaglandins of this report were evaluated as bronchodilators by the previously described procedure.[4] The candidate compounds were administered intravenously to guinea pigs suffering bronchconstrictions induced by serotonin, histamine, or acetylcholine. The results are summarized in Table I.

It is evident from these data that replacement of carbon with sulfur in the 11-deoxyprostaglandin series, e.g., *dl*-11-deoxy-3-thiaprostaglandin $E_1$ (**10**), affords congeners that are highly potent in this assay. For comparison, the bronchodilator profile of *dl*-11-deoxyprostaglandin $E_1$ (**20**),[15] *dl*-11-deoxy-15ξ-methylprostaglandin $E_1$ (**21**),[1] and *dl*-11-deoxy-16,16-dimethylprostaglandin $E_1$ (**22**)[1] has been included in Table I.

*dl*-11-Deoxy-3-thiaprostaglandin $E_1$ (**10**), when given in the anesthetized dog by aerosol administration, reduced pilocarpine bronchoconstriction[16] by 50% at doses of 1.6–3.2 μg/kg. In contrast to *l*-$PGE_1$, which was substantially more potent but short acting, these effects persisted for the duration of the experiment (1 h). On the other hand, the maximum effect (50%) that could be attained at any dose was significantly less than the maximum bronchodilator effect of *l*-$PGE_1$ (70% inhibition at 0.016–0.032 μg/kg) or of isoproterenol (80% inhibition at 16–32 μg/kg) similarly administered. The 15-methyl derivative **12** gave similar results in both assays and the 16,16-dimethyl derivative **13** seemed to show a somewhat diminished potency in the guinea pig assay. In the guinea pig assays the 15-methyl compound **12** did not demonstrate the initial but brief spasmogenic effect which we have observed in general for other 15-alkyl[1] and 16-alkyl[1,18] derivatives; however, the 16,16-dimethyl-3-thia derivative **13** was initially spasmogenic.

Homologation or abbreviation of the α chain furnished *dl*-11-deoxy-3-thiaprostaglandin $E_1$ congeners which were relatively ineffective in the guinea pig assay at the dose levels studied. The poor activity observed for the 4-nor compounds is surprising since examination of molecular models indicated a good similarity in chain length between the α chain of these compounds and that of $PGE_2$.

It is worth summarizing our observation to date concerning the bronchodilator structure–activity relationships with respect to variations of the $\alpha$ chain. Thus, we have found that the introduction of a methyl or phenyl group at $C_2$,[1] or a *gem*-dimethyl feature at $C_3$,[18] was not consistent with good activity in the guinea pig bronchodilator assays. However, substitution of oxygen[1] or sulfur for $C_3$ did furnish potent bronchodilators. We have also observed in this study and for a series of *dl*-11-deoxy-16,16-trimethyleneprostaglandin $E_1$ congeners[18] that homologation or abbreviation of the $\alpha$ chain did not afford congeners that were effective bronchodilators.

## Experimental Section

All organometallic reactions were performed under an inert atmosphere of argon or nitrogen. All organic extracts were dried with anydrous $MgSO_4$. Solvents were removed under reduced pressure using a Büchi evaporator.

Infrared spectra were recorded with neat samples on a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined in $CDCl_3$ using Varian A-60 or HA-100D spectrophotometers. Chemical shifts are given in parts per million downfield from an internal $(CH_3)_4Si$ standard. Those analytical results indicated by symbol only were within ±0.4% of their calculated values. Ultraviolet spectra were obtained using a Cary recording spectrophotometer in the indicated solvent. Mass spectra were recorded on an AEI MS-9 at 70 eV. Only certain characteristic spectral data are presented for each compound.

**General Conjugate Addition Procedure. Preparation of *dl*-11-Deoxy-15ξ-methyl-3-thiaprostaglandin $E_1$ Ethyl Ester.** To a stirred solution of 6.32 g (18.6 mmol) of (*E*)-1-iodo-3-trimethylsilyloxy-1-octene (**2**) and 15 mL of dry ether, cooled to −78 °C under an argon atmosphere, was slowly added 49 mL (39 mmol) of *t*-BuLi. After 40 min, the reaction mixture was warmed to −10 to −5 °C for 1 h and recooled to −78 °C, and to it was added a solution of 2.63 g (20.1 mmol) of copper(I) pentyne,[9a] 8.5 mL of hexamethylphosphorous triamide, and 35 mL of dry ether. The solution was stirred for 1 h when 20 mL of dry ether containing 4.74 g (18.5 mmol) of 2-(6-carbethoxyhexyl-5-thia)cyclopent-2-en-1-one (**8**)[12] was added. After 20 min, the reaction mixture was warmed to −15 to −10 °C for 1.5 h, poured into a saturated $NH_4Cl$ solution, and stirred for 1 h. The resulting blue solution was extracted with 500 mL of ether in three portions. The combined ether extracts were washed with 1% $H_2SO_4$ and brine, were dried, and concentrated in vacuo to furnish 8.09 g of an amber oil. A solution of the oil and 100 mL of acetic acid–THF–water (4:2:1) was stirred at ambient temperature for 30 min, diluted with toluene, and concentrated in vacuo providing 6.57 g of a brown oil. The oil was dry column chromatographed using 1300 g of silica gel (3 in. flat × 49 in. packed; EtOAc–benzene (1:4); 450 mL of eluent was collected).

Isolated from the column at $R_f$ 0.31–0.51 was 2.449 g (33%) of *dl*-11-deoxy-15ξ-methyl-3-thiaprostaglandin ethyl ester as a yellow oil: IR 3500, 1740, and 980 $cm^{-1}$; $^1H$ NMR $\delta$ 5.64 (m, 2 H, C-13,14 H), 4.20 (q, 2 H, $-OCH_2CH_3$, $J$ = 7 Hz), 3.20 (br s, 2 H, C-2 H), 1.28 (s, 3 H, $-CH_3$), and 0.88 (t, 3 H, C-20 H). Anal. ($C_{22}H_{38}O_4S$) C, H, S.

**General Saponification Procedure.** A solution of the ester and MeOH–$H_2O$ (1:1) containing KOH or NaOH (4 equiv) was stirred at ambient temperature under an argon atmosphere from 24 to 72 h. The reaction mixture was extracted with ether and the ether phase was discarded. The remaining aqueous phase was acidified with 5% HCl and extracted with ether. The ether extracts were washed with brine, dried, and concentrated in vacuo to give the product acid.

Obtained by this procedure was 800 mg (80%) of *dl*-11-deoxy-15ξ-methyl-3-thiaprostaglandin $E_1$ (**12**) as a yellow oil: IR 3500, 2800, 1740, and 975 $cm^{-1}$; $^1H$ NMR $\delta$ 7.20 (s, 2 H, OH), 5.63 (m, 2 H, C-13,14 H), 3.23 (s, 2 H, C-2 H), 2.67 (t, 2 H, C-4 H), 1.33 (s, 3 H, $-CH_3$), and 0.90 (t, 3 H, C-20 H). Anal. ($C_{20}H_{34}O_4S$) C, H, S.

For other *dl*-11-deoxy-3-thiaprostaglandins prepared in this manner see Table I.

**Guinea Pig Bronchodilator Assay.**[4] Hartley guinea pigs of either sex, weighing 250–500 g, were anesthetized by intraperitoneal injection of urethane (1.5 g/kg) and given an intravenous injection of gallamine. They were artificially ventilated through a tracheal cannula (60 strokes/min), the respiratory volume being adjusted according to the weight of the animal and the rate of the pump.[19] The two jugular veins were catheterized, the first one being used for curarization and administration of the drugs and the second for the injection of the spasmogenic agent. This injection was made at different selected speeds with a perfusion pump (Braun Unita 1). The intratracheal pressure was measured with a transducer (Sanborn 267 AC) connected to the tracheal cannula and recorded on a Sanborn polygraph.

Bronchial spasms were produced by intravenous injection of acetylcholine, histamine, or serotonin. The speed of injection of the spasmogenic solution and its concentration were chosen to produce an increase of the tracheal pressure of 20–50 cm of water. For acetylcholine that dose varied from 40 to 150 $\mu$g/kg, for histamine from 5.6 to 22.5 $\mu$g/kg, and for serotonin from 7.5 to 30 $\mu$g/kg.

Injections of 12-s duration were repeated every 5 min throughout the assay. When three successive control bronchoconstrictions of similar intensity were obtained, the animal was considered to be ready for the assay and received the first dose of the candidate drug 2 min later.

Soluble compounds (sodium salts) were injected through the jugular vein. The drug injection took 1 min and was repeated three or four times per animal at 15-min intervals so that three or four doses, in logarithmic progression, were assayed. Water-insoluble compounds (esters) were dispersed in 10% aqueous ethanol and administered in the same way.

The broncholytic activity of each compound was measured in at least four guinea pigs for each of the three spasmogenic substances. The amplitude of the three spasms (i.e., the difference between the maximum total tracheal pressure during the spasms and the normal insufflation pressure without spasm) following the administration of the drug was expressed in centimeters of water. For each spasm the mean difference vs. the control [i.e., $\Sigma$(treated spasm − control spasm)/control spasm] was calculated. For an easier expression of the results, the mean difference was transformed into a percentage of variation. When the percent of variation of the first spasm following any dose of the drug reached at least −50%, a regression line of the percent of variation vs. the dose was computed in a semilogarithmic system. The $ED_{50}$ (dose producing a −50% variation) was then calculated.

When a compound was not active enough to allow the calculation of an $ED_{50}$, the $ED_{50}$ was considered to be greater than the maximal dose administered.

**Acknowledgment.** The authors thank Mr. L. Brancone and staff for microanalysis and Messrs. W. Fulmor and G. O. Morton and Dr. R. T. Hargreaves and staff for spectral data and interpretation. We thank Drs. P. J. Kohlbrenner and K. Sax and Mr. J. Nocera for supplying ample quantities of key intermediates, Mr. J. F. Poletto for providing cyclopentenone **9**, and Mr. A. Cognioul for performing the guinea pig bronchodilator testing. Many helpful discussions with Drs. M. B. Floyd, A. Wissner, C. V. Grudzinskas, and J. E. Birnbaum are acknowledged.

## References and Notes

(1) For paper 15 in this series, see J. S. Skotnicki, R. E. Schaub, K. F. Bernady, G. J. Siuta, J. F. Poletto, M. J. Weiss, and F. Dessy, *J. Med. Chem.*, this issue.
(2) K. F. Bernady, J. F. Poletto, and M. J. Weiss, *Tetrahedron Lett.*, 765 (1975).
(3) For recent reviews concerning prostaglandin metabolism, see (a) T. O. Oesterling, W. Morozowich, and T. J. Roseman, *J. Pharm. Sci.*, **61**, 1861 (1972); (b) "The Prostaglandins", P. W. Ramwell, Ed., Plenum Press, New York, N.Y., 1973.
(4) F. Dessy, M. R. Maleux, and A. Cognioul, *Arch. Int. Pharmacodyn. Ther.*, **206**, 368 (1973).
(5) (a) E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974); (b) E. W. Yankee and G. L. Bundy, *ibid.*, **94**, 3651 (1972); (c) M. Hayashi, H. Miyake, T. Tanouchi, S. Iguchi, Y. Iguchi, and F. Tanouchi, *J. Org. Chem.*, **38**, 1250 (1973); (d) B. J. Magerlein, D. W. DuCharme, W. E. Magee, W. L. Miller, A. Robert, and J. R.

Weeks, *Prostaglandins*, **4**, 143 (1973).
(6) (a) G. Hansson and E. Granstrom, *Biochem. Med.*, **15**, 95 (1976); (b) J. R. Weeks, D. W. DuCharme, W. E. Magee, and W. L. Miller, *J. Pharmacol. Exp. Ther.*, **186**, 67 (1973); (c) G. L. Bundy, E. W. Yankee, J. R. Weeks, and W. L. Miller, *Adv. Biosci.*, **9**, 125 (1973).
(7) Compounds depicted with the 15-natural configuration are actually racemates containing 8-nat, 12-nat, 15-nat, and 8-epi, 12-epi, 15-epi enantiomers. Likewise, compounds depicted as 15-epi are actually racemates containing 8-nat, 12-nat, 15-epi and 8-epi, 12-epi, 15-nat enantiomers.
(8) C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, *J. Am. Chem. Soc.*, **97**, 865 (1975), and references cited therein.
(9) (a) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4071 (1966); (b) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
(10) The synthesis of cyclopentenones **8** and **9** will be described in a forthcoming publication from these laboratories; see also K. F. Bernady, J. F. Poletto, and M. J. Weiss, U.S. Patent 3 836 581 (Sept 17, 1974).
(11) We were unable to effect the separation of the 15-epimeric racemates of **12** and **16**, consistent with previous findings from these laboratories.[1]
(12) Only the 15-natural[7] congeners **15** and **19** were prepared and tested, although the conjugate addition did afford the esters of both epimeric racemates.
(13) Compound **7** was prepared by a direct extension of the cyclopentenone synthesis of Caton and co-workers.[14] Triethylamine-catalyzed Michael addition of ethyl 2-mercaptoacetate to acrolein, followed by condensation of the resulting aldehyde with 1-morpholinocyclopentene (Aldrich) and isomerization–transesterification (HCl–1-butanol, 100 °C, 2 h), provided **7**: IR (neat) 1745, 1705, and 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.43 (m, 1 H, C=CH), 4.17 (t, 2 H, $-OCH_2CH_2-$, $J$ = 7 Hz), 3.23 (s, 2 H, $-SCH_2COO-$), and 0.95 (t, 3 H, $-CH_2CH_3$, $J$ = 7 Hz); UV (EtOH) 223 nm. Anal. ($C_{14}H_{22}O_2S$) C, H; S: calcd, 11.86; found, 11.31.
(14) (a) T. S. Burton, M. P. L. Caton, E. C. J. Coffee, T. Parker, K. A. J. Stuttle, and G. L. Watkins, *J. Chem. Soc., Perkin Trans. 1*, 2550 (1976); (b) M. P. L. Caton, E. C. J. Coffee, T. Parker, and G. L. Watkins, *Synth. Commun.*, **4**, 303 (1974); (c) M. P. L. Caton, E. C. J. Coffee, and G. L. Watkins, *Tetrahedron Lett.*, 773 (1972).
(15) M. B. Floyd and M. J. Weiss, *Prostaglandins*, **3**, 921 (1973).
(16) A long-acting bronchial spasm is induced by an injection of 400 $\mu$g/kg, followed by perfusion of 4 $\mu$g/kg/min of pilocarpine. The increase of the airway's resistance must be at least 200–300% of the resting value. After a 15-min control period the compound is administered by means of an ultrasonic aerosol device (Monaghan 650). All the parameters are then followed for at least 1 h. The activity of the compound is expressed as percentage of inhibition of the induced spasm. Further details of this method are described by Lulling and co-workers.[17]
(17) (a) J. Lulling, F. El Sayed, and P. Lievens, *Med. Pharmacol. Exp.*, **16**, 481 (1967); (b) J. Lulling, P. Lievens, F. El Sayed, and J. Prignot, *Arzneim.-Forsch.*, **18**, 995 (1968).
(18) J. S. Skotnicki, R. E. Schaub, M. J. Weiss, and F. Dessy, *J. Med. Chem.*, **20**, 1042 (1977).
(19) L. I. Kleinman and E. P. Radford, *J. Appl. Physiol.*, **19**, 360 (1964).

# 3-(3-Substituted prop-1-enyl)cephalosporins[1]

Philip J. Beeby

*Division of Applied Organic Chemistry, CSIRO, G.P.O. Melbourne, VIC 3001 Australia*

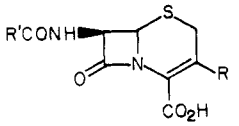
and J. A. Edwards*

*Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304.* *Received April 27, 1977*

The synthesis of cephalosporin derivatives possessing a 3-substituted prop-1-enyl group at the 3 position is described. This was achieved using the reaction of vinylmagnesium chloride with the 3-formyl derivative 1 to give a vinylcarbinol which readily underwent allylic rearrangements to give the desired side chains. The new derivatives exhibited potent in vitro and in vivo antibacterial activity.

Due to the important role played by cephalosporin antibiotics in current medical practice, considerable effort has been invested in the search for cephalosporin derivatives with improved therapeutic properties. While, as with penicillins, much of the effort involved attaching new acyl groups to the amino group at the 7 position, improvements in activity have also been achieved by varying the substituent at the 3 position.

Early work involved simply replacing the acetoxy group by other groups (A → B), where typically X can be H, alkoxy, acyloxyl, alkyl and arylthio, azido, pyridinium, and many others.[2] Recent work has involved more radical modification at this position (A → C), with Y being H,[3a] $CO_2Me$,[3b] CN,[3c] $CH{=}CHCO_2Me$,[3d] OMe,[3e] Cl,[3e] or NHCOMe[3f] to mention just a few.




A, R = $CH_2OAc$
B, R = $CH_2X$
C, R = Y
D, R = $CH{=}CHCH_2Z$

Our finding that the aldehyde group in the 3-formyl-2-cephem system readily undergoes Grignard reaction with vinylmagnesium chloride to give the 3-[(1-hydroxy)-prop-2-enyl] derivative provided us with an entry into the as yet undescribed 3-(3-substituted prop-1-enyl)cephalosporin system (D) with Z being acetoxy or arylthio, for example. Such a modification involves insertion of a trans olefinic unit (CH=CH) at the 3 position of the conventional cephalosporin (A or B).

**Chemistry.** When the aldehyde 1[4] was allowed to react with an excess of vinylmagnesium chloride at low temperature, the desired vinylcarbinol **2** was obtained in good yield as an approximately equal mixture of isomers. Attempts at inducing **2** to undergo an allylic substitution reaction were rewarded when treatment of **2** in 1:1 THF–acetic acid and a catalytic amount of *p*-TsOH at 40 °C led to the acetoxy derivative **4**. Similarly, treatment of **2** with 1.1 equiv of 5-mercapto-1-methyltetrazole and a catalytic amount of *p*-TsOH in THF at 40 °C led to the thioether **5**. Although *p*-TsOH was preferred as catalyst, other acids such as perchloric and hydrochloric acid were found to be similarly effective. The solvent was found to be an important variable, with THF giving superior results to nonbasic solvents such as $CH_2Cl_2$. The isomeric mixture