Tetrahedron Letters,Vol.24,No.18,pp 1867-1870,1983 0040-4039/83/181867-04$03.00/0
Printed in Great Britain

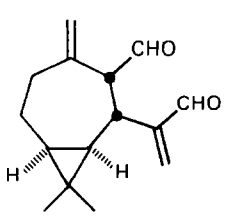
TOTAL SYNTHESIS OF (+)-HANEGOKEDIAL

Michael D. Taylor and Amos B. Smith, III*[1]

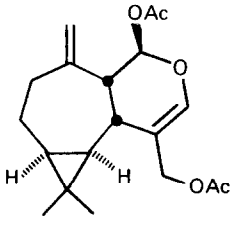
Department of Chemistry, Laboratory for Research on the Structure of Matter and The Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pa. 19104

Summary: The first total synthesis of (+)-hanegokedial (1), one of a large class of seco-aromadendrane natural products is reported.

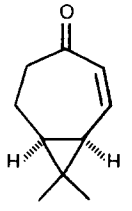
A large and growing class of seco-aromadendrane sesquiterpenes have been isolated recently from extracts of various species of liverwort (Hepaticae).[2] Many members of this class exhibit potent plant growth inhibitory properties and/or insect antifeedent activity.[3] Two representative examples are (+)-hanegokedial (1)[2a] and (+)-ovalifoliene (2).[2a] Recently we reported the preparation, in both racemic and chiral forms, of bicyclic enone 3, which we proposed to be a versatile intermediate for the synthesis of the seco-aromadendranes and other natural products containing the bicyclo[5.1.0]octane substructure.[4] Herein we illustrate the utilility of (-)-3 for the synthesis of (+)-hanegokedial (1) via a short, five-step sequence.



(1)



(2)

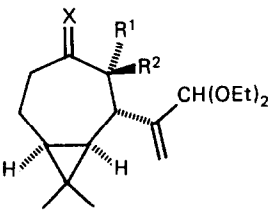


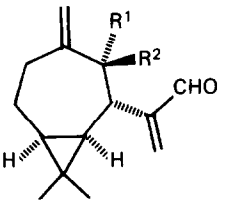
(3)

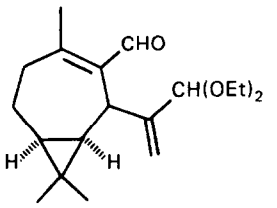
We envisioned the synthesis of 1 to proceed via cuprate addition of a three carbon unit to the β-carbon of 3. Such an addition was anticipated to proceed from the α-face due to the steric bias provided by the geminal methyl substituents on the cyclopropane ring. Introduction of the one-carbon unit at C(2) via capture of the resultant enolate with formaldehyde would then provide all carbons except the exo-methylene group at C(1). The stereochemical outcome of the latter step was less obvious. In fact, formation of a mixture of alcohols at C(2) appeared reasonable. Nonetheless, it was anticipated that epimerization at this center could be accomplished at a later stage if necessary.

In the event, treatment of (-)-3 with bis(1,1-diethoxy-2-propenyl) lithium cuprate[5] in ether followed by reaction of the resultant enolate with gaseous,

monomeric formaldehyde produced two isomeric alcohols 4[6] and 5[6] in a ratio of 2:1 (84%). The stereochemistry of 4 and 5 was assigned after conversion to 11 and 1, respectively (vide infra). Unfortunately, all attempts to epimerize the major alcohol (4) were unsuccessful. For example, mild acidic conditions led to acetal hydrolysis with little further change, while basic conditions, such as potassium t-butoxide in ether resulted in recovery of 4.







(4) R^1 = H, R^2 = CH_2OH, X = O
(5) R^1 = CH_2OH, R^2 = H, X = O
(6) R^1 = H, R^2 = CH_2OAc, X = O
(7) R^1 = H, R^2 = CH_2OH, X = CH_2
(8) R^1 = CH_2OH, R^2 = H, X = CH_2
(9) R^1 = H, R^2 = CHO, X = CH_2
(10) R^1 = CHO, R^2 = H, X = CH_2
(12) R^1 = R^2 = H, X = CH_2
(13) R^1 = R^2 = H, X = O

(11) R^1 = H, R^2 = CHO
(1) R^1 = CHO, R^2 = H

(14)

At this juncture the only alternative was to carry both 4 and 5 through the remainder of the synthesis. Towards this end the major alcohol (4) was found to react sluggishly with triphenylphoshine methylide in THF to give a low yield (<10%) of olefin 7[6]; in DMSO[7] the product isolated was 12, the result of a retro-aldol process. The same product (12) was also obtained from reaction of 13 with triphenylphosphine methylide (THF, 0°, 97%).

Reasonable amounts of 7, however, could be obtained by first protecting the alcohol as the acetate 6[6a] (Ac_2O, pyr, 93%). That is, reaction of 6 with triphenylphosphine methylide in THF at room temperature and then briefly at reflux, produced 7 in 62% yield. Oxidation of the alcohol to aldehyde 9[6] (Collins,[8] 56%) and hydrolysis of the acetal (acetone-water, oxalic acid, 82%) produced epihanegokedial 11[6]. The 250 MHz NMR spectrum of 11 differed significantly from that of the natural product[9] and thus was easily distinguished. All attempts to epimerize 9 or 11 were also unsuccessful. Mild acidic conditions converted 9 to 11 which did not change further. More rigorous conditions such as mineral acids destroyed the material. On the other hand treatment of 9 with amine bases or a trace of potassium t-butoxide caused rapid isomerization of the exocyclic double bond into conjugation with the aldehyde functionality to yield 14[6a], the latter deduced from the 250 MHz NMR spectrum which exhibited only two olefinic resonances and a three proton singlet at δ2.12.

The minor alcohol (5) upon reaction with triphenylphosphine methylide produced the olefin 8[6] (THF, 0-25°, 42%). Oxidation with Collin's reagent[8] and hydrolysis of the acetal led respectively to 10[6] (88%) and 1 (97%). The resultant product exhibited IR and NMR spectra identical to those of the natural product.[9] The optical rotation observed for synthetic 1 was +0.5° (C = 0.8, $CHCl_3$). The latter differed considerably from that reported for the natural material ($[\alpha]_D$ -10.4°).[2a,10] Nonetheless the NMR spectra of 1 and 5 in the presence of a chiral shift reagent[11] were consistent with the enantiomeric purity of the synthetic product.

Finally, several experiments were carried out to convert 1 to 2. In each case however, treatment under a variety of conditions (e.g. AcOH; Ac_2O; Ac_2O, H^+; etc.) led to recovery of the starting material or its destruction.

Acknowledgement. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant No. 22807. In addition, we thank Drs. G. Furst and T. Terwilliger of the University of Pennsylvania Spectroscopic Facilities for aid in obtaining the high-field NMR and MS spectral data, respectively.

References and Notes:

1. Camille and Henry Dreyfus Teacher-Scholar, 1978-1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980-1985.

2. a) Matsuo, A.; Atsumi, K.; Nakayama, M.; Hayashi, S.; Kuriyama, K. J. Chem. Soc., Chem. Commun. 1979, 1010. b) Matsuo, A.; Atsumi, K.; Nakayama, M.; Hayashi, S. J. Chem. Soc., Perkin Trans. I, 1981, 2816. c) Asakawa, Y.; Toyota, M.; Takemoto, T. Phytochem., 1980, 19, 567. d) Asakawa, Y.; Toyota, M.; Takemoto, T. Tetrahedron Lett. 1978, 1553, e) Asakawa Y.; Inoue, H.; Toyota, M. Takemoto, T. Phytochem. 1980, 19, 2623. A recent Chemical Abstracts on-line search found more than 130 examples of seco-aromadendrane natural products.

3. Asakawa, Y.; Toyota, M.; Takemoto, T.; Kubo, I. Nakanishi, K. Phytochem. 1980, 19, 2147.

4. Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B., III, J. Org. Chem. 1982, 43, 3960.

5. Enone 3 was inert to the alkenyllithium cuprate-SMe_2 complex as prepared by the method of Marino, J. P.; Ferino, J. S. Tetrahedron Lett. 1975, 3901. Good yields were obtained by preparing the reagent from the alkenyllithium and cuprous iodide in ether at -45° for 3 h.

6. (a) All new compounds gave high-field (250 MHz) ^1H NMR and IR spectra in accord with the assigned structures. b) This compound also gave a satisfactory high resolution mass spectrum. All Yields recorded here are based upon isolated material which was > 97% pure. The NMR and IR spectra of representative intermediates are given below.

   4: NMR (250 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.18 (s, 1H), 4.78 (s, 1H), 3.82-3.44 (comp m, 6H), 3.06 (br t, J = 6.0 Hz, 1H), 2.77 (m, 1H), 2.68 (dt, J = 13.5, 4.5 Hz, 1H), 2.94 (t, J = 11.5 Hz, 1H), 2.44 (m, 1H), 2.01 (m, 1H), 1.63 (m, 1H), 1.25 (t, J = 6.5 Hz, 6H), 1.10 (s, 3H), 1.01 (s, 3H), 0.92 (app t, J = 9.5 Hz, 1H), 0.78 (m, 1H); IR ($CHCl_3$): 3750-3350 (br), 2990 (s), 2960 (s), 2900 (m), 660 (m), 1120 (m), 1065 (s) cm^{-1}.

5: NMR (250 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.22 (s, 1H), 4.84 (s, 1H), 3.95 (br t, J = 7.5 Hz, 1H), 3.80-3.58 (comp m, 3H), 3.46 (m, 2H), 3.16 (m, 1H), 2.80-2.50 (comp m, 4H), 2.08 (m, 1H), 1.53 (m, 1H), 1.26 (t, J = 6.4 Hz, 3H), 1.24 (t, J = 6.5 Hz, 3H), 1.11 (s, 3H), 0.97 (s, 3H), 0.86 (m, 2H); IR ($CHCl_3$): 2980(s), 2930 (s), 2880 (s), 1680 (m), 1470 (m), 1390 (m), 1130 (m), 1080 (s) cm^{-1}.

11: NMR (250 MHz $CDCl_3$) δ 9.51 (s, 1H), 9.48 (d, J = 2.6 Hz, 1H), 6.42 (s, 1H), 9.48 (d, J = 2.6 Hz, 1H), 6.42 (s, 1H), 6.07 (s, 1H), 5.08 (s, 1H), 5.08 (s, 1H), 5.00 (s, 1H), 3.61 (dd, J = 10.3 Hz, 2.6 Hz, 1H), 3.06 appt, J = 10.3 Hz, 1H), 2.37 (m, 2H), 1.87 (m, 1H), 1.6-1.35 (comp m, 1H), 1.04 (s, 3H), 1.00 (s, 3H), 0.91 (dd, J = 10.3, 9.0 Hz, 1H), 0.71 (m, 1H); IR 2940 (s), 1710 (s), 1680 (s), 910 (s) cm^{-1}.

1: NMR (250 MHz $CDCl_3$) δ 9.74 (d, J = 0.9 Hz, 1H), 9.62 (s, 1H), 6.58 (d, J = 1.6 Hz, 1H), 6.23 (d, J = 0.9 Hz, 1H), 4.99 (s, 1H0, 4.89 (s, 1H), 3.36 (br s, 1H), 2.62 (br d, J = 11.5 Hz, 1H), 2.43 (dd, J = 11.5, 5.0 Hz, 1H), 2.39 (t, J = 12.5 Hz, 1H), 2.08 (m, 1H), 1.3-0.9 (comp m, 3H), 1.09 (s, 3H), 0.88 (s, 3H); IR 3020 (m,) 2980 (m), 2940 (s0, 2865 (m), 2825 (m), 2725 (w), 1720 (s), 1690 (s), 1145 (s), 970 (m), 925 (m) cm^{-1};

7. Greenwald, R.; Chaykovsky, M.; Corey, E. J. J. Org. Chem. 1963, 28, 1128.

8. Collins, J. C.; Hess, W. W.; Frank, F. J. Tetrahedron Lett. 1968, 3363.

9. We are grateful to Dr. A. Matsuo of Hiroshima University for providing spectra of the natural hanegokedial. However, due to the instability of the natural product, a sample for direct comparison could not be obtained.

10. Hanegokedial was observed to be unstable on storage, particularly when neat. Samples which were not freshly purified by thin-layer chromatography exhibited UV active impurities and gave large negative (ca. 100°) optical rotations. That the antipode prepared here actually corresponds to the natural compound results from the correlation of the absolute configuration of 1 as determined by Matsuo, et al.[2b] to d-carvone, the starting material for preparation of (-)-3.

11. The shift reagent employed was tris[3-(heptaflouropropylhydroxymethylene)-d-camphorato] europium(III) available from Aldrich. At concentrations of of 5 - 10 mole per cent, of the shift reagent, (±)-5 exhibited splitting of the olefinic and acetal proton resonances. However, 5 prepared from (-)-3 showed no such splitting indicating >90% enantiomeric purity. Similarly, synthetic 1 also exhibited no evidence of racemization.

(Received in USA 8 February 1983)