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TOTAL SYNTHESIS OF THE (+)-PHEROMONE OF THE MALE SWIFT MOTH *HEPIALUS HECTA* L.

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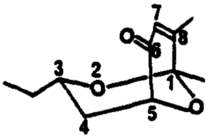
ABSTRACT The (+)-enantiomer of the pheromone of the male swift moth has been synthesized in 6 steps with an overall yield of 16%.

The isolation and structure determination of the pheromones (1 and 2) of the male swift moth *Hepialus hecta L*. were reported by Francke *et al*. in 1985.[2] The structures of 1 and 2 were deduced from mass spectral fragmentation patterns and analysis of the $^{1}H/^{13}C$ NMR spectra. However, the small quantities of material available from natural sources (ca. 200 μg of 1 and 2, respectively) precluded determination of the absolute stereochemistry of the pheromones.



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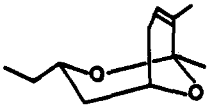

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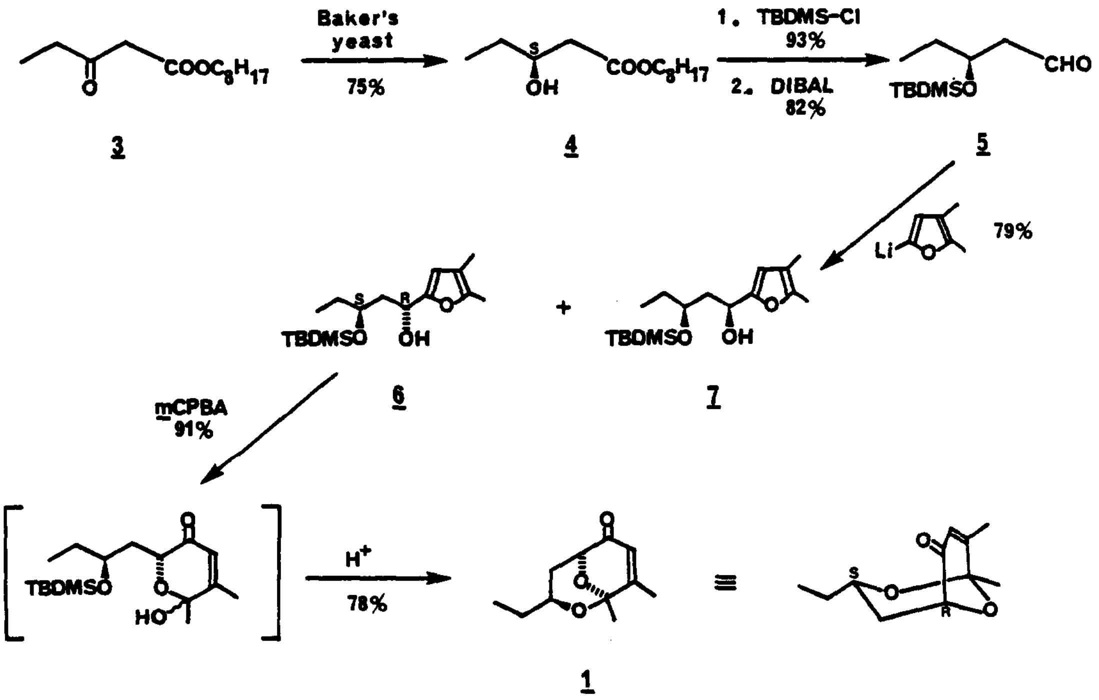
As part of our research program for the total synthesis of the dienoyl tetramic acid antibiotics tirandamycin A/B and streptolydigin, we had previously developed a general approach to the synthesis of bicyclic ketal moieties similar to 1 and 2.[3] In this Communication, we report a six step synthesis of the (+)-enantiomer of 1 which confirms the structure of the natural product and establishes the absolute stereochemistry for this enantiomer as 1R, 3S, 5R.

Reduction of β-keto ester 3 with baker's yeast[4] gave *S*-alcohol 4[5] in 75% isolated yield and >95% enantiomeric excess. This reduction can be routinely performed on 10-20 gram quantities of the ester and facilitated preparation of multigram quantities of synthetic intermediates.

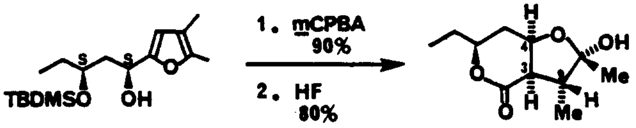
As outlined in the Scheme, protection of the alcohol function as the TBDMS silyl ether[6] under standard conditions (93%) and reduction of the ester with DIBAL[7] produced *S*-aldehyde 5[8] in 82% yield. Condensation of aldehyde 5 with 5-lithio-2,3-dimethylfuran[3] (Et_2O, -78°C) gave a 1:1 mixture of furan-alcohols 6[9] and 7[10,11] (79%). The stereochemistry of the sidechain oxygen functionalities in 6 and 7 were assigned by analogy with related substances[3] and was confirmed by subsequent transformations (*vide infra*).

Treatment of *anti*-alcohol 6 with *m*CPBA in CH_2Cl_2[3] gave a mixture of pyranones (91%) which were cyclized to (+)-1[12] by treatment with dilute HF in aqueous acetonitrile (78%). The spectral data and GC characteristics of synthetic (+)-1 were identical to the reported spectral data[2,13] and thus confirmed the original structure assignment. Using this six step synthesis, (+)-1 was prepared in an overall yield of 16% from readily available starting materials.

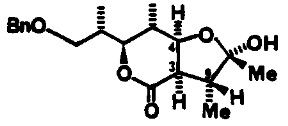
Scheme



Oxidation of alcohol 7 with mCPBA followed by HF treatment produced lactone 8[14] by rearrangement of the intermediate pyranone mixture. The stereochemistry of 8 was assigned by analysis of the ^1H NMR spectrum which was similar to the ^1H NMR spectrum of lactone 9.[3] The structure of lactone 9 had been determined previously by single crystal X-ray analysis.[15]



7 8



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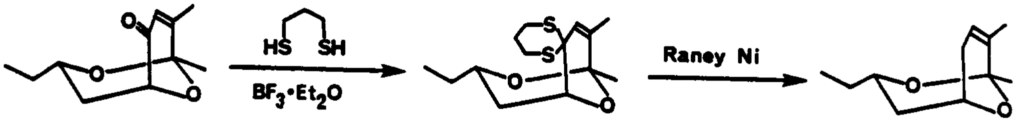
Thioketalization of 1 (propanedithiol, $BF_3 \cdot Et_2O$) gave dithiane 10[16] which upon Raney nickel desulfurization furnished alkene 2, albeit in low yield. We are presently engaged in improving the yield of the desulfurization procedure.



1 10 2

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References and Notes

1. Present address: Department of Chemistry, University of Maryland, College Park, MD 20742.
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3. DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *J. Am. Chem. Soc.* 1985, 107, 5219, and references cited therein.
4. Sih, C. J.; Zhou, B. N.; Gopalan, A. S.; Shieh, W. R.; Van Middlesworth, F. in W. Bartmann, B. Trost: Selectivity-A Goal for Synthetic Efficiency, Workshop Conferences Hoechst Vol. 14, Verlag Chemie, Weinheim 1983, p. 251, and references cited therein.

5. S-Alcohol 4: $[\alpha]^{20}_{D}$=+21.9° (C=2.7, $CHCl_3$), $[\alpha]^{23}$ (Lit.[4])=+21.7° (C=5.9, $CHCl_3$); IR (CCl_4) 3540, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J=7), 0.96 (t, 3, J=7), 1.15-1.71 (m, 14), 2.39 (dd, 1, J=16, 9), 2.52 (dd, 1, J=16, 4), 3.87-3.99 (m, 1), 4.10 (t, 2, J=7).
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7. Winterfeldt, E. *Synthesis*, 1975, 617.
8. S-Aldehyde 5: $[\alpha]^{20}_{D}$=+2.9° (C=2.39, $CHCl_3$); IR (CCl_4) 2710, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3), 0.07 (s, 3), 0.87 (s, 9), 0.90 (t, 3, J=7), 1.49-1.63 (m, 2), 2.51 (dd, 2, J=6, 2), 4.08-4.19 (m, 1), 9.81 (t, 1, J=2).
9. Alcohol 6: $[\alpha]^{20}_{D}$=+24.7° (C=2.47, $CHCl_3$); IR (CCl_4): 3610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 3), 0.12 (s, 3), 0.90 (t, 3, J=7), 0.91 (s, 9), 1.56-1.70 (m, 2), 1.91 (s, 3), 1.80-2.14 (m, 2), 2.19 (s, 3), 3.29 (d, 1, J=3), 3.90-3.98 (m, 1), 4.89 (dt, 1, J=10, 3), 6.00 (s, 1).
10. Alcohol 7: $[\alpha]^{20}_{D}$=+10.6° (C=2.55, $CHCl_3$); IR (CCl_4) 3610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 3), 0.11 (s, 3), 0.89 (dd, 3, J=10, 7), 0.91 (s, 9), 1.49-1.63 (m, 2), 1.91 (s, 3), 1.94-1.98 (m, 2), 2.19 (s, 3), 3.25 (d, 1, J=2), 3.83-3.89 (m, 1), 4.76 (td, 1, J=6, 2), 6.01 (s, 1).
11. Alcohol 7 could be converted into anti-alcohol 6 by oxidation with $BaMnO_4$ (80%)[3] followed by reduction with $Zn(BH_4)_2$ (90%) to give a 1:1 mixture of 6 and 7. Attempted conversion of 7 to alcohol 6 by inversion under Mitsunobu-like conditions led to extensive decomposition of the starting alcohol.
12. Enone 1: $[\alpha]^{20}_{D}$=+346.4° (C=1.94, $CHCl_3$); IR (CCl_4) 1685, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3, J=7), 1.52 (s, 3), 1.37-1.91 (m, 4), 1.95 (d, 3, J=1), 3.56-3.67 (m, 1), 4.31 (dt, 1, J=6, 1), 6.15 (s, 1). ^{13}C NMR ($CDCl_3$) δ 9.1, 19.3, 24.7, 29.0, 32.1, 69.2, 75.0, 95.9, 126.8, 156.8, 197.1. Exact mass calcd. for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1100.
13. Professor W. Francke, Institut für Organische Chemie, Hamburg, has confirmed that a sample of (+)-1 prepared by synthesis was spectroscopically and chromatographically identical with the natural material.
14. Lactone 8: IR (CCl_4) 3600, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, 3, J=7), 1.29 (d, 3, J=7), 1.48 (s, 3), 1.61-1.81 (m, 3), 2.20-2.32 (m, 2), 2.90 (t, 1, J=10), 4.03-4.15 (m, 1), 4.56 (ddd, 1, J=11, 10, 7).
15. The structure of lactone 9[3] has been determined by single crystal X-ray analysis; P. DeShong, M. Parvez, M.-T. Lin, unpublished results. The ^1H NMR spectrum of 9 (360 MHz) displays $J_{3,4}$=10 Hz and $J_{3,9}$=10 Hz, respectively. The ^1H NMR spectrum of 8 has $J_{3,4}$=10 Hz and $J_{3,9}$=10 Hz.
16. Dithiane 10: ^1H NMR ($CDCl_3$) δ 0.90 (t, 3, J=7), 1.26-1.62 (m, 2), 1.46 (s, 3), 1.69 (d, 3, J=1.5), 1.73-2.12 (m, 3), 2.23 (ddd, 1, J=14, 3, 1), 2.69-2.81 (m, 3), 2.98 (ddd, 1, J=14, 11, 4), 3.55-3.69 (m, 1), 4.52 (d, 1, J=6), 5.77 (t, 1, J=1.5). Exact mass calcd. for $C_{14}H_{22}O_2S_2$: 286.1061. Found: 286.1056.

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