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SYNTHESIS OF OPTICALLY ACTIVE FORMS OF FARANAL, THE TRAIL PHEROMONE OF PHARAOH'S ANT[1]

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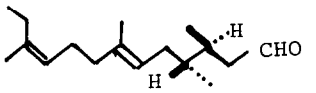
Summary: (3S, 4R)-(+)-Faranal and its antipode were synthesized. The former was comparable in bioactivity with that of the natural pheromone.

In 1977 Ritter et al. isolated faranal as the true trail pheromone of the Pharaoh's ant, Monomorium pharaonis, and identified it as (3R,4S,6E,10Z)-3,4,7 11-tetramethyl-6,10-tridecadienal or its antipode.[2,3] A recent bioorganic synthesis established its (3S,4R)-stereochemistry.[4] We now report a synthesis of both enantiomers of faranal with known absolute configuration.

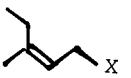
The structure of faranal 1 was so similar to Juvenile Hormone II that we adopted the strategy previously used in our juvenile hormone synthesis.[5] The key intermediates were a phenylsulfone 2b and a chiral bromide 3. The former cf.9 (2b), mp 39°,[6,7] was readily obtainable from 2a[8] by treatment with $NaSO_2Ph$/DMF.

The synthesis of the chiral bromide 3 started from cis-3,4-dimethylcyclopentanone 4 obtainable from butadiene and maleic anhydride via 7 steps.[10] This was treated with m-chloroperbenzoic acid in $CHCl_3$ to give a δ-lactone 5 (90% yield), bp 73-76°/0.55mm. This was hydrolyzed (NaOH) and the resulting (±)-6a was resolved with (R)-(+)-α-phenethylamine. After recrystallizing 5 times from acetone a salt, mp 135.5-136.5°, $[\alpha]_D^{22}$ + 5.02° (c=2.25, MeOH), was obtained in 12.2% yield. This was acidified (HCl) to give 92% optically pure (3S, 4S)-5, $[\alpha]_D^{22}$-47.2° (c=1.23, MeOH). The lactone enriched in (+)-5 was recovered from the mother liquor of the recrystallization and it was resolved with (S)-(-)-α-phenethylamine to give another salt, mp 133-134°, $[\alpha]_D^{22}$-4.96° (c=2.34, MeOH) in 9.1% yield. The salt was decomposed to give 90% optically pure (3R, 4R)-5, $[\alpha]_D^{22}$ + 46.3° (c=1.85, MeOH).[11,12]

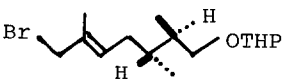
Reduction of (3R, 4R)-(+)-5 with DIBALH gave a lactol 7 (86% yield). This was submitted to the Horner condensation with triethyl α-phosphonopropionate (NaOEt/DMF) to give an ester 8a (53% yield) contaminated with 15% of its (Z)-isomer as revealed by GLC analysis. After protecting the OH group as a THP ether, the ester 8b was reduced (LAH-$AlCl_3$/THF-ether) to give an allylic alcohol 9 (78% yield). This was converted to the desired bromide (3S, 4R)-3 (52% yield) by treatment with n-BuLi-TsCl-LiBr in ether-HMPA.[14] Alkylation of a carbanion derived from 2b (n-BuLi/THF-HMPA) with (3S, 4R)-3 yielded 10 (92% yield).[cf.9]



(3S, 4R)-1



2a X=Br
b X=SO_2Ph



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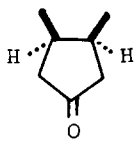

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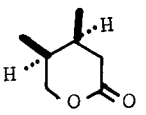
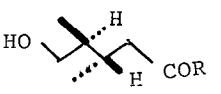
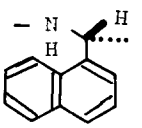
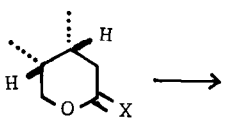


(±)-5

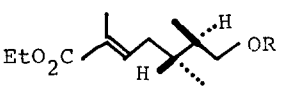


(±)-6a R=OH
(3S, 4S)-6b R=

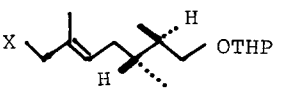




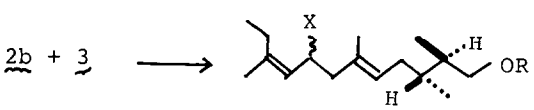
(3R, 4R)-5 X=O
7 X=H, OH



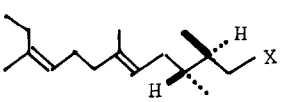
8a R=H
b R=THP



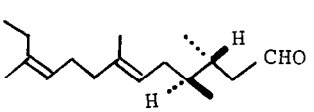
9 X=OH
3 X=Br



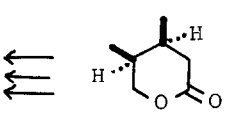
10 R=THP, X=SO_2Ph
11a R=THP, X=H
b R=H , X=H
c R=Ts, X=H



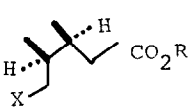
12 X=CN
13 X=CO_2H
14 X=CH_2OH
(3S,4R)-1 X=CHO



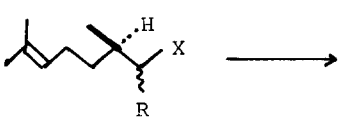
(3R, 4S)-1



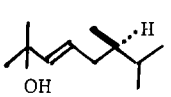
4S)-5



15 R=Et, X=Br
(S)-16 R=H, X=H



(R)-17 R=H, X=CO_2H
(S)-18 R=Me, X=CO_2H
19a R=Me, X=CH_2OH
b R=Me, X=CH_2OTs
20 R=Me, X=Me



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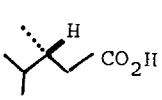

(R)-16

This was reduced with $Li/EtNH_2$ to give (3S, 4R)-11a (61% yield). The THP protecting group was removed (TsOH/MeOH) to give 11b (87% yield). For the purpose of one-carbon elongation 11b was converted to 11c ($TsCl/C_5H_5N$, 98% yield). The tosylate 11c was then treated with NaCN/DMSO to give (3S, 4R)-12 (98% yield). This was hydrolyzed ($NaOH/EtOH-H_2O$, 97% yield) to 13. Reduction of 13 with LAH/THF gave 14 (93% yield), whose oxidation with pyridinium chlorochromate[15] yielded crude product 1 (72% yield). This was purified by preparative GLC (20% PEG-20M, 1m x 3mm at 160°) to give (3S, 4R)-faranal 1, $[\alpha]_D^{23}$ + 16.2° (c=0.50, n-hexane); MS : m/e 250.2327 (M^+, Calcd. for $C_{17}H_{30}O$: 250.41) ; νmax 2700 (w), 1720 (s) cm^{-1}; δ (400 MHz, C_6D_6) 0.69 (3H, d, J=7Hz), 0.72 (3H, d, J=7Hz), 0.94 (3H, t, J=7.5 Hz), 1.55 (3H, s), 1.69 (3H, s), 5.15 (1H, m), 5.19 (1H, m), 9.39 (1H, q, J_1=1.5Hz, J_2=2.5Hz). Similarly (3S, 4S)-5 yielded (3R, 4S)-faranal 1, $[\alpha]_D^{23}$ - 16.4° (c=0.22, n-hexane). The faranal enantiomers were thought to be ~90% optically pure reflecting the optical purity of the starting lactone enantiomers 5. GLC analysis showed that the both enantiomers of 1 contained ~10% of its (10E)-isomer, although no (6Z)-isomer was detected. Their 300 MHz NMR spectra taken at TNO were identical with that of the natural faranal except for some smaller signals probably due to (10E)-isomer. The bioassay of our faranal enantiomers revealed that (3S, 4R)-(+)-isomer was far more active than the (-)-isomer and comparable in activity with that of the natural pheromone.[16]

In conclusion the present work established the absolute configuration of the natural faranal to be (3S, 4R) by organic synthetic means combined with the bioassay data.

Acknowledgements. We are grateful to Drs. F.J. Ritter, C.J. Persoons and I.E.M. Brüggemann, TNO, Delft, for their kind co-operation in bioassay and 300 MHz NMR measurement of our samples. We thank Dr. T. Chuman (Japan Tobacco and Salt Corporation) for prep. GLC. Our thanks are due to Messrs. T. Umemura and S. Kuwahara (this Laboratory) for their help in preparing (R)-16. Financial support by Otsuka Pharmaceutical Co., Ltd. is acknowledged with thanks. This work was partly supported by a Grant-in-Aid for Special Project Research (Grant No. 511608) from Ministry of Education, Japan.

REFERENCES AND FOOTNOTES

1 This work was presented by K.M. at the XVIth International Congress of Entomology in Kyoto, Japan, on August 8, 1980.

2 Isolation and structure proposal: F.J. Ritter, I.E.M. Brüggemann-Rotgans, P.E.J. Verwiel, C.J. Persoons and E. Talman, Tetrahedron Lett., 2617 (1977).

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5 K. Mori, M. Ohki and M. Matsui, Tetrahedron, 30, 715 (1974).

6 Satisfactory spectral and analytical (combustion or MS) data were obtained for all the compounds described in this communication.

7 This sulfone 2b was shown by NMR to contain ~10% of its (E)-isomer. It could not be removed by usual recrystallization.

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11 The optical purity of the resolved lactones 5 was determined by analyzing the diastereomeric ratio of the amide derivatives (3S, 4S)-6b and (3R, 4R)-6b by HPLC (Zorbax SIL 25cm x 6.2 mm, EtOAc-MeOH 20:1, 1ml/min) and shown to be 90% in the case of (3R, 4R)-(+)-5 and 92% in the case of (3S, 4S)-(-)-5.

12 The absolute configuration of the resolved lactone 5 was determined by converting it to 3,4-dimethylpentanoic acid 16. Thus partially resolved (-)-5, $[\alpha]_D^{23}$ - 34.1° (c=1.5, MeOH), was treated with HBr/EtOH to give a bromo ester 15, bp 87-90°/1.0mm, whose hydrogenation (H_2/Pd-C, $CaCO_3$, MeOH) followed by hydrolysis (NaOHaq) yielded (-)-16, bp 92°/4mm, $[\alpha]_D^{24}$ -7.64° (c= 2.5, $CHCl_3$). An authentic sample of (R)-16 was prepared from (R)-(+)-citronellic acid 17. (R)-17 was alkylated (LDA/THF-HMPA ; MeI) to (S)-18. This was reduced (LAH) to 19a. Tosylation followed by LAH reduction of 19a gave 20 via 19b. Treatment of the olefin 20 with PhSeSePh-35% H_2O_2-$MgSO_4$-t-BuOOH/CH_2Cl_2 [13] yielded 21, whose ozonolysis followed by oxidation gave (R)-16, bp 87-92°/8mm, $[\alpha]_D^{23.5}$ +13.7° (c=1.5, $CHCl_3$). The positive optical rotation of (R)-16 allowed the assignment of (S)-configuration to (-)-16. The (-)-lactone was therefore (3S, 4S)-5, while the (+)-lactone was (3R,4R)-5. Utilization of (R)-16 for the synthesis of brassinolide, a new steroidal plant growth promotor, will be reported in due course.

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15 E.J. Corey and J.W. Suggs, Tetrahedron Lett.,2647 (1975).

16 When artificial trails of faranal enantiomers were directly compared in a competitive test at equal concentration (about 0.05 and about 0.5ng/cm),the trail of (+)-faranal was clearly preferred. When the enantiomers were tested separately, the trail of (+)-faranal was very well followed by the workers of the Pharaoh's ant over a concentration range of 0.005 to 0.5ng/cm. A trail of (-)-faranal, when tested in the absence of the (+)-isomer, was follwed very well at 0.5ng/cm only.

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