

CYCLIZATION OF POLYENES XVII¹. SYNTHESIS AND PHEROMONE ACTIVITY OF DL-NEOCEMBRENE

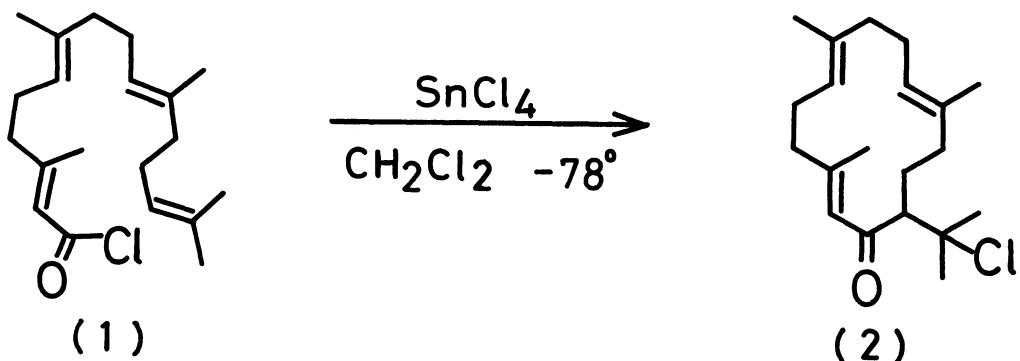
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Neocembrene (4), a scent trail pheromone isolated recently by one of us (B. P. M.) from Australian termites, was synthesized in a dl-form starting from chloroketone (2), which was obtained from trans geranyl geranic acid chloride (1) by biogenetic type reaction. dl-Neocembrene exhibited the pheromone activity of the same order as that of the natural pheromone.

In view of our recent findings that a terminal double bond in acyclic precursors of terpenoids is selectively acylated when treated with RCOCl in the presence of SnCl_4 or AlCl_3 ², we have examined the intramolecular acylation of polyenyl acid chlorides and have found that the cembrene skeleton (2) is effectively (71% yield) constructed, along biogenetic lines, by intramolecular acylation of trans-geranyl geranic acid chloride (1). We have also carried out the conversion of chloroketone (2) to dl-mukulol (3a)³, a naturally occurring cembrene type diterpenoid⁴.



In this communication we wish to report the synthesis⁵ and pheromone activity of neocembrene (4), the natural form of which was isolated by one of us from an Australian termite as a trail pheromone⁶.

Elaboration of the chloroketone (2) to the dl-neocembrene (4) was accomplished by treating 2 with LiBr/Li₂CO₃ in DMF at 105° for 36 hrs to give a mixture of 5 and 6 (9:1) in 86% yield. These isomers could be easily separated by silica gel chromatography [n-hexane/C₆H₆ (1:1)]. The formation of 5 vs 6 is susceptible to reaction conditions and a ratio between 5 and 6 of 1:2 resulted when 2 was dehydrochlorinated with LiCl at 105° for 24 hrs. 5 $\lambda_{\text{max}}^{\text{MeOH}}$ 244 nm ($\epsilon = 7216$); $\nu_{\text{max}}^{\text{neat}}$ 1680, 1610 cm⁻¹; δ (CCl₄) 1.54 and 1.62 (each 3H, bs), 1.67 (3H, t, 1 Hz), 2.07 (3H, d, 1 Hz), 4.7~5.1 (4H, bm), and 5.90 (1H, bs) ppm. 6 $\lambda_{\text{max}}^{\text{MeOH}}$ 254 nm ($\epsilon = 9072$); $\nu_{\text{max}}^{\text{neat}}$ 1660, 1610 cm⁻¹; δ (CCl₄) 1.55 (3H x 2, s), 1.74 (3H x 2, s) 2.10 (3H, s), 4.90 (2H, bm), and 5.95 (1H, bs) ppm.

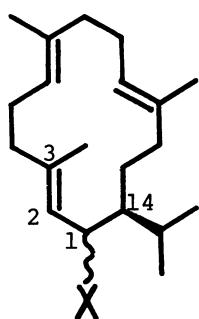
Treatment of 5 with ice-cooled ethereal LiAlH₄ followed by SiO₂ chromatography with n-hexane/AcOEt (10:1) afforded two isomeric alcohols (7a and 7b)³ in 55 and 34% yields, respectively. The relative stereochemistry at C₁ and C₁₄ of these alcohols was deduced from physical evidence in comparison with that from mukulol (3a) and its isomer (3b)⁷.

In the NMR spectra of dl-mukulol (3a) and its isomer (3b), each multiplet centered at 1.24 ppm appeared separately from other signals and was assigned to the C₁₄-proton by decoupling experiments. A cis relation of the C₁- and C₁₄-protons in 3a was unequivocally demonstrated by the observation of 4% nOe between these protons⁸. The C₁-proton of 3a at 4.45 ppm appeared as a doublet of doublets showing couplings with the C₂-H with 9 Hz and the C₁₄-H with 1 Hz, respectively. Meanwhile, the C₁-H of 3b exhibited a clear triplet (9 Hz) showing couplings of the same magnitude with the C₂- and C₁₄-protons. These coupling modes were confirmed by decoupling experiments. The large coupling (9 Hz) between the C₁- and C₂-protons in both 3a and 3b suggests that the dihedral angle of these protons is near 180°, which is supported by the observation of 10% nOe between the C₁-H and C₃-Me in both compounds. The small coupling (1 Hz) between the C₁- and C₁₄-protons in mukulol indicates that the dihedral angle of these protons is near 80°. On the other hand, a dihedral angle of 180° is considered reasonable between the C₁- and C₁₄-protons of the isomer 3b, where a large coupling constant was observed with the lack of nOe between these protons.

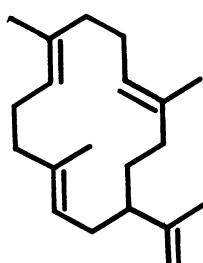
In compounds 7a and 7b, the chemical shifts and coupling modes of C₂-C₁-C₁₄

protons are quite similar to those of 3a and 3b. This evidence as well as the shift values caused by $\text{Eu}(\text{fod})_3$ ⁹ shows that the respective conformations of 7a and 7b are quite similar to those of 3a and 3b respectively, indicating that the hydroxy group is cis in 7a and trans in 7b with respect to the neighboring isopropenyl group.

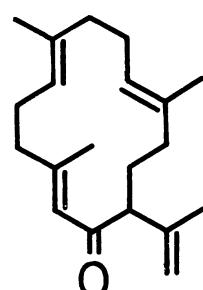
Compounds 7a and 7b, were quantitatively converted to the corresponding acetates, 8a and 8b, under usual acetylation conditions. Treatment of 7a with Li in EtNH_2 at -78° afforded a crude mixture, which was passed through a silica gel column impregnated with 10% AgNO_3 to give dl-neocembrene (4) in 51% yield. Similarly, the acetate (8b) was transformed into 4 in 35% yield under the same conditions¹⁰. IR, NMR in solutions and the mass fragmentation of the synthetic compound (4) are indistinguishable from those of a natural specimen. 8a (oil) $\nu_{\text{max}}^{\text{neat}}$ 3070, 1725; 1665, 1635, 885 cm^{-1} ; δ (CCl_4) 1.57 (3H x 2, bs), 1.70 (3H x 2, bs), 1.91 (3H, s), 4.70 and 4.82 (each 1H, bs), 5.06 (2H, bm), 5.25 (1H, bd, 9 Hz), and 5.57 (1H, dd, 9 and 1.5 Hz) ppm, 8b, mp 70°. $\nu_{\text{max}}^{\text{KBr}}$ 1725, 1660, 1635, 890 cm^{-1} ; δ (CCl_4) 1.60 (3H x 3, bs), 1.75 (3H, bs), 1.88 (3H, s), 4.70~5.15 (5H, bm), and 5.40 (1H, t, 9.5 Hz) ppm.



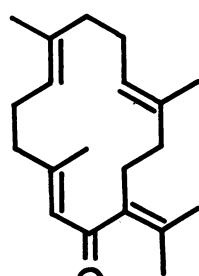
3a $X = \beta - \text{OH}$
3b $= \alpha - \text{OH}$



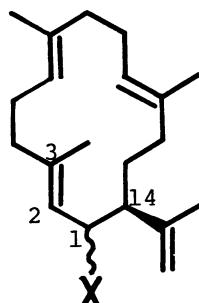
(4)



(5)



(6)



7a $X = \beta - \text{OH}$
7b $= \alpha - \text{OH}$
8a $= \beta - \text{OAc}$
8b $= \alpha - \text{OAc}$

The synthetic dl-neocembrene (4) has been subjected to test¹¹ for trail-laying activity against three species¹² of Nasutitermes and the results were strongly positive in each case. The activity of synthetic material was of the same order as that of the natural pheromone, although no specimen of the latter was available for direct comparison in the biological test. In view of the extremely high order of activity of the dl-mixture, and the limited sensitivity of the biological test, it was not possible to determine whether both stereoisomers of synthetic neocembrene showed similar trail-laying activity, but it is clear from the results at hand that whichever is the natural isomer, the presence of its enantiomorph does not result in any marked inhibition of overall activity, and this is an important finding.

Compounds 7a and 7b also showed trail-laying activity but were effective only at concentrations some 10^3 x those required for the natural pheromone; compound 2 proved entirely inactive.

References

- * To whom correspondence should be addressed.
- ** The grateful acknowledgement is expressed to Takasago Perfumery Co., Ltd., (Tokyo Central P. O. Box 1033) for allowing T. Kobayashi to participate in the present work and for the donation of some of the chemicals.
- 1. Part XVI of this series, T. Kato, T. Kobayashi, and Y. Kitahara, *Tet. Letts.*, 3299 (1975).
- 2. a) T. Kato, S. Kumazawa, C. Kabuto, T. Honda, and Y. Kitahara, *Tet. Letts.*, 2319 (1975); b) S. Kumazawa, Y. Nakano, T. Kato, and Y. Kitahara, *ibid.*, 1757 (1974).
- 3. Only one stereoisomer of the dl-forms was depicted in this paper.
- 4. See ref. 1 and T. Kobayashi, S. Kumazawa, T. Kato, and Y. Kitahara, *Chem. Letts.*, 301 (1975).
- 5. Another synthesis of 4; M. Kodama, Y. Matsuki, S. Ito, *Tet. Letts.*, 3065 (1975).
- 6. a) B. P. Moore, *Nature*, 211, 746 (1966); b) A. J. Birch, W. V. Brown, J. E. T. Corrie, and B. P. Moore, *J. C. S. Perkin I*, 2653 (1972).
- 7. 3a and 3b were obtained from 2 by successive treatments with Bu_3SnH and then $LiAlH_4$ followed by SiO_2 chromatography.
- 8. The same conclusion was obtained by Sukh Dev (private communication), to whom we deeply acknowledge.
- 9. Details will be published elsewhere.
- 10. The yields were not optimized in each case.
- 11. A. J. Birch, K. B. Charmberlain, B. P. Moore, and V. H. Powell, *Aust. J. Chem.*, 23, 2337 (1970).
- 12. exitiosus (Hill), graveolus (Hill) and fumigatus (Brauer).

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